Clinical significance of tumor infiltrating lymphocytes in association with hormone receptor expression patterns in epithelial ovarian cancer

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Clinical significance of tumor infiltrating lymphocytes in association with hormone receptor expression patterns in epithelial ovarian cancer

Directed by Professor Jae-Hoon Kim

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As I finish my doctoral dissertation, I recall there were many difficult moments along the way while working at the hospital, with my graduate school classes as well as proceeding with my thesis. However today, I am glad that I forged on and I was able to graduate safely.

I would like express my gratitude towards those who gave me great deal of help in this acknowledgement.

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Thank you.

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ABSTRACT

Clinical significance of tumor infiltrating lymphocytes in association with hormone receptor expression patterns in epithelial ovarian cancer

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Hormone receptor expression patterns often correlate with infiltration of specific lymphocytes in tumors. Specifically, the presence of specific tumor infiltrating lymphocytes (TILs) with particular hormone receptor expression is reportedly associated with breast cancer, however, this has not been revealed in epithelial ovarian cancer (EOC). Therefore, we investigated the association between hormone receptor expression and TILs in EOC. Immunohistochemical analysis of estrogen receptor (ER)α, androgen receptor (AR), glucocorticoid receptor (GR), progesterone receptor (PR), ERβ, $CD3^+$, $CD4^+$, $CD8^+$, $FoxP3^+$, PD-1, and PD-L1 was performed using tissue microarray analysis or whole sections. NanoString analyses compared normal epithelial and EOC tissues, which were clustered based on hormone receptor expression patterns using complementary bioinformatic approaches. ERα, AR, and GR expression increased in EOC, while PR was significantly reduced and ERβ expression showed a reduced trend compared to normal epithelium. Cluster analysis indicated poor disease free survival (DFS) in AR$^+$/GR$^+$/PR$^+$ subgroup (triple dominant group); while Cox proportional-hazards model highlighted the triple dominant group as an independent prognostic factor for DFS. In addition, significant upregulation of FoxP3$^+$ TILs, PD-1, and PD-L1 was observed in the triple dominant group compared to other groups. NanoString analyses further suggested that tumor necrosis factor (TNF) and/or NF-κB signaling pathways were activated with significant upregulation of *RELA*, *MAP3K5*, *TNFAIP3*, *BCL2L1*, *RIPK1*, *TRAF2*, *PARP1*, and *AKT1* in the triple dominant EOC group. The triple dominant subgroup correlates with poor prognosis in EOC. Moreover, the TNF and/or NF-κB signaling pathways may be responsible for hormone-mediated inhibition of the immune microenvironment.

Key words : epithelial ovarian cancer, hormone receptors, triple dominant group, tumor infiltrating lymphocytes, regulatory t cell

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Ⅰ. INTRODUCTION

Epithelial ovarian cancer (EOC) is one of the most lethal gynecologic malignancy, responsible for more than 100,000 cancer-related deaths annually, worldwide[1]. Majority of patients are diagnosed at the advanced stage because of the lack of specific symptoms and effective cancer screening methods at the early stages. To date, the standard treatment for EOC is primary cytoreductive surgery followed by platinum-based chemotherapy. However, most patients experience relapse within 2 years and develop chemotherapy resistance. Emerging evidence has highlighted the potential of targeted therapies, such as anti-angiogenic therapy with bevacizumab or poly (ADP-ribose) polymerase (PARP) inhibitors. However, their contribution toward improving survival and prognosis remains modest[2]. Although current clinical trials on single-agent programmed cell death protein 1 (PD-1) blockade demonstrated promising results in EOC, the overall response rate is considerably lower than that achieved in melanoma, lung cancer, and renal cell cancer[3].

Many studies have identified EOC as an immunogenic tumor, recognizable by the host immune system[4]. Thus, evaluating the tumor infiltrating lymphocytes (TILs) in EOC have recently gained attention[5,6]. TILs are the type of white blood cell present in the tumor islets and stroma that recognize tumor cells and elicit an immune response. In EOC, $CD8^+$, $CD4^+$ T-helper 1 (Th1), and natural killer (NK) cells reportedly participate in tumor suppression responses, whereas $CD4^+$ T-helper 2 (Th2), $FoxP3^+$ T-regulatory (Treg), and dendritic cells contribute to immunosuppression[7]. However, the activity and presence of TILs can be modulated by many factors, including endocrine and pro-inflammatory molecules. Estrogen receptor (ER)α influences cancer development by regulating cellular development and differentiation, whereas ERβ prevents EOC development. Notably, the androgen receptor (AR) has been suggested as a favorable prognostic factor in EOC. Moreover, at low concentrations, the progesterone receptor (PR) stimulates EOC progression, while suppressing it at high concentrations[8-11]. As nearly all immune cells express hormone receptors and several immune-related genes possess AR and ER response elements in their promoters, hormone receptors can modulate B cell, T cell, macrophages, neutrophils, and NK cell behaviors[12-16]. Indeed, studies on the breast cancer tumor microenvironment (TME) suggest that hormone receptor-positive breast tumors may be immunologically “colder” than their triple-negative and human epidermal development element receptor 2 (HER2) positive counterparts[17]. These observations suggest that hormone receptors influence the expression of TILs in cancers. However, little is known regarding the expression of TILs in relation to specific hormone receptor expression profiles in EOC.

EOC is a highly heterogeneous disease, and emerging evidence suggests that targeted therapy is applicable based on subgroup-specific prognostic and predictive biomarkers. Therefore, we aimed to comparatively analyze the relationships between the properties of TILs and hormone receptor expression patterns in EOC. Furthermore, we aimed to evaluate the usefulness of a subgroup-specific prognostic biomarker for immunotherapy.

Ⅱ. MATERIALS and METHODS

1. Patients and tumor specimens

Two hundred and twelve EOCs, 57 borderline ovarian tumors, 153 benign epithelial ovarian tumors, and 79 nonadjacent normal epithelial tissue samples were obtained from patients who underwent primary surgery in Gangnam Severance Hospital between 2004 and 2012 and some of the samples were obtained from the Korea Gynecologic Cancer Bank as part of the Bio & Medical Technology Development Program of the Ministry of the National Research Foundation (NRF), funded by the Korean government (MIST) (NRF-2017M3A9B8069610). The International Federation of Gynecology and Obstetrics (FIGO) classification was used for tumor staging and clinical information, including surgical procedure, survival time, survival status, and age were collected by reviewing the medical records of patients. The patients’ response to therapy was assessed by computed tomography with Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1). Tumor grade and cell type were evaluated by reviewing pathological reports, and all tumor samples were histologically examined by two gynecologic pathologists. All biological samples were collected after obtaining informed consent from participants, following the guidelines of the institutional review board (IRB) of Gangnam Severance Hospital (IRB No. 3-2018-0122).

2. Tissue microarray and immunohistochemistry

Tissue microarray (TMA) blocks comprising tissue cores (1 mm) with a sufficient proportion of tumor cells obtained from formalin-fixed paraffin-embedded (FFPE) tumor tissue blocks were used for immunohistochemistry (IHC) analysis of ERα, AR, glucocorticoid receptor (GR), PR, ERβ, PD-1, and programmed cell death protein ligand-1 (PD-L1) (5-μm-thick sections cut using a rotary microtome), whereas whole tissue sections were used for the IHC of CD4+, CD8+, CD3+, and FoxP3+. The sections were deparaffinized and rehydrated with graded ethanol. Then, the sections were treated with 3% H_2O_2 solution in methanol to suppress endogenous peroxidase activity for 30 min. Thereafter, heat-induced antigen retrieval was done by incubating the sections in a target retrieval buffer at pH 6.0 (Dako, Carpinteria, CA, USA) by a steam pressure cooker (Pascal; Dako) for 20 min, and the slides were stained with the primary antibodies listed in Table 1 with Autostainer Plus (Dako) for 1 h at room temperature. Then, EnVision+ Dual Link System-HRP (Dako) and DAB+ (3,3′-diaminobenzidine; Dako) were used for visualization of antigen-antibody reactions. After dehydrating and counterstaining with hematoxylin the stained slides, they were mounted in Faramount Aqueous Mounting Medium (Dako). A proper positive and negative controls were in cluded.

Table 1. Primary antibodies used in this study

Antibody	Raised in	Clone/ Catalog No.	Dilution	Sourcea
ERα	mouse	ER-6F11-L-CE	1:300	Leica
AR	rabbit	760-4605	1:300	Roche
GR	rabbit	3660S	1:300	Cell Signaling Technology
PR	rabbit	NCL-L-PGR-312	1:300	Leica
ERβ	rabbit polyclonal	PU385-UP	1:300	BioGenex
CD3+	rabbit polyclonal	Ab5690	1:300	Abcam
CD4+	rabbit	EPR6855	1:100	Abcam
CD8+	rabbit polyclonal	ab4500	1:200	Abcam
FoxP 3+	mouse	14-4777-82	1:300	eBioscience
PD-1	mouse	315M-95	1:100	CellMarque
PD-L1	mouse	M365329-2	1:100	Dako

[a] Leica, Buffalo Grove, IL; Roche, Rocklin, CA; Cell Signaling Technology, Danvers, MA; BioGenex, Fremont, CA; Abcam, Cambridge, MA; eBioscience, San Diego, CA; CellMarque, Rocklin, CA; DAKO, Carpinteria, CA

3. Evaluation of immunohistochemical (IHC) staining

The stained TMA sections were scanned with a high-resolution optical scanner (NanoZoomer 2.0 HT; Hamamatsu Photonics K.K., Hamamatsu City, Japan) at 20× objective magnification (0.5 μm resolution). In the case of ERα, AR, GR, PR, and ERβ, the scanned sections were analyzed using Visiopharm software, version 4.5.1.324 (VIS; Visiopahrm, Hφrsholm, Denmark). Brown staining intensity was scored semi-quantitatively using the immunoreactive score (IRS) with predefined algorithm and settings. The IRS was obtained as the product of immunostaining intensity (0 = negative, 1 = weak, 2 = moderate, 3 = strong), while the overall immunostaining score was calculated by multiplying the percentage of positive cells and immunostaining intensity (possible range: 0–300). For PD-1 and PD-L1 scoring, tumor areas were automatically outlined, followed by manual editing to exclude necrotic tissues, and PD-1 and PD-L1 were quantified by analyzing the percentage of DAB+ using Visiopharm software, version 4.5.1.324 (VIS; Visiopahrm). Lastly, TILs were evaluated following the recommendation of the International TILs Working Group[18]. Six independent regions of interest (ROS) with highest TILs, comprising 2 mm^2 stromal areas with the highest number of TILs from entire tumor sections, were selected and evaluated for TILs using Visiopharm software, version 4.5.1.324 (VIS; Visiopahrm). The area for stromal TIL evaluation was set within the invasive tumor borders that did not include immune infiltration in the adjacent normal tissue of EOCs. Additionally, mononuclear stromal cells which were not directly contacting with cancer cells were considered as stromal TILs. Positive staining was assessed quantitatively, and the results expressed as a percentage of positively stained area relative to the total

ROI. The results for each section's ROIs were then averaged.

4. Oncomine database analysis

To quantify the mRNA expression of ERα, AR, GR, PR, and ERβ in EOC, the Oncomine database (https://www.oncomine.org), a public database consisting of publicly available and previously published microarray data was used[19]. The mRNA expression fold change analysis was filtered by selecting ovarian carcinoma vs. normal.

5. RNA extraction and quality control

FFPE slides of normal ovarian epithelial tissues and EOCs were stained with hematoxylin and eosin to identify and mark normal ovarian epithelial tissues and EOC regions by a gynecological pathologist. In case of EOC, FFPE sections consisting of more than 85% tumor cells within each specimen were used for laser captured microdissection (LCM). After sectioning FFPE tissues, they were placed on slides coated with polyethylene terephthalate membrane (Leica Microsystems Inc., IL, USA), and LCM was performed using the Leica AS LMD laser microdissection system (Leica Microsystems Inc.) by the manufacturer's instructions. Total RNA was extracted using the RNeasy FFPE kit (Qiagen, Valencia, CA, USA), according to the manufacturer's instructions. RNA concentration was quantified by using a Nanodrop spectrophotometer (Thermo Scientific, Waltham, MA, USA), and its quality was verified on formaldehyde agarose gels.

6. Quantification of gene expression and analysis of differentially expressed genes (DEGs) using the NanoString nCounter platform

Three hundred nanograms of isolated RNA from each sample was used for hybridization with the PanCancer IO 360 Panel Gene Expression Panel (NanoString Technologies, Inc., Seattle, WA, USA), according to the manufacturer’s instructions, and transferred to the Digital Analyzer (NanoString Technologies, Inc.) for analysis. After background correction, gene expression was normalized using the target to housekeeping gene expression ratio, with nSolver Analysis Software version 4.0 (NanoString Technologies, Inc.). Finally, DEGs between the normal ovarian epithelial tissues and EOCs were Log_2 transformed. Group analyses for DEGs were performed using in-house Rscripts. The scatter plots for the gene expression values, volcano plots for the expression fold-changes, and *p*-values between the two selected samples were similarly calculated using in-house R scripts.

7. Network analysis

To construct the ovarian tissue-specific protein-protein interaction (PPI) network with the minimum- or zero-order network model, 169 upregulated DEGs were used as an input for Network analyst (https://www.networkanalyst.ca/)[20].

8. Gene Ontology analysis

Upregulated DEGs were analyzed with g:Profiler (https://biit.cs.ut.ee/gprofiler/gost) with default parameters to investigate the affected pathways[21]. The analyzed parameters for the statistical domain scope included “only annotated genes”, “g:SCS threshold” for the significance threshold, and 0.05 as an user threshold.

9. Statistical analysis

Statistical analyses of hormone receptors, TILs, PD-1, and PD-L1 expression data were performed using either Mann–Whitney U-test or Kruskal–Wallis test, as appropriate. Kaplan–Meier method was used to assess disease free survival (DFS) and overall survival (OS). Survival was analyzed using the log-rank test with the cut-off values that had the highest discriminative power. A clustering analysis was performed to identify EOC with similar hormone receptor expression patterns. Cox proportional-hazards model was used to estimate the hazard ratios (HR) and confidence intervals (CIs) in both univariate and multivariate models. Statistical analyses were performed using SPSS version 25.0 (SPSS, Chicago, IL, USA). Results with a p-value < 0.05 were considered statistically significant.

Ⅲ. RESULTS

1. Expression of hormone receptors in EOC tissues

The representative IHC results for ERα, AR, GR, PR, and ERβ are shown in Figure 1A, and IHC scores are summarized in Table 2. The data showed significantly higher expression of ERα, AR, and GR in EOCs than in nonadjacent normal epithelial tissues ($p < 0.001$, for all; Table 2). Conversely, PR expression was significantly lower in EOCs than in nonadjacent normal epithelial tissues ($p < 0.001$; Table 2). Although not significant, a trend of low ERβ expression in EOCs was observed compared with that in nonadjacent normal epithelial tissues ($p = 0.060$; Table 2). Next, we confirmed the expression level of ERα, AR, PR, and ERβ hormone receptors using a publicly available dataset, which showed good agreement with the trends observed in our study (Figure 1B). However, GR expression showed the opposite result, which might be due to mRNA post-translation modifications.

We then investigated clinicopathological characteristics based on hormone receptor expression patterns. The immunoreactivity of ERα and PR was significantly associated with serous cell type ($p = 0.027$, $p = 0.008$, respectively; Table 2), and AR overexpression significantly correlated with positive CA125 ($p = 0.024$; Table 2). In addition, ERβ and GR overexpression were significantly associated with early ($p = 0.047$; Table 2), and advanced FIGO stage ($p = 0.050$; Table 2), respectively.

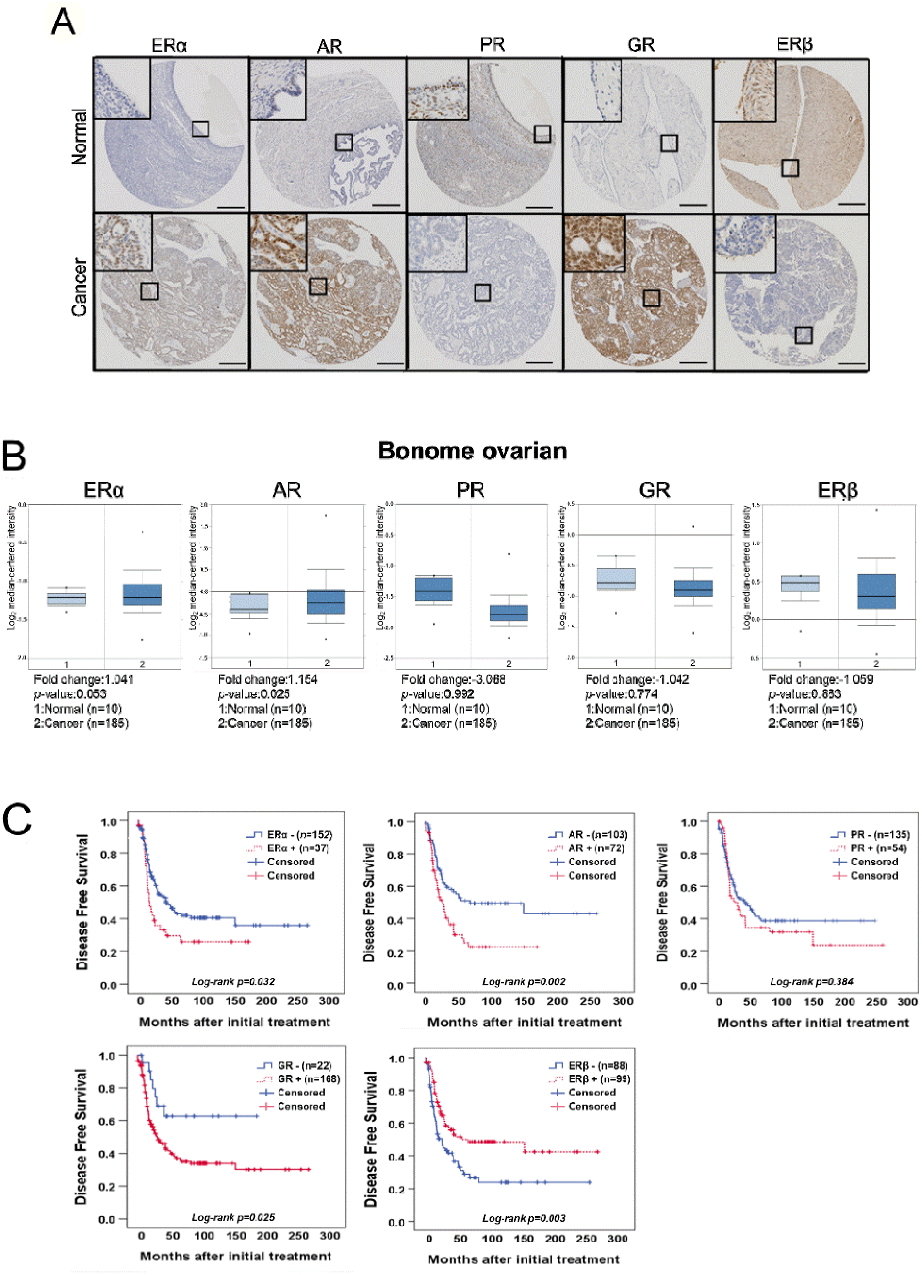
Next, we examined the relationship between hormone receptor expression and DFS and OS in patients with EOC by Kaplan–Meier plots. Results showed that ERα or GR overexpression correlated with poorer DFS ($p = 0.032$, $p = 0.025$, respectively; Figure 1C) and OS ($p = 0.002$, $p = 0.017$, respectively; Figure ID). On the contrary, ERβ overexpression significantly correlated with improved DFS and OS ($p = 0.003$, $p = 0.048$, respectively; Figure 1C and ID). AR overexpression significantly correlated with poor DFS, whereas AR overexpression showed a statistically non-significant correlation with better OS ($p = 0.002$, $p = 0.089$, respectively; Figure 1C and ID). Notably, PR expression was lower in EOCs than in nonadjacent normal epithelial tissues, however, its overexpression in EOCs showed a trend toward poor DFS ($p = 0.384$; Figure 1C).

Table 2. Clinico pathological characteristics of hormone receptors in epithelial ovarian cancer.

	ERα[a]			AR[b]			PR[c]			GR[d]			ERβ[e]		
	Low n (%)	High n (%)	Total n (%)	Low n (%)	High n (%)	Total n (%)	Low n (%)	High n (%)	Total n (%)	Low n (%)	High n (%)	Total n (%)	Low n (%)	High n (%)	Total n (%)
Diagnosis	$p < 0.001$			$p < 0.001$			$p < 0.001$			$p < 0.001$			$p = 0.060$		
Normal	75 (94.9)	4 (5.1)	79 (100)	56 (70.9)	23 (29.1)	79 (100)	36 (46.2)	42 (53.8)	78 (100)	39 (49.4)	40 (50.6)	79 (100)	33 (41.8)	46 (58.2)	79 (100)
Benign	104 (94.5)	6 (5.5)	110 (100)	83 (74.8)	28 (25.2)	111 (100)	53 (47.3)	59 (52.7)	112 (100)	14 (11.4)	109 (88.6)	123 (100)	60 (55.6)	48 (44.4)	108 (100)
Borderline	47 (83.9)	9 (16.1)	56 (100)	32 (58.2)	23 (41.8)	55 (100)	37 (68.5)	17 (31.5)	54 (100)	1 (1.8)	56 (98.2)	57 (100)	19 (34.5)	36 (65.5)	55 (100)
Cancer	166 (80.2)	41 (19.8)	207 (100)	76 (39.6)	116 (60.4)	192 (100)	153 (73.6)	55 (26.4)	208 (100)	21 (10.0)	188 (90.0)	209 (100)	96 (46.8)	109 (53.2)	205 (100)
FIGO stage	$p = 0.134$			$p = 0.092$			$p = 0.953$			$p = 0.050$			$p = 0.047$		
I-II	52 (86.7)	8 (13.3)	60 (100)	19 (33.9)	37 (66.1)	58 (100)	43 (71.7)	17 (28.3)	60 (100)	11 (18.3)	49 (81.7)	60 (100)	21 (35.6)	38 (64.4)	59 (100)
III-IV	99 (77.3)	29 (22.7)	128 (100)	54 (45.8)	64 (54.2)	118 (100)	91 (71.1)	37 (28.9)	128 (100)	11 (8.5)	118 (91.5)	129 (100)	72 (56.7)	55 (43.3)	127 (100)
Cell type	$p = 0.027$			$p = 0.126$			$p = 0.008$			$p = 0.391$			$p = 0.682$		
Serous	165 (81.3)	38 (18.7)	203 (100)	111 (56.9)	84 (43.1)	195 (100)	120 (59.1)	83 (40.9)	203 (100)	13 (6.5)	187 (93.5)	200 (100)	93 (46.7)	106 (53.3)	199 (100)

Others	153 (89.5)	18 (10.5)	171 (100)	81 (49.4)	83 (50.6)	164 (100)	123 (72.4)	47 (27.6)	170 (100)	15 (8.9)	154 (91.1)	169 (100)	81 (47.9)	88 (52.1)	169 (100)
Tumor grade	*p = 0.580*			*p = 0.080*			*p = 0.602*			*p = 0.090*			*p = 0.382*		
Well/Moderate	73 (82.0)	16 (18.0)	89 (100)	29 (34.1)	56 (65.9)	85 (100)	64 (71.9)	25 (28.1)	89 (100)	15 (16.9)	74 (83.1)	89 (100)	38 (42.7)	51 (57.3)	89 (100)
Poor	82 (78.8)	22 (21.2)	104 (100)	41 (43.6)	53 (56.4)	94 (100)	96 (75.2)	25 (24.8)	101 (100)	9 (8.7)	94 (91.3)	103 (100)	50 (49.0)	52 (51.0)	102 (100)
CA125	*p = 0.203*			*p = 0.024*			*p = 0.339*			*p = 0.787*			*p = 0.666*		
Negative	102 (88.7)	13 (11.3)	115 (100)	65 (60.2)	43 (39.8)	108 (100)	74 (64.9)	40 (35.1)	114 (100)	9 (8.2)	101 (91.8)	110 (100)	53 (47.3)	59 (52.7)	112 (100)
Positive (>35U/ml)	165 (83.3)	33 (16.7)	198 (100)	87 (46.5)	100 (53.5)	187 (100)	137 (69.5)	60 (30.5)	197 (100)	18 (9.1)	180 (90.9)	198 (100)	88 (45.6)	105 (54.4)	193 (100)
Chemosensitivity	*p = 0.784*			*p = 0.850*			*p = 0.111*			*p = 0.401*			*p = 0.115*		
Sensitive	137 (79.2)	36 (20.8)	173 (100)	64 (40.3)	95 (59.7)	170 (100)	128 (71.3)	49 (28.7)	171 (100)	21 (12.2)	151 (87.8)	172 (100)	76 (44.7)	94 (52.3)	170 (100)
Resistant	13 (76.5)	4 (23.5)	17 (100)	7 (43.8)	9 (56.2)	16 (100)	16 (88.9)	2 (11.1)	18 (100)	1 (5.6)	17 (94.4)	18 (100)	11 (64.7)	6 (35.3)	17 (100)

[a] cut-off value of **ERα** is over 49.2 of IHC score; [b] cut-offvalueofAR is over 10.85 of IHC score; [c] cut-off value of PR is over 21.18 of IHC score; [d] cut-off value of GR is over 8.65 of IHC score;
[e] cut-off value of ER**β**is over 105.97 of IHC score; FIGO, International Federation of Gynecology and Obstetrics


A
ERα
AR
PR
GR
ERβ
Normal
Cancer
B
Bonome ovarian
ERα
AR
PR
GR
ERβ
Log₂ median-centered intensity
1
2
Fold change:1.041
p-value:0.053
1:Normal (n=10)
2:Cancer (n=185)
Fold change:1.154
p-value:0.025
1:Normal (n=10)
2:Cancer (n=185)
Fold change:-3.068
p-value:0.992
1:Normal (n=10)
2:Cancer (n=185)
Fold change:-1.042
p-value:0.774
1:Normal (n=10)
2:Cancer (n=185)
Fold change:-1.059
p-value:0.833
1:Normal (n=10)
2:Cancer (n=185)
C
Disease Free Survival
Months after initial treatment
0.0
0.2
0.4
0.6
0.8
1.0
0
50
100
150
200
250
300
ERα - (n=152)
ERα + (n=37)
Censored
Censored
Log-rank p=0.032
AR - (n=103)
AR + (n=72)
Censored
Censored
Log-rank p=0.002
PR - (n=135)
PR + (n=54)
Censored
Censored
Log-rank p=0.384
GR - (n=22)
GR + (n=168)
Censored
Censored
Log-rank p=0.025
ERβ - (n=88)
ERβ + (n=99)
Censored
Censored
Log-rank p=0.003

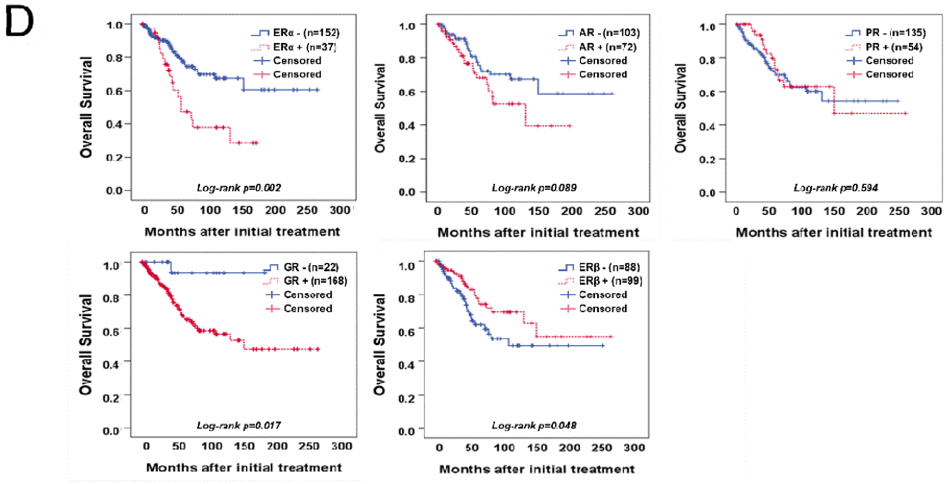
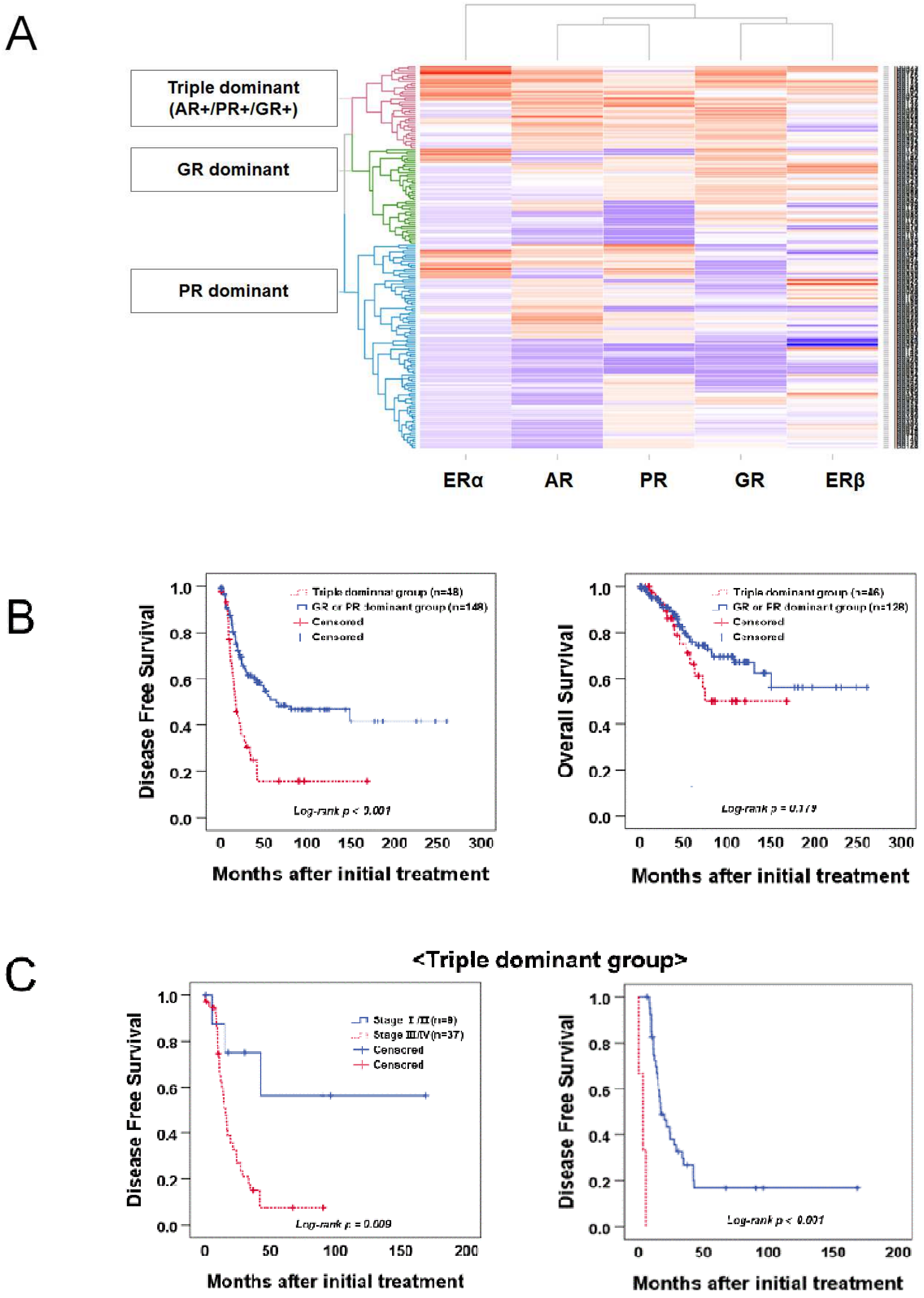


Figure 1. Expression of hormone receptors in EOC tissues. (A) Representative immunohistochemical images of ERα, AR, PR, GR, and ERβ in nonadjacent ovarian epithelial tissues (Normal) and epithelial ovarian cancer (Cancer) tissue samples (scale bar: 50 μm). The analysis of ERα, AR, PR, GR, and ERβ expression in 212 EOCs, 61 borderline ovarian tumors, 130 benign tumors, and 81 nonadjacent normal epithelial tissues was performed by IHC; however, a few samples were lost during sectioning and TMA staining. Thus, 207 EOCs, comprising 56 borderline ovarian tumors, 110 benign tumors, and 79 nonadjacent normal epithelial tissues, were used to estimate ERα expression. AR expression was investigated in 192 EOCs, including 55 borderline ovarian tumors, 111 benign tumors, and 79 nonadjacent normal epithelial tissues, whereas PR expression was estimated in 208 EOCs, 54 borderline ovarian tumors, 112 benign tumors, and 78 nonadjacent normal epithelial tissues. A total of 209 EOCs, 57

borderline ovarian tumors, 123 benign tumors, and 79 nonadjacent normal epithelial tissues were used to quantify GR expression, whereas 205 EOCs, 55 borderline ovarian tumors, 108 benign tumors, and 79 nonadjacent normal epithelial tissues were analyzed for ERβ expression. (B) Publicly available data on the mRNA expression of ERα, AR, PR, GR, and ERβ gathered from the Oncomine database (http://www.oncomine.com). (C) The DFS of patients with EOC depends on ERα, AR, PR, GR, and ER β expression. For the DFS analysis, 189 patients with EOC for ERα, 175 patients with EOC for AR, 189 patients with EOC for PR, 190 patients with EOC for GR, and 187 patients with EOC for ERβ were included. (D) The OS of patients with EOC depends on ERα, AR, PR, GR, and ER β expression. For the OS analysis, 189 patients with EOC for ERα, 175 patients with EOC for AR, 189 patients with EOC for PR, 190 patients with EOC for GR, and 187 patients with EOC for ERβ were included. The cut-off value of ERα was over 49.2 of the IHC score, cut-off value of AR was over 10.85 of the IHC score, cut-off value of PR was over 21.18 of the IHC score, and the cut-off value of GR was over 8.65 of the IHC score.

2. Hierarchical clustering analysis of hormone receptors in EOCs

After evaluating the clinicopathological characteristics based on a single hormone receptor, hierarchical clustering analysis was performed to identify subgroups based on hormone receptor expression patterns related to prognosis (Figure 2A). Thus, EOC was categorized into three subgroups: triple dominant ($AR^+/PR^+/GR^+$), GR dominant, and PR dominant, depending on hormonal expression patterns (Figure3A). The triple dominant group was significantly associated with a more advanced FIGO stage, serous cell type, and poor grade compared with GR- or PR-dominant groups (p = 0.015, p = 0.042, p = 0.042, respectively; Figure 3B). Moreover, we observed that the triple dominant group was significantly associated with poor DFS ($p < 0.001$; Figure 2B). Cox multivariate proportional-hazards analysis further revealed that the triple dominant group was an independent prognostic factor for poor DFS (HR = 2.176, 95% CI = 1.023–2.672; $p < 0.001$; Table 3). Notably, only the triple dominant group showed statistical significance in Cox multivariate proportional-hazards analysis compared with the single hormone receptors (Table 3). Moreover, we performed separate subgroup analyses in the triple dominant, GR-, and PR-dominant groups (Figure 2C). Survival analysis showed that triple dominant, GR-, and PR-dominant groups were significantly associated with poor DFS in patients at a more advanced stage, who developed platinum resistance (p = 0.009, $p < 0.001$, p = 0.002, $p < 0.001$, $p < 0.001$, $p < 0.001$, respectively; Figure 2C). The subgroup analysis results with respect to cell type, grade, and positive CA125 are presented in Figure 4


A
Triple dominant (AR+/PR+/GR+)
GR dominant
PR dominant
ERα
AR
PR
GR
ERβ
B
Disease Free Survival
1.0
0.8
0.6
0.4
0.2
0.0
Triple dominnat group (n=48)
GR or PR dominant group (n=148)
Censored
Censored
Log-rank p < 0.001
0
50
100
150
200
250
300
Months after initial treatment
Overall Survival
Triple dominant group (n=46)
GR or PR dominant group (n=128)
Censored
Censored
Log-rank p = 0.179
Months after initial treatment
C
<Triple dominant group>
Disease Free Survival
Stage Ⅰ/Ⅱ (n=9)
Stage Ⅲ/Ⅳ (n=37)
Censored
Censored
Log-rank p = 0.009
Months after initial treatment
Disease Free Survival
Log-rank p < 0.001
Months after initial treatment

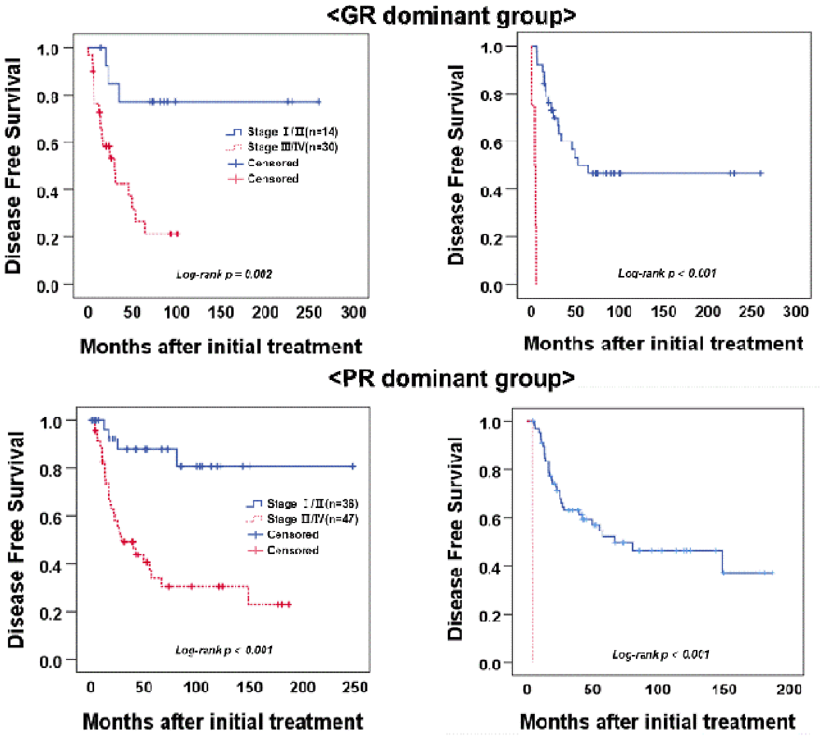


Figure 2. Hierarchical clustering analysis of hormone receptors in EOCs. (A) Hierarchical clustering analysis of all patients in whom staining for all five receptor isoforms was performed. In the left, the three subgroups were identified using the clustering analysis are indicated. Vertically, the expression of different receptors is depicted: orange indicating positive expression and purple indicating negative expression. Color scaling was based on the semi-quantitative immunoscores. (B) DFS and OS of patients with EOC between the triple dominant group and GR- or PR-dominant group. Forty-eight patients with EOC in the triple dominant group and 148 patients with EOC in the GR- or PR-dominant group were included. (C) Subgroup DFS analysis in the triple dominant group was based on the FIGO stage and platinum sensitivity (n = 196). (D) Subgroup DFS analysis in

the GR dominant group was based on the FIGO stage and platinum sensitivity (n = 46). (E) Subgroup DFS analysis in the PR-dominant group was based on the FIGO stage and platinum sensitivity (n = 83).

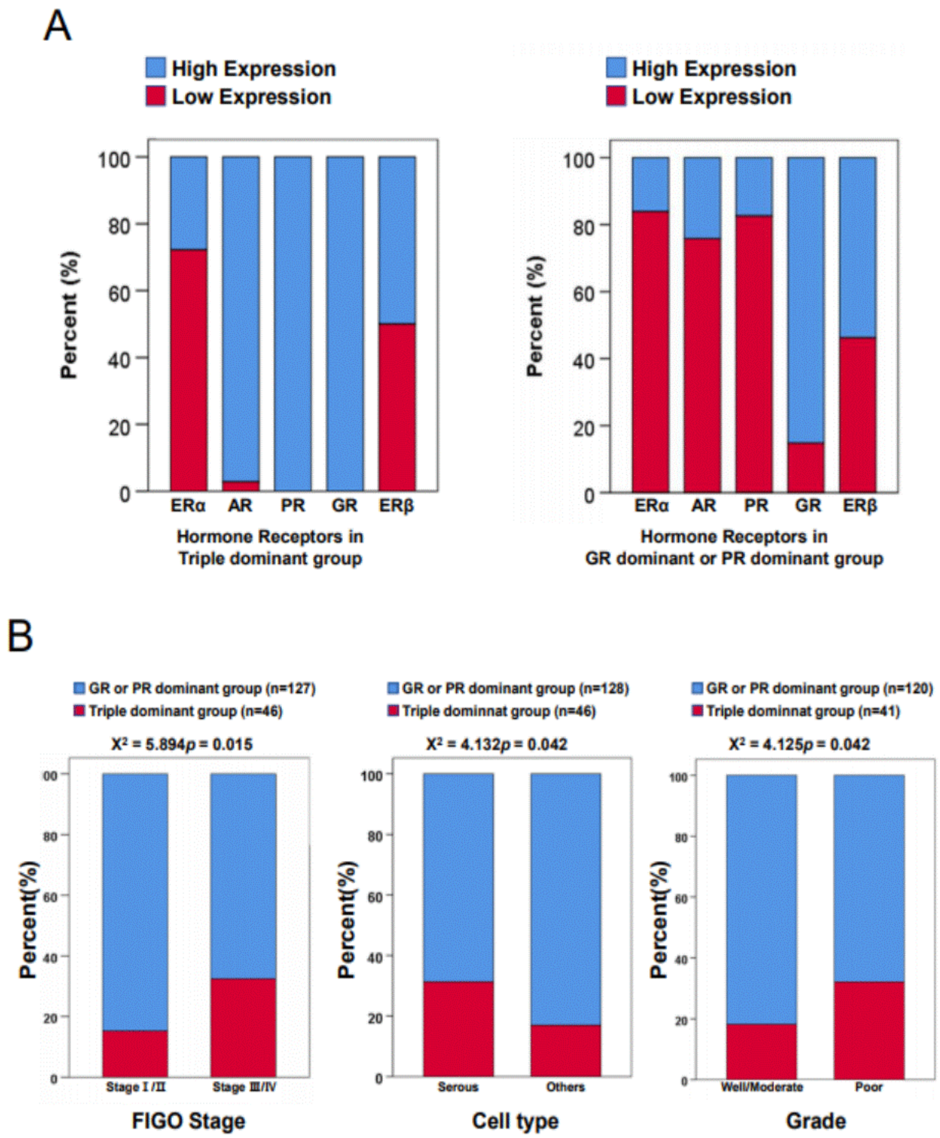


Figure 3. Characteristics of EOC subgroups clustered by hormone receptor expression pattern (A) Expression patterns of hormone receptors in the triple dominant group and GR- or PR-dominant group. (B) Clinicopathological analysis of the triple dominant group

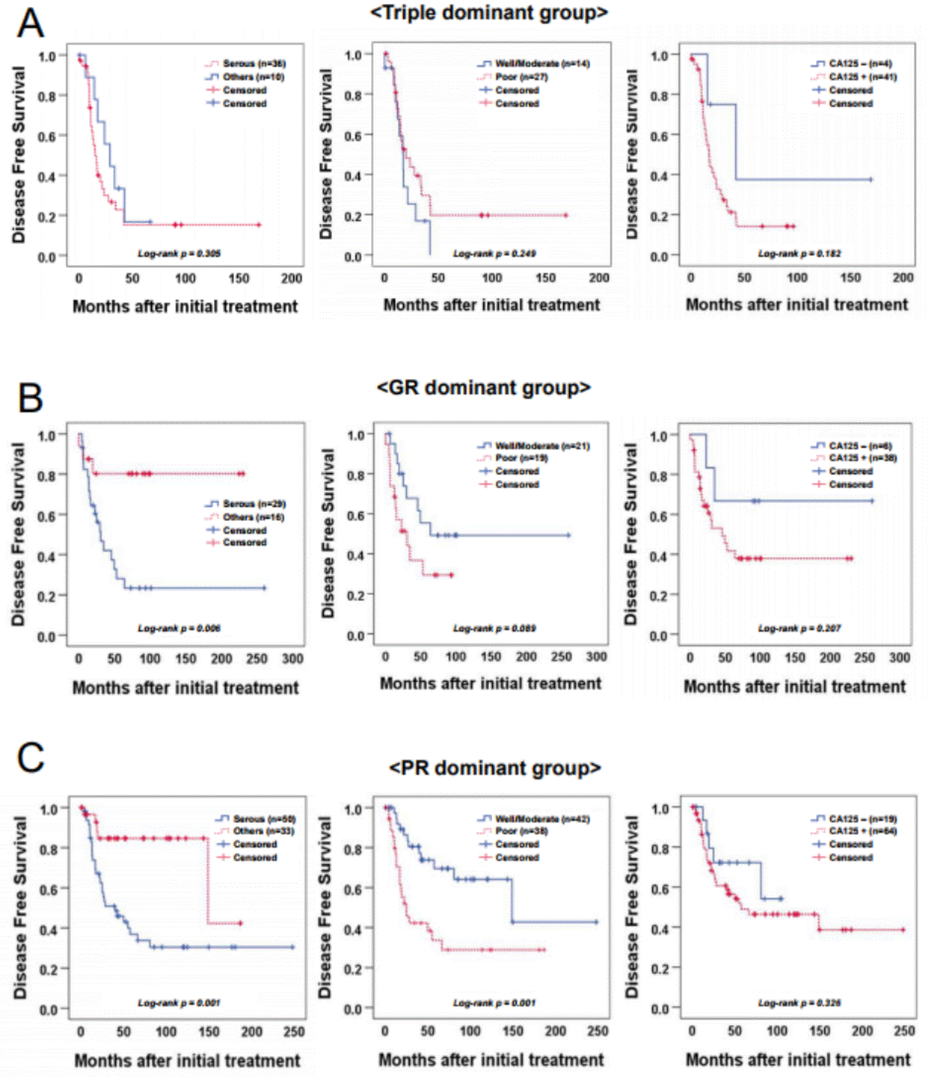


Figure 4. Subgroup disease free survival (DFS) analysis in the triple dominant, GR-dominant, and PR-dominant EOC groups. (A) DFS analysis in the triple dominant group based on cell type, grade, and CA125. (B) DFS analysis in the GR-dominant group based on cell type, grade, and CA125. (C) DFS analysis in the PR dominant group based on cell type, grade, and CA125.

Table 3. Univariate and multivariate analyses of the association between prognostic variables and disease-free survival rates in epithelial ovarian cancer

Variables	Univariate analysis		Multivariate analysis	
	Hazard ratio [95%CI*]	*p* -value	Hazard ratio [95%CI*]	*p* -value
FIGO stage (III-IV)	6.427 [3.335-12.386]	<0.001	4.604 [2.260-9.380]	<0.001
Cell type (Serous)	0.337 [0.202-0.561]	<0.001	0.525 [0.294-0.939]	0.030
Tumor grade (Poor)	1.949 [1.286-2.954]	0.002	1.646 [1.074-2.518]	0.022
CA 125 + (>35U/ml)	2.397 [1.208-4.753]	0.012	1.004 [0.471-2.141]	0.992
Age (>50)	1.577 [1.064-2.339]	0.023	1.231 [0.810-1.872]	0.330
ERα +[a]	1.625 [1.038-2.542]	0.034	1.363 [0.842-2.207]	0.207
AR +[b]	1.887 [1.245-2.860]	0.002	1.546 [0.998-2.396]	0.051
PR +[c]	1.201 [0.794-1.815]	0.386	NA	
GR +[d]	2.610 [1.143-5.958]	0.023	1.892 [0.823-4.351]	0.133
ERβ +[e]	1.824 [1.226-2.714]	0.003	1.403 [0.918-2.543]	0.118
Heatmap (Triple dominant)	2.668 [1.728-4.118]	<0.001	2.176 [1.361-3.487]	0.001

[a] cut-off value of **ERα** is over 49.2 of IHC score; [b] cut-offvalueofAR is over 10.85 of IHC score; [c] cut-off value of PR is over 21.18 of IH Cscore; [d] cut-off value of GR is over 8.65 of IHC score;
[e] cut-off value of ER**β**is over 105.97 of IHC score; CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; NA: Not available

3. TILs and EOC

Given the importance of hormone receptors in the prognosis of EOC, we hypothesized that they contribute to the behavior of TILs as the nuclear factor (NF)-κB pathway is involved in both hormone receptor signaling and TIL biology. To verify this hypothesis, we first evaluated the expression of $CD4^+$, $CD8^+$, $CD3^+$, and $FoxP3^+$ in whole tissue sections, the representative IHC staining of which is shown in Figure 5A. We identified that high $CD4^+$, $CD3^+$, and $FoxP3^+$ infiltration was associated with advanced stage($p = 0.021$, $p = 0.033$, $p < 0.001$, respectively; Table 4) and serous cell type ($p = 0.017$, $p = 0.049$, $p < 0.001$, respectively; Table 4). Additionally, high infiltration of $CD3^+$ cells was associated with poor grade ($p = 0.017$, Table 4), and high infiltration of $CD4^+$, and $CD8^+$, as well as an increased $CD3^+/FoxP3^+$ ratio showed a significant association with positive CA125 ($p < 0.001$, $p = 0.012$, $p = 0.042$, respectively; Table 4). We also examined the prognostic significance of TIL infiltration and their ratio with Kaplan–Meier plots. A high infiltration of $FoxP3^+$ was associated with poor DFS and OS ($p = 0.011$, $p < 0.001$, respectively; Figure 5B) and increased $CD3^+/FoxP3^+$ ratio was associated with favorable DFS and OS ($p = 0.049$, $p = 0.011$, respectively; Figure 5B).

4. Association between TIL infiltration and EOC subgroups by hormone receptors

We further analyzed whether hormone receptor expression might influence the behavior of TILs in EOC, and found that FoxP3$^+$ was significantly more abundant in the triple dominant group compared to GR-and PR-dominant groups (*p* = 0.014; Figure 5B). In addition, the CD3$^+$/FoxP3$^+$ ratio significantly decreased in the triple dominant group (*p* = 0.070, Figure 5C). We performed a survival analysis using Kaplan–Meier plots for both FoxP3$^+$ infiltration and CD3$^+$/FoxP3$^+$ ratio for the triple dominant group; however, the differences were not significant, likely due to the small sample size (datanotshown).

5. Association between PD-1 or PD-L1 expression and EOC subgroups by hormone receptors

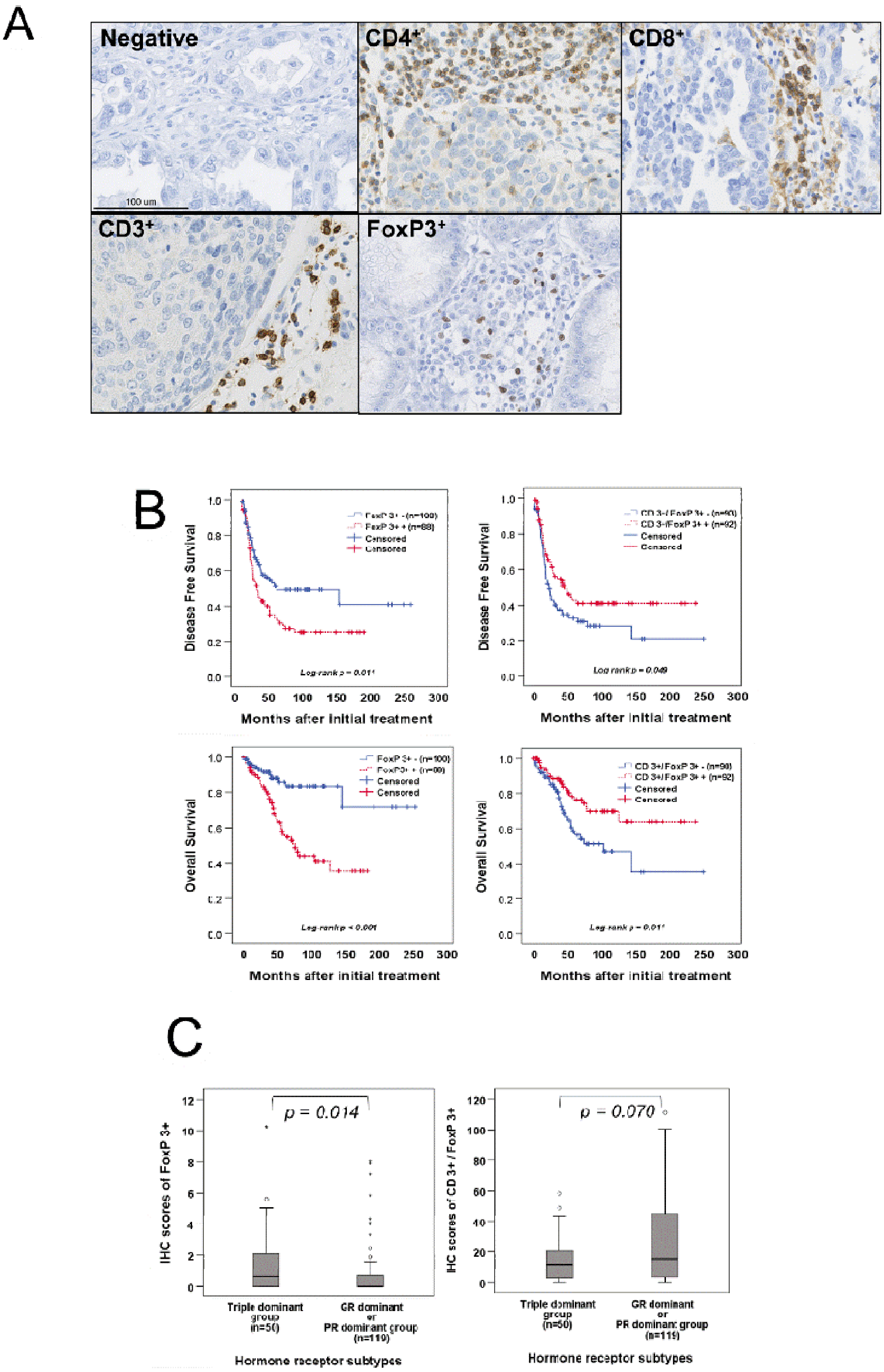
As recognizing FoxP3$^+$ alone does not sufficiently define Tregs, we also performed a similaran alysis to determine the association between PD-1 or PD-L1 expression and the triple dominant group, a subgroup of EOC. Before verifying their association, we first evaluated PD-1 or PD-L1 expression in EOC. A representative IHC image is shown in Figure 5D. We found that both PD-1 and PD-L1 were associated with advanced FIGO stage (*p* = 0.016, *p* = 0.018, respectively) and poor grade (*p* = 0.018, *p* = 0.040, respectively; Table 4). However, neither PD-1 nor PD-L1 revealed a significant association with DFS (*p* = 0.322, *p* = 0.069, respectively) or OS (*p* = 0.308, *p* = 0.201, respectively; Figure 5E). Importantly, the triple dominant group had significantly upregulated PD-1 and PD-L1 expression compared with other groups (*p* = 0.036, *p* = 0.044, respectively; Figure 5F).

Table 4. Clinico pathological characteristics of tumor infiltrating lymphocytes. PD-1 and PD-L1 in epithelial ovarian cancer.

Characteristic	CD 4^{+a}			CD 8^{+b}			CD 4^{+}/CD8^{+c}			CD 3^{+d}			FoxP 3^{+e}			CD 3^{+}/FoxP3^{+f}			PD-1+ ^{g}			PD-L1+^{h}		
	Low	High	Total	Low	High	Total	Low	High	Total	Low	High	Total	Low	High	Total	Low	High	Total	Low	High	Total	Low	High	Total
	- (n)	+ (n)	n (%)	- (n)	+ (n)	n (%)	- (n)	+ (n)	n (%)	- (n)	+ (n)	n (%)	- (n)	+ (n)	n (%)	- (n)	+ (n)	n (%)	- (n)	+ (n)	n (%)	- (n)	+ (n)	n (%)
FIGO stage	$p = 0.021$			$p = 0.051$			$p = 0.071$			$p = 0.033$			$p < 0.001$			$p = 0.621$			$p = 0.016$			$p = 0.018$		
I-II	19 (32.2)	40 (67.8)	59 (100)	33 (55.9)	26 (44.1)	59 (100)	52 (96.3)	2 (3.7)	54 (100)	50 (86.2)	8 (13.8)	58 (100)	45 (75.0)	15 (25.0)	60 (100)	26 (46.4)	30 (53.6)	56 (100)	45 (75.0)	15 (25.0)	60 (100)	36 (60.0)	24 (40.0)	60 (100)
III-IV	22 (17.2)	106 (82.8)	128 (100)	52 (40.6)	76 (59.4)	128 (100)	105 (87.5)	15 (12.5)	120 (100)	92 (71.9)	36 (28.1)	128 (100)	54 (42.5)	73 (57.5)	127 (100)	63 (46.4)	62 (49.6)	125 (100)	74 (56.1)	58 (43.9)	132 (100)	55 (41.7)	77 (58.3)	132 (100)
Cell type	$p = 0.352$			$p = 0.017$			$p = 0.431$			$p = 0.049$			$p < 0.001$			$p = 0.794$			$p = 0.068$			$p = 0.211$		
Serous	25 (19.8)	101 (80.2)	126 (100)	50 (39.7)	76 (60.3)	126 (100)	106 (89.1)	13 (10.9)	119 (100)	91 (72.2)	35 (27.8)	126 (100)	53 (42.4)	72 (57.6)	125 (100)	60 (48.8)	63 (51.2)	123 (100)	80 (55.9)	63 (44.1)	143 (100)	63 (43.8)	81 (56.3)	144 (100)
Others	16 (25.8)	46 (74.2)	62 (100)	36 (58.1)	26 (41.9)	62 (100)	52 (92.9)	4 (7.1)	56 (100)	52 (85.2)	9 (14.8)	61 (100)	47 (53.2)	16 (25.4)	63 (100)	30 (50.8)	29 (49.2)	59 (100)	47 (69.1)	21 (30.9)	68 (100)	36 (52.9)	32 (47.1)	68 (100)
Tumor grade	$p = 0.210$			$p = 0.099$			$p = 0.811$			$p = 0.017$			$p = 0.119$			$p = 0.244$			$p = 0.018$			$p = 0.040$		
Well/Moderate	21 (25.9)	60 (74.1)	81 (100)	43 (53.1)	38 (46.9)	81 (100)	67 (89.3)	8 (10.7)	75 (100)	68 (84.0)	13 (16.0)	81 (100)	48 (58.5)	34 (41.5)	82 (100)	35 (45.5)	42 (54.5)	77 (100)	60 (68.2)	28 (31.8)	88 (100)	47 (52.8)	42 (47.2)	89 (100)
Poor	16 (18.0)	73 (82.0)	89 (100)	36 (40.4)	53 (59.6)	89 (100)	76 (90.5)	8 (9.5)	84 (100)	60 (68.2)	28 (31.8)	88 (100)	41 (46.6)	47 (53.4)	88 (100)	48 (54.5)	40 (45.5)	88 (100)	54 (51.4)	51 (48.6)	105 (100)	40 (38.1)	65 (61.9)	105 (100)
CA125	$p < 0.001$			$p = 0.012$			$p = 0.286$			$p = 0.477$			$p = 0.285$			$p = 0.042$			$p = 0.561$			$p = 0.290$		
Negative	15 (53.6)	13 (46.4)	28 (100)	19 (67.9)	9 (32.1)	28 (100)	24 (96.0)	1 (4.0)	25 (100)	22 (81.5)	5 (18.5)	27 (100)	18 (62.1)	11 (37.9)	29 (100)	18 (66.7)	9 (33.3)	27 (100)	23 (65.7)	12 (34.3)	35 (100)	19 (54.3)	16 (45.7)	35 (100)
Positive (>35 U/mL)	26 (16.6)	131 (83.4)	157 (100)	66 (42.0)	91 (58.0)	157 (100)	131 (89.1)	16 (10.9)	147 (100)	118 (75.2)	39 (24.8)	157 (100)	80 (51.3)	76 (48.7)	156 (100)	69 (45.4)	83 (54.6)	152 (100)	104 (60.5)	68 (39.5)	172 (100)	77 (44.5)	96 (55.5)	173 (100)

Chemosensitivity	p = 0.216			p = 0.287			p = 0.635			p = 0.758			p = 0.375			p = 0.576			p = 0.355			p = 0.594		
Sensitive	33 (20.9)	125 (79.1)	128 (100)	67 (42.4)	91 (57.6)	158 (100)	129 (89.0)	16 (11.0)	145 (100)	118 (75.2)	39 (24.8)	157 (100)	77 (48.7)	81 (51.3)	158 (100)	75 (49.3)	77 (50.7)	152 (100)	104 (59.1)	72 (40.9)	176 (100)	80 (45.5)	96 (54.5)	176 (100)
Resistant	1 (7.1)	13 (92.9)	14 (100)	8 (57.1)	6 (42.9)	14 (100)	13 (92.9)	1 (7.1)	14 (100)	10 (71.4)	4 (28.6)	14 (100)	8 (61.5)	5 (38.5)	13 (100)	8 (57.1)	6 (42.9)	14 (100)	12 (70.6)	5 (29.4)	17 (100)	7 (38.9)	11 (61.1)	18 (100)
Hormone receptor	p = 0.656			p = 0.258			p = 0.389			p = 0.831			p = 0.008			p < 0.001			p = 0.001			p = 0.002		
Triple dominant	11 (26.8)	30 (73.2)	41 (100)	16 (39.0)	25 (61.0)	41 (100)	37 (94.9)	2 (5.1)	39 (100)	32 (78.0)	9 (22.0)	41 (100)	16 (38.1)	26 (61.9)	42 (100)	32 (78.0)	9 (22.0)	41 (100)	22 (44.0)	28 (56.0)	50 (100)	14 (28.0)	36 (72.0)	50 (100)
GR and PR dominant	29 (23.4)	95 (76.6)	124 (100)	61 (49.2)	63 (50.8)	124 (100)	104 (90.4)	11 (9.6)	115 (100)	94 (76.4)	29 (23.6)	123 (100)	78 (61.4)	49 (38.6)	127 (100)	45 (38.1)	73 (61.9)	118 (100)	84 (70.6)	35 (29.4)	119 (100)	64 (53.8)	55 (46.2)	119 (100)

[a]cut-off value of **CD 4+** is over 0.19 of IHC score; [b]cut-off value of CD8+ is over 1.33 of IHC score; [c]cut-off value of CD4+/CD8+ is over 4.73 of IHC score; [d]cut-off value of CD3+ is over 24.53 of IHC score; [e]cut-off value of FoxP 3+ is over 0.36 of IHC score; [f]cut-off value of CD 3+/FoxP 3+ is over 23.21 of IHC score FIGO, [g]cut-off value of PD-1 is over 1.2; [h]cut-off value of PD-L1 is 1.6; International Federation of Gynecology and Obstetrics


A
Negative
100 um
CD4+
CD8+
CD3+
FoxP3+
B
Disease Free Survival
1.0
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FoxP 3+ - (n=100)
FoxP 3+ + (n=88)
Censored
Censored
Log-rank p = 0.011
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250
300
Months after initial treatment
CD 3-/ FoxP 3+ - (n=90)
CD 3-/FoxP 3+ + (n=92)
Censored
Censored
Log rank p = 0.049
Overall Survival
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FoxP3+ + (n=88)
Censored
Censored
Log-rank p < 0.001
CD 3+/ FoxP 3+ - (n=90)
CD 3+/ FoxP 3+ + (n=92)
Censored
Censored
Log-rank p = 0.011
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IHC scores of FoxP 3+
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10
8
6
4
2
0
p = 0.014
Triple dominant group (n=50)
GR dominant or PR dominant group (n=119)
Hormone receptor subtypes
IHC scores of CD 3+ / FoxP 3+
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100
80
60
40
20
0
p = 0.070
Triple dominant group (n=50)
GR dominant or PR dominant group (n=119)
Hormone receptor subtypes

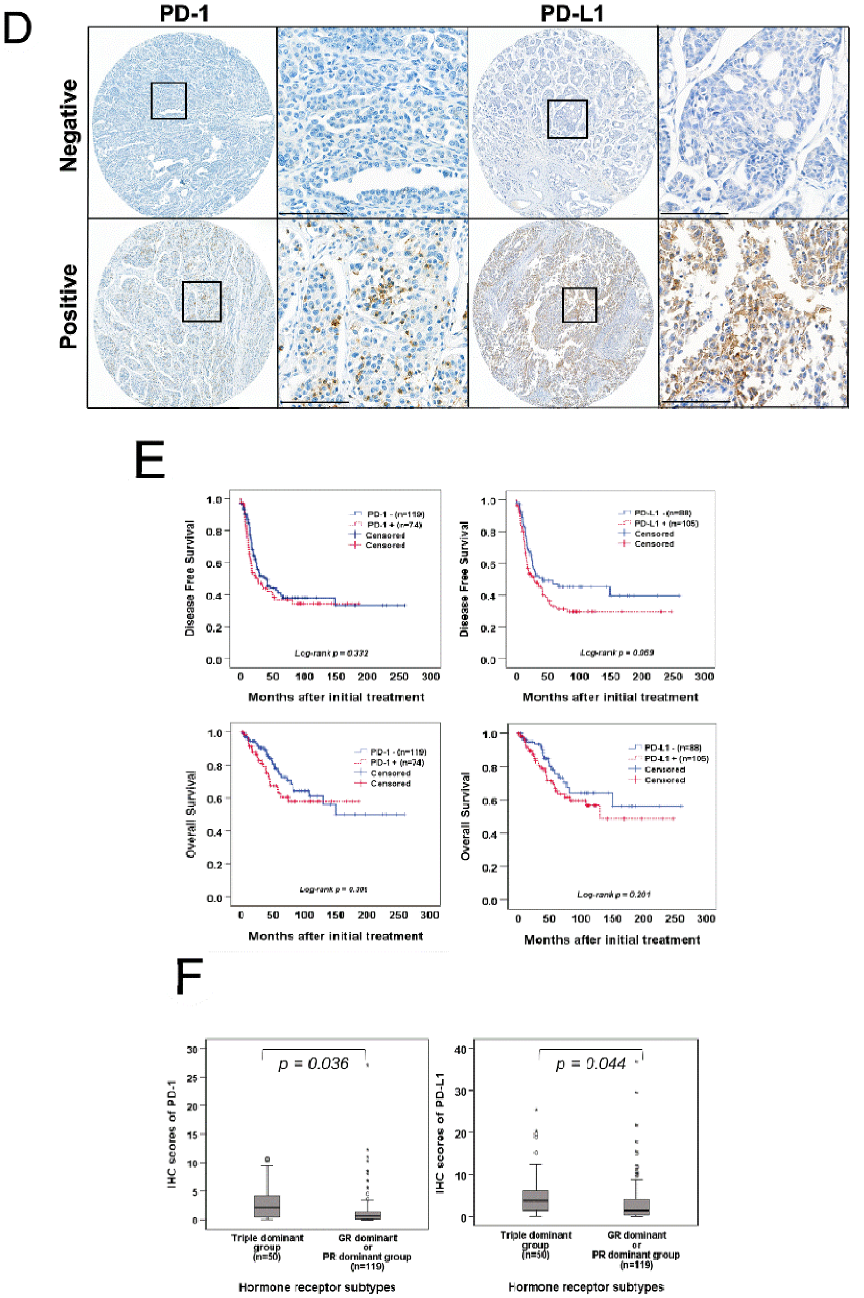


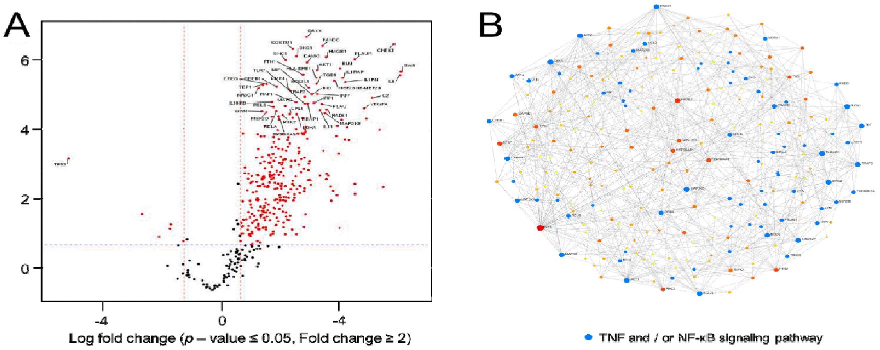
Figure 5. PD-1 and PD-L1 expression on EOC and their association with tumor infiltrating lymphocytes and EOC subgroups clustered by hormone receptor expression pattern. (A)

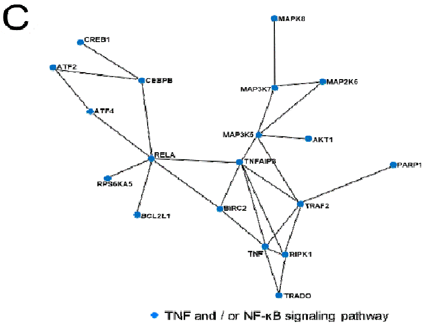
Representative immunohistochemical images of CD4$^+$, CD8$^+$, CD3$^+$, and FoxP3$^+$ in EOCs. The TILs were observed in cancer stroma (scale bar: 100 μm). (B) DFS and OS of patients with EOC was based on FoxP3$^+$ infiltration and CD3$^+$/FoxP3$^+$ ratio. (C) A boxplot of FoxP3$^+$ infiltration or CD3$^+$/FoxP3$^+$ ratio and subgroups clustered by hormone receptor expression pattern. (D) Representative immunohistochemical images of PD-1 and PD-L1 in EOCs (scale bar: 100 μm). (E) The DFS and OS of patients with EOC was based on PD-1, and PD-L1 expression in patients with EOC. (F) A boxplot of PD-1 infiltration or PD-L1 expression in subgroups clustered by hormone receptor expression patternin EOC.

6. NanoString analysis of the triple dominant group

We then analyzed the DEGs with mRNA extracted from six normal ovarian epithelial tissues and six EOC tissues in the triple dominant EOC group to gain insight into the molecular details of the triple dominant group[22]. A total of 228 upregulated DEGs were identified with an adjusted *p*-value cut-off of 0.05 (Figure 6A, Supplementary Table S1). Expectedly, several upregulated genes were classified as cytokine-related genes. To gain further biological insights, we constructed ovarian tissue-specific PPI networks using NetworkAnalyst [20] with the identified upregulated DEGs (n = 169). The results showed that *γ-rel avian reticuloendotheliosis viral oncogene homolog A* (*RELA*), *mitogen-activated protein kinase kinase kinase 5* (*MAP3K5), tumor necrosis factor α induced protein 3* (*TNFAIP3*), *BCL2-like protein 1 (BCL2L1*), *receptor-interacting protein kinase 1* (*RIPK1*), *tumor necrosis factor receptor-*

associated factor 2 (*TRAF2*), *PARP1*, and *v-akt murine thymoma viral oncogene homolog 1* (*AKT1*) were the most highly connected genes in the minimum-order network (Figure 6B). Moreover, *RELA*, *MAP3K5*, and *TNFAIP3* showed the highest connection in a zero-order network (Figure 6C and 6D). Gene Ontology analysis of the network components also indicated that genes involved in the TNF (adjusted p-value < 2.16e-38) and/or NF-κB (adjusted p-value < 6.17e-27) signaling pathways were significantly enriched with respect to the upregulated DEG (Figure 6E). Overall, the DEG and PPI network analyses indicated that *RELA*, *MAP3K5*, *TNFAIP3*, *BCL2L1*, *RIPK1*, *TRAF2*, *PARP1*, and *AKT1* profoundly influence the triple dominant group of EOC through the TNF and/or NF-κB signaling pathways. We also conducted a comprehensive Gene Ontology analysis using g:profiler[21]. As expected, many genes were found to be involved in cytokine signaling and the immune system. Interestingly, we found that some pathways were related to the suppressive mechanism of Tregs, such as interleukin (IL)-10 signaling (adjusted p-value < 1.96e-16), PD-L1 expression and PD-1 checkpoint pathways in cancer (adjusted p-value < 6.89e-15), and activation of protein kinase activity (adjusted p-value < 1.31e-21) in the triple dominant group. This finding indicates that the triple dominant group activates host defense system and contributes to the expansion and differentiation of Treg FoxP3$^+$ lymphocytes (Supplementary Table S2).





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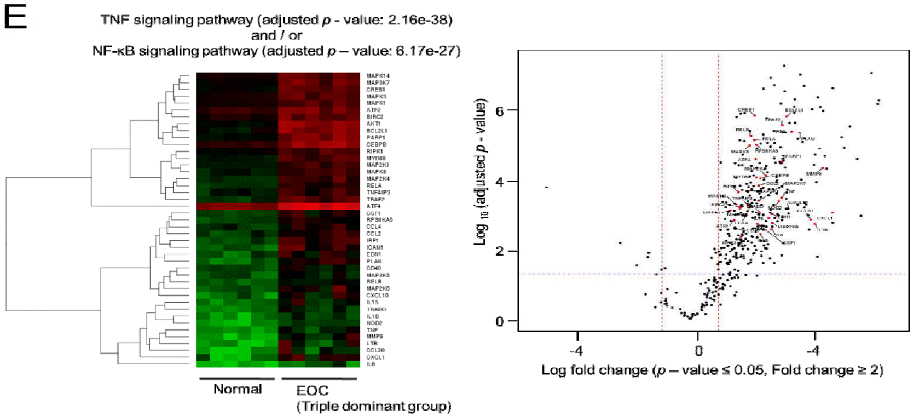
Number of nodes in the minimum – order (or zero – order) network

PARP1	47 (4)	TRAF2	36 (6)
RELA	47 (10)	MAP3K5	43 (10)
AKT1	45 (5)	TNFAIP3	29 (8)
ATF2	38 (7)	HIF1A	27 (3)



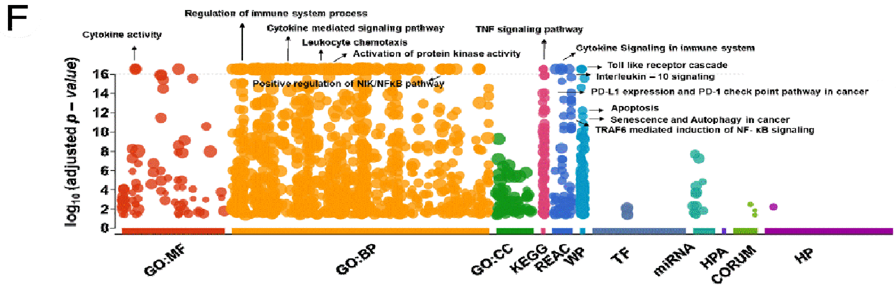


Figure 6. Analysis of differentially expressed genes (DEGs) in the triple dominant EOC group compared to normal ovarian epithelial tissues. Analysis of differentially expressed genes (DEGs) in the triple dominant EOC group compared with that in normal ovarian epithelial tissues. (A) Volcano plot shows the upregulated DEGs in the triple dominant EOC group compared with those in normal ovarian epithelial tissues. (B) Minimum-order and (C) zero-order protein–protein interaction (PPI) network was constructed with 167 upregulated DEGs using NetworkAnalyst (https://www.networkanalyst.ca/) (D) Genes with a higher number of PPI interactions are listed. (E) Most significantly upregulated pathways identified in the PPI networks are shown by Heatmap and volcano plot. (F) g:Profiler (https://biit.cs.ut.ee/gprofiler/) was used to dissect molecular pathways of 167 upregulated in the triple dominant EOC group compared with those in normal ovarian epithelial tissues with the following categories: [GO:MF—molecular function; GO:BP—biologic process; GO:CC—cellular component; KEGG—Kyoto Encyclopedia of Genes and Genomes; REAC—reactome; WP—Wikipathways; TF—TRANSFAC; miRNA—miRTarBase; HPA—human protein atlas; CORUM—CORUM protein complexes; HP—human phenotype ontology.]

Ⅳ. DISCUSSION

The endocrine organs and hormone receptor expression may be associated with the occurrence, progression and overall prognosis of EOC. However, previous studies have primarily focused on investigating the prognostic value of a single hormone receptor. Although, Feng *et al.*[23] and Kruchten *et al.*[24] performed cluster analysis over single isoform of hormone receptors, their results were less conclusive. Also, studies involving cluster analysis using steroid hormones, such as GR and AR, in addition to ERα, PR, and ERβ in EOC, are lacking. Meanwhile, herein we demonstrated that the triple dominant ($AR^+/PR^+/GR^+$) subgroup represents an independent prognostic factor for prognosis in the multivariate analysis whereas single steroid hormone receptors did not yield significant results. Taken together, our results suggest that the triple dominant subgroup may play an important role in predicting the treatment and prognosis of EOC.

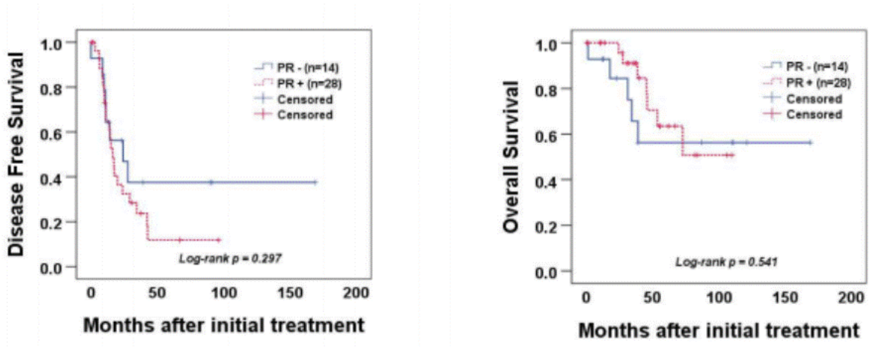
Interestingly, we found an association between PR activity and EOC prognosis. In general, PR is considered a good prognostic factor for EOC. However, its activity was altered based on which hormone receptors were simultaneously expressed. For example, in the triple dominant subgroup where GR and AR were co expressed, PR overexpression was associated with poor prognosis unlike in the PR- or GR-dominant subgroups of EOC (Figure 7). Similarly, PR activation is associated with the increased occurrence and progression of breast cancer whereas GR is related to growth suppression and differentiation. Ogara *et al.*[25] reported that GR negatively regulates the PR activity by modulating PR target genes as GR and PR share structural and functional similarities. They also suggested that GR-PR heterocomplex formation increases negative regulation of PR activity[26]. In addition to PR, GR regulates the expression of AR target genes, while AR and PR have 88% sequence homology[27,28]. Therefore, we hypothesized that GR may modulate both AR and PR directly and indirectly. The role of hormone receptor crosstalk in cancer is becoming increasingly relevant, although the mechanisms involved remain controversial, particularly in EOC. Thus, our findings suggest the possibility of different transcriptional outcomes for the triple dominant group in EOC. Further investigation in this regard could explain the prognosis associated with the triple dominant group in more detail and contribute to the development of new endocrine combined therapies in future.

To date, several studies on EOC have reported that an elevated number of Tregs significantly correlates with worse prognosis[29]. Nevertheless, evaluating TILs in the context of hormone receptors is important as altered expression of hormones and their cognate receptors, represent mediators of immune trafficking and inflammatory processes affecting the TME. For instance, several important mechanisms modulated by GR related to apoptosis, differentiation and proliferation of Tregs have been reported. One such mechanism involves GR enhancing the expression of immunosuppressive cytokines, IL-10 and TGF-β, which are capable of subsequently augmenting FoxP3$^+$expression[30,31]. Furthermore, Huang *et al.*[32] reported that simultaneous overexpression of *BCL-2* and GR effectively inhibits glucocorticoid dependent apoptosis of Tregs. Moreover, Bereshchenko *et al.*[33] demonstrated that following its translocation to the nucleus, GR induces glucocorticoid-induced leucin zipper (GILZ) production, a protein induced by glucocorticoid, as well as enhanced FoxP3$^+$ differentiation in native T cells. Furthermore, GR- or AR-biding regions have been identified in FoxP3$^+$, which may modulate the activities of $FoxP3^+$ in Treg[34,35]. However, functional studies to better understand the molecular mechanisms associated with the triple dominant subgroup of EOC are necessary. In addition, we plan to incorporate larger numbers of specific histological subgroups to generalize our findings as we did not find a significant difference in prognosis in the triple dominant group depending on $FoxP3^+$ expression, which is a limitation of our study.

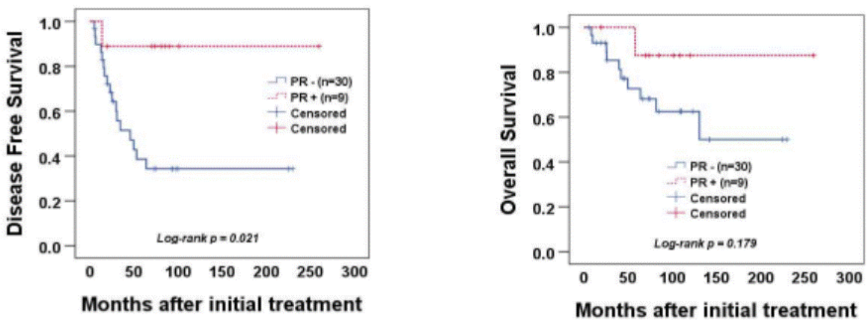
The TNF and/or the NF-κB signaling pathways are key regulators of innate and adaptive immune responses, functioning to regulate cell death and survival[29,36]. RELA is a subunit of the NF-κB signaling pathway, while MAP3K5 functions as a positive regulator by phosphorylating IKKβ. Moreover, *BCL2L1*, *RIPK1*, *TRAF2*, *PARP1* and *AKT1* are protooncogenes upregulated by the NF-κB signaling pathway. Additionally, *TNFAIP3* is an anti-apoptotic gene that is rapidly upregulated upon activation of the TNF and/or NF-κB signaling pathway[29,37]. Furthermore, *TNFAIP3* is constitutively expressed by T and B cells to inhibit Treg lymphocytes and hyperactivate Th and cytotoxic T cells[37,38]. However, in EOC, the role of *TNFAIP3* remains controversial. Therefore, future studies should evaluate its role in EOC and incorporate the role of *TNFAIP3* with the triple dominant subgroup of EOC to identify its potential as a prognostic or therapeutic target.

Lastly, as the abundance of Tregs, and their functionality, have been associated with steroid hormone receptors, reducing the expression of these receptors could subsequently reduce the Treg population, which may improve patient survival. Generail *et al.*[39,40] performed a Phase II randomized controlled trial of letrozole with, or without, the immunomodulatory agent cyclophosphamide in breast cancer patients. Results showed a significant reduction of Treg number and significant correlation between the reduced Tregs and the number of patients who achieved complete remission when treated with letrozole in combination with cyclophosphamide, as estrogen has been shown to increase Treg number and functionality. Therefore, in the triple dominant subgroup, inhibiting AR, PR and GR via combination immunotherapy may also improve the number of EOC patients achieving complete remission.

<Triple dominant group>



<GR dominant group>



<PR dominant group>

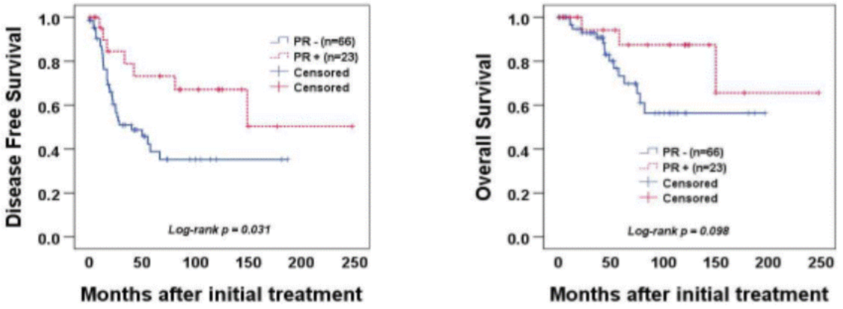


Figure 7. Disease free survival (DFS) and overall survival (OS) analyses of the triple dominant, GR-dominant, and PR-dominant group depends on PR expression.

Ⅴ. CONCLUSION

In conclusion, we identified an EOC subgroup based on hormone receptor expression that displays prognostic significance. Moreover, our newly constructed EOC subgroup classification revealed important TIL features. Although additional studies are necessary to clarify the underlying mechanism, our newly classified triple dominant EOC subgroup has prognostic and predictive value. Overall, the proposed hormone receptor expression-based classification may contribute to precision medicine in EOC and determine the most efficient therapeutic course.

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APPENDIX

Supplementary Table S1. Upregulated DEGs between normal ovarian epithelial tissues and the triple dominant groups which were identified with an adjusted p- value cut-off of 0.05

DEG-selection pair : Normal vs. Primary_Tumor
DEG-selection condition : (|fold-change| ≥ 2) n (q-value ≤ 0.05)
Count of total DEGs : 236
Count of the top-ranked DEGs, those selected for anlaysis : 228
Count of the gene symbols mapped to enrichment DB : 228

Species	Mapping to g:Profiler	Official Gene Symbol	Normal	Primary Tumor	Status	Log2FC	p-value	q-value	Ensembl Gene ID
H.sapeins	Success	BIRC5	2.34	241.67	OK	6.69	0.0000005	0	ENSG00000089685
H.sapeins	Fail	IL8	2.53	256.01	OK	6.66	0.00000063	0	-
H.sapeins	Success	CHEK1	5.13	445.81	OK	6.44	0.00000008	0	ENSG00000149554
H.sapeins	Success	CA9	1.14	75.71	OK	6.06	0.00105359	0.01	ENSG00000107159
H.sapeins	Success	CFB	47.69	2915.61	OK	5.93	0.00002407	0	ENSG00000243649
H.sapeins	Success	C2	12.89	657.19	OK	5.67	0.00000281	0	ENSG00000166278
H.sapeins	Success	TNFRSF11B	1.64	72.46	OK	5.47	0.00001152	0	ENSG00000164761
H.sapeins	Success	VEGFA	71.17	2964.09	OK	5.38	0.00000571	0	ENSG00000112715
H.sapeins	Fail	CD133	5.34	177.55	OK	5.06	0.0016707	0.02	-
H.sapeins	Success	PLAUR	7.99	266.54	OK	5.06	0.00000022	0	ENSG00000011422
H.sapeins	Success	CXCL1	5.6	186.02	OK	5.05	0.00085956	0.01	ENSG00000163739
H.sapeins	Success	SLC2A1	7.96	227.87	OK	4.84	0.00004659	0	ENSG00000117394
H.sapeins	Success	BCL6	24.16	664.51	OK	4.78	0.0000201	0	ENSG00000113916
H.sapeins	Success	IL1RN	1.58	41.6	OK	4.72	0.00000099	0	ENSG00000136689
H.sapeins	Success	MMP9	3.37	87.55	OK	4.7	0.00004441	0	ENSG00000100985
H.sapeins	Success	IL1RAP	17.08	419.1	OK	4.62	0.00000076	0	ENSG00000196083
H.sapeins	Success	GADD45G	1.81	43.4	OK	4.59	0.00001215	0	ENSG00000130222
H.sapeins	Success	BLM	4.69	108.56	OK	4.53	0.00000041	0	ENSG00000197299
H.sapeins	Success	TERC	183.08	4077.92	OK	4.48	0.00011542	0	ENSG00000270141
H.sapeins	Success	IL6R	11.75	253.29	OK	4.43	0.00001825	0	ENSG00000160712
H.sapeins	Success	LTB	3.43	73.51	OK	4.42	0.0018304	0.02	ENSG00000227507
H.sapeins	Success	ITGB6	2.22	47.09	OK	4.4	0.00003616	0	ENSG00000115221
H.sapeins	Fail	MEF2BNB-MEF2B	3.12	62.88	OK	4.33	0.0000009	0	-
H.sapeins	Success	CCL20	3.04	58.9	OK	4.28	0.001357	0.02	ENSG00000115009
H.sapeins	Success	PTGS1	29.99	559.35	OK	4.22	0.0026409	0.03	ENSG00000095303
H.sapeins	Success	SERPINE1	14.82	270.08	OK	4.19	0.00102559	0.01	ENSG00000106366
H.sapeins	Success	TERT	1.28	22.01	OK	4.11	0.00050362	0.01	ENSG00000164362

H.sapeins	Success	HSH2D	6.28	104.41	OK	4.06	0.00044648	0.01	ENSG00000196684
H.sapeins	Success	RAD51	2.03	33.81	OK	4.06	0.00000622	0	ENSG00000051180
H.sapeins	Success	CXCL6	1.31	21.75	OK	4.05	0.00061992	0.01	ENSG00000124875
H.sapeins	Success	HMGB1	108.58	1791.8	OK	4.04	0.00000019	0	ENSG00000189403
H.sapeins	Success	MAP3K9	4.46	71.03	OK	3.99	0.00000786	0	ENSG00000006432
H.sapeins	Success	ICAM-1	18.86	289.55	OK	3.94	0.00009627	0	ENSG00000090339
H.sapeins	Success	FANCC	7.31	109.96	OK	3.91	0.00000009	0	ENSG00000158169
H.sapeins	Success	PLAU	13.63	200.49	OK	3.88	0.00000429	0	ENSG00000122861
H.sapeins	Success	IGFBP2	98.15	1381.82	OK	3.82	0.00050463	0.01	ENSG00000115457
H.sapeins	Success	IL11	1.28	18.05	OK	3.82	0.00000643	0	ENSG00000095752
H.sapeins	Success	IRF7	19.11	251.77	OK	3.72	0.00000221	0	ENSG00000185507
H.sapeins	Success	AKT1	100.47	1315.85	OK	3.71	0.00000046	0	ENSG00000142208
H.sapeins	Success	HLA-DRB1	498.23	6448.62	OK	3.69	0.00000075	0	ENSG00000196126
H.sapeins	Success	ITGB8	134.45	1729.56	OK	3.69	0.00000112	0	ENSG00000105855
H.sapeins	Success	IRF1	26.75	324.63	OK	3.6	0.00000399	0	ENSG00000125347
H.sapeins	Success	BID	13.94	161	OK	3.53	0.00000223	0	ENSG00000015475
H.sapeins	Success	MIF	485.77	5628.44	OK	3.53	0.00000224	0	ENSG00000240972
H.sapeins	Success	SMAD6	19.96	223.5	OK	3.49	0.0009094	0.01	ENSG00000137834
H.sapeins	Success	OASL	3.12	34.63	OK	3.47	0.00066504	0.01	ENSG00000135114
H.sapeins	Success	NOD1	8.66	94.53	OK	3.45	0.00018938	0	ENSG00000106100
H.sapeins	Success	CXCL10	11	119.32	OK	3.44	0.00064765	0.01	ENSG00000169245
H.sapeins	Success	ALOX5	30.28	325.31	OK	3.43	0.0002238	0	ENSG00000012779
H.sapeins	Success	BCL2L1	101.27	1082.9	OK	3.42	0.00000144	0	ENSG00000171552
H.sapeins	Success	THBS1	171.12	1815.72	OK	3.41	0.00034428	0.01	ENSG00000137801
H.sapeins	Success	MX2	23.71	249.54	OK	3.4	0.00066044	0.01	ENSG00000183486
H.sapeins	Success	KEAP1	38.62	401.02	OK	3.38	0.00000416	0	ENSG00000079999
H.sapeins	Success	IRF5	7.05	72.66	OK	3.37	0.00004263	0	ENSG00000128604
H.sapeins	Success	ICAM-3	18.31	188.06	OK	3.36	0.00000027	0	ENSG00000076662
H.sapeins	Success	DAXX	46.07	465.57	OK	3.34	0.00000005	0	ENSG00000204209
H.sapeins	Success	CCL11	1.41	13.85	OK	3.3	0.00001964	0	ENSG00000172156
H.sapeins	Success	CHEK2	11.09	109.31	OK	3.3	0.00002713	0	ENSG00000183765
H.sapeins	Success	TIMP1	276.12	2706.67	OK	3.29	0.0000237	0	ENSG00000102265
H.sapeins	Success	TLR7	2.84	27.5	OK	3.28	0.00000416	0	ENSG00000196664
H.sapeins	Success	TRAF2	48.97	474.05	OK	3.28	0.00000263	0	ENSG00000127191
H.sapeins	Success	ITGB5	67.23	649.74	OK	3.27	0.00015178	0	ENSG00000082781
H.sapeins	Fail	MMP-12	1.14	10.98	OK	3.27	0.00114965	0.02	-
H.sapeins	Success	PARP1	95.25	920.75	OK	3.27	0.00002951	0	ENSG00000143799
H.sapeins	Success	ITGB3	7.21	69.13	OK	3.26	0.00140892	0.02	ENSG00000259207
H.sapeins	Success	TNF	6.49	61.83	OK	3.25	0.00031797	0.01	ENSG00000232810
H.sapeins	Success	IL10	1.48	13.81	OK	3.23	0.0000324	0	ENSG00000136634

H.sapeins	Success	FTH1	5903.53	55112.2	OK	3.22	0.00000061	0	ENSG00000167996
H.sapeins	Success	COL1A2	328.82	3041.08	OK	3.21	0.00001105	0	ENSG00000164692
H.sapeins	Success	ATR	65.01	588.23	OK	3.18	0.00002966	0	ENSG00000175054
H.sapeins	Success	CCL3	20.4	182.12	OK	3.16	0.00016575	0	ENSG00000277632
H.sapeins	Success	NOD2	4.15	36.73	OK	3.15	0.00039675	0.01	ENSG00000167207
H.sapeins	Success	TLR9	4.53	39.74	OK	3.13	0.00101902	0.01	ENSG00000239732
H.sapeins	Success	CXCR4	65.46	560.24	OK	3.1	0.00153848	0.02	ENSG00000121966
H.sapeins	Success	DDIT3	70.79	605.03	OK	3.1	0.00097784	0.01	ENSG00000175197
H.sapeins	Success	PTGER2	45.33	383.07	OK	3.08	0.00010025	0	ENSG00000125384
H.sapeins	Success	RIPK2	36.47	305.81	OK	3.07	0.00024422	0.01	ENSG00000104312
H.sapeins	Success	GADD45A	93.73	780.59	OK	3.06	0.0000797	0	ENSG00000116717
H.sapeins	Success	IL18	13.58	113.26	OK	3.06	0.0002357	0.01	ENSG00000150782
H.sapeins	Success	SNAI1	5.16	43.04	OK	3.06	0.00011367	0	ENSG00000124216
H.sapeins	Fail	sTNFRII	18.92	154.65	OK	3.03	0.00003052	0	-
H.sapeins	Success	LDHA	367.19	2921.94	OK	2.99	0.0000084	0	ENSG00000134333
H.sapeins	Success	DKC1	90.02	710.37	OK	2.98	0.00000018	0	ENSG00000130826
H.sapeins	Success	ROCK2	112.46	887.06	OK	2.98	0.00002299	0	ENSG00000134318
H.sapeins	Success	RAF1	87.97	690.6	OK	2.97	0.00000378	0	ENSG00000132155
H.sapeins	Success	ATG5	46.91	360.44	OK	2.94	0.00018316	0	ENSG00000057663
H.sapeins	Success	MAP2K6	22.07	166.15	OK	2.91	0.00169379	0.02	ENSG00000108984
H.sapeins	Success	PDGFB	5.14	38.68	OK	2.91	0.00214078	0.03	ENSG00000100311
H.sapeins	Success	EDN1	22.24	164.63	OK	2.89	0.0009472	0.01	ENSG00000078401
H.sapeins	Success	IL6	2.13	15.71	OK	2.88	0.00258508	0.03	ENSG00000136244
H.sapeins	Success	SQSTM1	25.8	187.44	OK	2.86	0.00000011	0	ENSG00000161011
H.sapeins	Success	TLR2	7.87	57.03	OK	2.86	0.00070696	0.01	ENSG00000137462
H.sapeins	Success	LTB4R2	27.98	201.67	OK	2.85	0.00001058	0	ENSG00000213906
H.sapeins	Success	CTGF	199.33	1429.21	OK	2.84	0.00086382	0.01	ENSG00000118523
H.sapeins	Success	ITGB2	48.1	335.09	OK	2.8	0.00018457	0	ENSG00000160255
H.sapeins	Success	IFIT1	25.55	177.12	OK	2.79	0.00027548	0.01	ENSG00000185745
H.sapeins	Success	IL15	11.82	82.03	OK	2.79	0.00121569	0.02	ENSG00000164136
H.sapeins	Success	CFL1	633.14	4234.28	OK	2.74	0.00000834	0	ENSG00000172757
H.sapeins	Success	IL23A	1.28	8.55	OK	2.74	0.00005955	0	ENSG00000110944
H.sapeins	Success	LIMK1	37.59	247.11	OK	2.72	0.00000164	0	ENSG00000106683
H.sapeins	Success	GZMB	2.32	15.13	OK	2.71	0.00214007	0.03	ENSG00000100453
H.sapeins	Success	RAC1	298.27	1943	OK	2.7	0.00003928	0	ENSG00000136238
H.sapeins	Success	MKNK1	64.38	414.84	OK	2.69	0.00151444	0.02	ENSG00000079277
H.sapeins	Success	MAP2K4	48.62	310.78	OK	2.68	0.00007223	0	ENSG00000065559
H.sapeins	Success	HMGN1	220.08	1395.76	OK	2.66	0.0000461	0	ENSG00000205581
H.sapeins	Success	SERPINH1	433.91	2661.67	OK	2.62	0.00009588	0	ENSG00000149257
H.sapeins	Success	PRKG2	1.52	9.25	OK	2.61	0.00207661	0.03	ENSG00000138669

H.sapeins	Success	INHBE	1.14	6.9	OK	2.6	0.0026662	0.03	ENSG00000139269
H.sapeins	Success	SHC1	200.81	1220.72	OK	2.6	0.00000023	0	ENSG00000160691
H.sapeins	Success	MAFG	28.06	169.26	OK	2.59	0.00000487	0	ENSG00000197063
H.sapeins	Success	PRDX1	519.84	3126.33	OK	2.59	0.00016863	0	ENSG00000117450
H.sapeins	Success	TREM2	5.17	31.05	OK	2.59	0.00100125	0.01	ENSG00000095970
H.sapeins	Success	SMAD7	60.36	352.14	OK	2.54	0.00204996	0.03	ENSG00000101665
H.sapeins	Success	GREM1	1.77	10.23	OK	2.53	0.00051085	0.01	ENSG00000166923
H.sapeins	Success	ATG3	123.21	708.62	OK	2.52	0.00017572	0	ENSG00000144848
H.sapeins	Success	GCLM	42.1	241.94	OK	2.52	0.00254579	0.03	ENSG00000023909
H.sapeins	Success	IFI44	62.04	354.27	OK	2.51	0.00030793	0.01	ENSG00000137965
H.sapeins	Success	PTK2	220.08	1242.94	OK	2.5	0.00000889	0	ENSG00000169398
H.sapeins	Success	BECN1	119.6	670.26	OK	2.49	0.00020681	0	ENSG00000126581
H.sapeins	Success	CEBPB	244.86	1373.09	OK	2.49	0.0000866	0	ENSG00000172216
H.sapeins	Success	IL1B	6.52	36.68	OK	2.49	0.00360545	0.04	ENSG00000125538
H.sapeins	Success	TLR3	14.46	80.24	OK	2.47	0.00003197	0	ENSG00000164342
H.sapeins	Success	TRADD	9.46	52.21	OK	2.46	0.00084057	0.01	ENSG00000102871
H.sapeins	Success	TXNRD1	192.12	1060.21	OK	2.46	0.00024354	0.01	ENSG00000198431
H.sapeins	Success	IL7	2.67	14.64	OK	2.45	0.00116659	0.02	ENSG00000104432
H.sapeins	Success	STAT2	63.34	345.13	OK	2.45	0.00096991	0.01	ENSG00000170581
H.sapeins	Success	CCL2	37.59	202.87	OK	2.43	0.00014066	0	ENSG00000108691
H.sapeins	Success	MAP3K7	123.5	664.09	OK	2.43	0.00038908	0.01	ENSG00000135341
H.sapeins	Success	TXN	475.78	2555.52	OK	2.43	0.00097705	0.01	ENSG00000136810
H.sapeins	Success	ELK1	44.82	238.77	OK	2.41	0.00257943	0.03	ENSG00000126767
H.sapeins	Success	RAD9A	60.37	321.44	OK	2.41	0.00211948	0.03	ENSG00000172613
H.sapeins	Success	CSF1	34.34	180.35	OK	2.39	0.001833	0.02	ENSG00000184371
H.sapeins	Success	MEF2A	248.48	1301.14	OK	2.39	0.00021029	0	ENSG00000068305
H.sapeins	Fail	TR	11.7	61.06	OK	2.38	0.00453157	0.05	-
H.sapeins	Success	LEAP2	7.91	40.83	OK	2.37	0.00001197	0	ENSG00000164406
H.sapeins	Success	MAPKAPK5	83.94	431.93	OK	2.36	0.00004347	0	ENSG00000089022
H.sapeins	Success	TERF1	48.8	251.08	OK	2.36	0.00046752	0.01	ENSG00000147601
H.sapeins	Success	MYD88	80.75	412.43	OK	2.35	0.00008327	0	ENSG00000172936
H.sapeins	Success	RPS6KA5	32.15	163.68	OK	2.35	0.00000954	0	ENSG00000100784
H.sapeins	Success	COL3A1	1441.01	7275.43	OK	2.34	0.00084641	0.01	ENSG00000168542
H.sapeins	Success	ATF4	866.31	4350.22	OK	2.33	0.00002435	0	ENSG00000128272
H.sapeins	Success	IFIT2	30.34	152.5	OK	2.33	0.00300694	0.04	ENSG00000119922
H.sapeins	Success	GNAS	778.43	3855.06	OK	2.31	0.00239634	0.03	ENSG00000087460
H.sapeins	Success	MCL1	428.19	2123.98	OK	2.31	0.00114694	0.02	ENSG00000143384
H.sapeins	Success	CREB1	111.7	544.71	OK	2.29	0.00000136	0	ENSG00000118260
H.sapeins	Fail	sTNFRI	186.69	911.03	OK	2.29	0.00036349	0.01	-
H.sapeins	Success	RELA	44.73	216.29	OK	2.27	0.0000069	0	ENSG00000173039

H.sapeins	Success	PARN	140.52	667.75	OK	2.25	0.00007297	0	ENSG00000140694
H.sapeins	Success	PTGIR	2.11	10.03	OK	2.25	0.00014885	0	ENSG00000160013
H.sapeins	Success	IL13RA2	1.43	6.76	OK	2.24	0.00238889	0.03	ENSG00000123496
H.sapeins	Success	CD163	33.98	157.92	OK	2.22	0.0043586	0.05	ENSG00000177575
H.sapeins	Success	IGFBP7	564.04	2632.65	OK	2.22	0.00255079	0.03	ENSG00000163453
H.sapeins	Success	IRF3	47.58	222.42	OK	2.22	0.00080103	0.01	ENSG00000126456
H.sapeins	Success	STAT1	348.16	1619.49	OK	2.22	0.00118961	0.02	ENSG00000115415
H.sapeins	Success	ITGA3	114.07	516.75	OK	2.18	0.00018865	0	ENSG00000005884
H.sapeins	Success	OAS2	53.25	241.58	OK	2.18	0.00416438	0.05	ENSG00000111335
H.sapeins	Success	PDGFA	20.01	90.44	OK	2.18	0.00018444	0	ENSG00000197461
H.sapeins	Success	PIGF	63.27	287.21	OK	2.18	0.00005388	0	ENSG00000151665
H.sapeins	Success	TGFBR1	78.09	351.83	OK	2.17	0.00003842	0	ENSG00000106799
H.sapeins	Success	RELB	19.66	87.93	OK	2.16	0.00000519	0	ENSG00000104856
H.sapeins	Success	MAP2K1	36.33	161.74	OK	2.15	0.00011791	0	ENSG00000198517
H.sapeins	Success	TNFAIP3	1.14	4.97	OK	2.13	0.00049556	0.01	ENSG00000132693
H.sapeins	Success	CCL4	513.38	2235.04	OK	2.12	0.00007639	0	ENSG00000164733
H.sapeins	Success	MAP3K1	103.82	450.13	OK	2.12	0.00000375	0	ENSG00000243646
H.sapeins	Success	MAP3K5	23.02	99.11	OK	2.11	0.00027898	0.01	ENSG00000119917
H.sapeins	Success	BIRC2	71.9	310.09	OK	2.11	0.00001	0	ENSG00000107643
H.sapeins	Success	RIPK1	86.1	366.36	OK	2.09	0.00062694	0.01	ENSG00000177426
H.sapeins	Success	CD40	1.48	6.23	OK	2.08	0.00052776	0.01	ENSG00000130427
H.sapeins	Success	ATF2	589.08	2492.74	OK	2.08	0.00015493	0	ENSG00000150093
H.sapeins	Success	MAFK	75.57	314.94	OK	2.06	0.00020342	0	ENSG00000169032
H.sapeins	Success	C3AR1	16.9	69.84	OK	2.05	0.00039967	0.01	ENSG00000171860
H.sapeins	Success	SP1	127.47	528.02	OK	2.05	0.0002133	0	ENSG00000185591
H.sapeins	Success	CRP	68.58	284.27	OK	2.05	0.00053312	0.01	ENSG00000118503
H.sapeins	Success	NFATC3	65.68	269.84	OK	2.04	0.00047301	0.01	ENSG00000072736
H.sapeins	Success	PPP1R12B	25.31	103.03	OK	2.03	0.00078557	0.01	ENSG00000077157
H.sapeins	Success	HLA-DRA	1051.45	4237.14	OK	2.01	0.0002073	0	ENSG00000204287
H.sapeins	Success	HRAS	14.77	59.67	OK	2.01	0.0001264	0	ENSG00000174775
H.sapeins	Success	CTSB	43.19	171.23	OK	1.99	0.00104122	0.01	ENSG00000275302
H.sapeins	Success	PTGER1	1.14	4.51	OK	1.99	0.00340931	0.04	ENSG00000160951
H.sapeins	Success	HSP90B1	364.01	1432.43	OK	1.98	0.00098307	0.01	ENSG00000166598
H.sapeins	Success	CCR3	1.14	4.45	OK	1.97	0.00490861	0.05	ENSG00000183625
H.sapeins	Success	IL10RB	105.36	403.03	OK	1.94	0.00104783	0.01	ENSG00000095015
H.sapeins	Success	EREG	1.39	5.31	OK	1.93	0.00000114	0	ENSG00000124882
H.sapeins	Success	MEF2D	195.84	742.63	OK	1.92	0.00000743	0	ENSG00000116604
H.sapeins	Success	CD4	22.94	85.56	OK	1.9	0.00301438	0.04	ENSG00000010610
H.sapeins	Success	HMGB2	109.34	403.64	OK	1.88	0.00238673	0.03	ENSG00000164104
H.sapeins	Success	GRB2	208.71	762.04	OK	1.87	0.00030724	0.01	ENSG00000177885

H.sapeins	Success	ATG7	87.63	318.3	OK	1.86	0.00001826	0	ENSG00000197548
H.sapeins	Success	CCR4	1.37	4.91	OK	1.85	0.00102029	0.01	ENSG00000183813
H.sapeins	Success	CDC42	565.21	2028.22	OK	1.84	0.00003667	0	ENSG00000070831
H.sapeins	Success	MRE11	89.93	323.01	OK	1.84	0.00056835	0.01	ENSG00000020922
H.sapeins	Fail	NBS1	159.39	569.96	OK	1.84	0.00362662	0.04	-
H.sapeins	Success	RAPGEF2	42.18	150.98	OK	1.84	0.00019344	0	ENSG00000109756
H.sapeins	Success	TLR5	43.97	157.9	OK	1.84	0.0040027	0.05	ENSG00000187554
H.sapeins	Success	TGFB1	79.64	282.46	OK	1.83	0.00051738	0.01	ENSG00000105329
H.sapeins	Success	GSTP1	1076.78	3767.68	OK	1.81	0.00053287	0.01	ENSG00000084207
H.sapeins	Success	IFIT3	22.73	79.75	OK	1.81	0.00429366	0.05	ENSG00000197442
H.sapeins	Success	MAFF	26.53	92.6	OK	1.8	0.00086248	0.01	ENSG00000185022
H.sapeins	Success	TEP1	27.96	96.61	OK	1.79	0.0000012	0	ENSG00000129566
H.sapeins	Success	MAPK8	172.81	587.91	OK	1.77	0.00059619	0.01	ENSG00000110330
H.sapeins	Success	C8A	1.17	3.99	OK	1.77	0.00014215	0	ENSG00000157131
H.sapeins	Success	MAPK14	158.61	540.99	OK	1.77	0.00063936	0.01	ENSG00000112062
H.sapeins	Success	WRN	33.99	115.39	OK	1.76	0.00000699	0	ENSG00000165392
H.sapeins	Success	GSR	111.54	369.78	OK	1.73	0.00003687	0	ENSG00000104687
H.sapeins	Success	MAPKAPK2	75.85	248.57	OK	1.71	0.00386436	0.04	ENSG00000162889
H.sapeins	Success	TGIF1	115.97	380.43	OK	1.71	0.00021882	0	ENSG00000137275
H.sapeins	Success	SMAD4	234.15	757.75	OK	1.69	0.00097525	0.01	ENSG00000141646
H.sapeins	Success	NR3C1	223.13	699.15	OK	1.65	0.00000149	0	ENSG00000113580
H.sapeins	Success	HDAC4	53.26	164.72	OK	1.63	0.00008501	0	ENSG00000068024
H.sapeins	Success	HSP90AA1	1540.93	4783.87	OK	1.63	0.00245385	0.03	ENSG00000080824
H.sapeins	Success	MAPK3	169.33	523.63	OK	1.63	0.00049434	0.01	ENSG00000102882
H.sapeins	Success	EPO	29.6	90.67	OK	1.61	0.00257296	0.03	ENSG00000101017
H.sapeins	Success	IGFBP3	408.76	1244.96	OK	1.61	0.00252284	0.03	ENSG00000146674
H.sapeins	Success	NLRP3	8.86	27.06	OK	1.61	0.00099525	0.01	ENSG00000162711
H.sapeins	Success	TFF1	1.31	3.99	OK	1.6	0.0000323	0	ENSG00000160182
H.sapeins	Success	RHOA	388.2	1170.66	OK	1.59	0.0022603	0.03	ENSG00000067560
H.sapeins	Success	SMAD2	219.55	662.78	OK	1.59	0.00047396	0.01	ENSG00000175387
H.sapeins	Success	C1R	432.34	1280.63	OK	1.57	0.00075428	0.01	ENSG00000159403
H.sapeins	Success	HUS1	131.24	390.97	OK	1.57	0.00015134	0	ENSG00000136273
H.sapeins	Success	MYL2	1.14	3.38	OK	1.57	0.00248403	0.03	ENSG00000111245
H.sapeins	Success	ITGB1	270.68	798.87	OK	1.56	0.00143047	0.02	ENSG00000115966
H.sapeins	Success	ITGAV	341.54	927.59	OK	1.44	0.0014967	0.02	ENSG00000138448
H.sapeins	Success	MAPK1	159.38	429.67	OK	1.43	0.00073936	0.01	ENSG00000100030
H.sapeins	Success	ARNT	188.47	499.06	OK	1.4	0.00051253	0.01	ENSG00000143437
H.sapeins	Success	IL5	1.14	2.99	OK	1.39	0.00412943	0.05	ENSG00000113525
H.sapeins	Success	ITGA1	97.21	250.33	OK	1.36	0.00080816	0.01	ENSG00000213949
H.sapeins	Success	TCF4	204.67	525.11	OK	1.36	0.00343028	0.04	ENSG00000196628

H.sapeins	Success	TRF2	58.85	148.71	OK	1.34	0.00264653	0.03	ENSG00000132604
H.sapeins	Success	TINF2	64.14	155.46	OK	1.28	0.0004375	0.01	ENSG00000092330
H.sapeins	Success	LMNA	728.67	1760.71	OK	1.27	0.00060452	0.01	ENSG00000160789
H.sapeins	Success	IL6ST	802.35	1893.37	OK	1.24	0.00130834	0.02	ENSG00000134352
H.sapeins	Success	ILK	200.31	447.69	OK	1.16	0.00028929	0.01	ENSG00000166333
H.sapeins	Success	NFE2L2	289.3	641.53	OK	1.15	0.00041826	0.01	ENSG00000116044
H.sapeins	Success	GNAQ	193.68	412.66	OK	1.09	0.00003029	0	ENSG00000156052
H.sapeins	Success	TOLLIP	94.34	199.13	OK	1.08	0.00270651	0.03	ENSG00000078902
H.sapeins	Success	TP53	104.43	3.07	OK	-5.09	0.00015963	0	ENSG00000141510

Supplementary Table S2. The list of Gene Ontology analysis using g:profiler.

source	term name	term id	adjusted p value	negative log10 of adjusted p value	term size	query size	intersection size	effective domain size	intersections
GO:MF	cytokine receptor binding	GO:0005126	1.11E-32	31.95480304	274	157	38	18602	IL8,VEGFA,CXCL1,IL1RN,IL1RAP,IL6R,LTB,CCL20,CXCL6,IL11,BID,MIF,SMAD6,CXCL10,CCL11,TRAF2,ITGB3,TNF,IL10,CCL3,TLR9,IL18,IL6,IL15,IL23A,SHC1,SMAD7,GREM1,IL1B,TRADD,IL7,CCL2,CSF1,MYD88,STAT1,TGFBR1,CCL4,RIPK1
GO:MF	cytokine activity	GO:0005125	1.46E-24	23.83619971	234	124	28	18602	IL8,TNFRSF11B,VEGFA,CXCL1,IL1RN,LTB,CCL20,CXCL6,HMGB1,IL11,MIF,CXCL10,CCL11,TIMP1,TNF,IL10,CCL3,IL18,EDN1,IL6,IL15,IL23A,INHBE,GREM1,IL1B,IL7,CCL2,CSF1
GO:MF	growth factor receptor binding	GO:0070851	1.65E-11	10.78302632	142	147	16	18602	VEGFA,IL1RN,IL1RAP,IL6R,IL11,ITGB3,IL10,TLR9,PDGFB,IL6,SHC1,GREM1,IL1B,IL7,MYD88,PDGFA
GO:MF	chemokine activity	GO:0008009	1.49E-07	6.828154857	49	153	9	18602	IL8,CXCL1,CCL20,CXCL6,CXCL10,CCL11,CCL3,CCL2,CCL4
GO:MF	chemokine receptor binding	GO:0042379	2.23E-07	6.651815285	71	153	10	18602	IL8,CXCL1,CCL20,CXCL6,CXCL10,CCL11,CCL3,CCL2,STAT1,CCL4
GO:MF	growth factor binding	GO:0019838	7.40E-07	6.130501336	137	149	12	18602	IL1RN,IL6R,IGFBP2,THBS1,ITGB3,COL1A2,PDGFB,SHC1,COL3A1,IGFBP7,PDGFA,TGFBR1
GO:MF	MAP kinase kinase kinase activity	GO:0004709	1.08E-06	5.9666473	26	157	7	18602	MAP3K9,RIPK2,RAF1,MAP3K7,MAP3K1,MAP3K5,RIPK1
GO:MF	tumor necrosis factor receptor superfamily binding	GO:0032813	5.10E-06	5.292652657	49	157	8	18602	LTB,BID,TRAF2,TNF,TRADD,MYD88,STAT1,RIPK1
GO:MF	chemoattractant activity	GO:0042056	8.94E-06	5.048537948	37	82	6	18602	VEGFA,HMGB1,MIF,CXCL10,CCL3,PDGFB
GO:MF	integrin binding	GO:0005178	1.59E-05	4.798039848	148	145	11	18602	ITGB6,HMGB1,ITGB8,THBS1,ITGB5,ITGB3,ITGB2,PTK2,IL1B,COL3A1,ITGA3
GO:MF	pattern recognition receptor activity	GO:0038187	5.24E-05	4.280323424	24	86	5	18602	NOD1,TLR7,NOD2,TLR9,TLR2
GO:MF	growth factor activity	GO:0008083	5.30E-05	4.275976885	164	147	11	18602	VEGFA,CXCL1,IL11,TIMP1,IL10,PDGFB,IL6,INHBE,IL7,CSF1,PDGFA
GO:MF	cytokine binding	GO:0019955	0.000101508	3.99349958	136	149	10	18602	IL1RN,IL6R,HMGB1,THBS1,TRAF2,ITGB3,CXCR4,GREM1,IL13RA2,TGFBR1
GO:MF	protease binding	GO:0002020	0.000140371	3.852723638	138	152	10	18602	SERPINE1,MIF,TIMP1,ITGB3,TNF,COL1A2,RIPK2,COL3A1,ITGA3,TNFAIP3
GO:MF	collagen binding	GO:0005518	0.000760797	3.118731472	68	147	7	18602	MMP9,THBS1,PDGFB,SERPINH1,SMAD7,ITGA3,PDGFA
GO:MF	protein	GO:0004712	0.00114396	2.941589052	45	151	6	18602	MAP3K9,AKT1,MAP2K6,MAP2K4,MAPKAPK5,

	serine/threonine/ tyrosine kinase activity								MAP2K1
GO:MF	CCR chemokine receptor binding	GO:0048020	0.001606353	2.794159108	47	153	6	18602	CCL20,CCL11,CCL3,CCL2,STAT1,CCL4
GO:MF	SMAD binding	GO:0046332	0.002123792	2.672887943	78	149	7	18602	SMAD6,PARP1,COL1A2,SMAD7,MEF2A,COL3A1,TGFBR1
GO:MF	tumor necrosis factor receptor binding	GO:0005164	0.003107085	2.507646807	32	144	5	18602	LTB,TRAF2,TNF,TRADD,STAT1
GO:MF	G protein-coupled receptor binding	GO:0001664	0.003877937	2.41139929	292	153	12	18602	IL8,CXCL1,CCL20,CXCL6,CXCL10,CCL11,CCL3,EDN1,CCL2,GNAS,STAT1,CCL4
GO:MF	ubiquitin protein ligase binding	GO:0031625	0.005397968	2.26776967	292	158	12	18602	BID,SMAD6,DAXX,CHEK2,TRAF2,CXCR4, SQSTM1,SMAD7,BECN1,RELA,RIPK1,CD40
GO:MF	protein N-terminus binding	GO:0047485	0.027731889	1.557020555	110	156	7	18602	TERT,DAXX,PARP1,GADD45A,RELA,MAP2K1, BIRC2
GO:MF	fibronectin binding	GO:0001968	0.038073203	1.419380581	27	145	4	18602	VEGFA,THBS1,ITGB3,ITGA3
GO:MF	histone acetyltransferase binding	GO:0035035	0.049554714	1.304915025	29	144	4	18602	CEBPB,MEF2A,CREB1,STAT1
GO:BP	positive regulation of MAP kinase activity	GO:0043406	1.83E-21	20.73814059	267	158	30	18017	VEGFA,GADD45G,MAP3K9,MIF,NOD1,THBS1, DAXX,TRAF2,TNF,NOD2,TLR9,CXCR4,RIPK2, GADD45A,RAF1,MAP2K6,PDGFB,EDN1, MAP2K4,SHC1,IL1B,MAP3K7,MAPKAPK5,PDGFA,TGFBR1,MAP2K1,MAP3K1,MAP3K5,RIPK1,CD40
GO:BP	leukocyte chemotaxis	GO:0030595	5.29E-21	20.27624951	233	124	26	18017	IL8,VEGFA,CXCL1,IL6R,CCL20,SERPINE1, CXCL6,HMGB1,MIF,CXCL10,ALOX5,THBS1, CCL11,IL10,CCL3,CXCR4,PDGFB,EDN1,IL6, ITGB2,IL23A,GREM1,PTK2,IL1B,CCL2,CSF1
GO:BP	myeloid leukocyte migration	GO:0097529	1.39E-19	18.85579351	225	129	25	18017	IL8,VEGFA,CXCL1,IL6R,CCL20,SERPINE1, CXCL6,HMGB1,MIF,CXCL10,THBS1,CCL11, CCL3,PDGFB,EDN1,IL6,ITGB2,IL23A,TREM2, GREM1,PTK2,IL1B,CCL2,CSF1,MYD88
GO:BP	positive regulation of NIK/NF-kappaB signaling	GO:1901224	4.83E-17	16.31643839	80	137	17	18017	HMGB1,NOD1,TLR7,TRAF2,TNF,NOD2,TLR9, IL18,EDN1,TLR2,IL23A,GREM1,IL1B,TLR3, TRADD,MAP3K7,RELA
GO:BP	cellular response tolipopolysaccharide	GO:0071222	9.38E-17	16.02785611	211	158	24	18017	IL8,CXCL1,SERPINE1,CXCL6,HMGB1,AKT1, MIF,CXCL10,TNF,IL10,CCL3,NOD2,RIPK2,IL18, IL6,TLR2,CEBPB,IL1B,CCL2,MYD88,RELA,IRF3, TNFAIP3,CD40
GO:BP	positive regulation	GO:0051091	2.55E-16	15.59399092	273	159	26	18017	VEGFA,IL1RAP,AKT1,NOD1,TRAF2,TNF,IL10,

	of DNA-binding transcription factor activity							NOD2,TLR9,RIPK2,IL18,EDN1,IL6,TLR2,ITGB2,GREM1,IL1B,TLR3,TRADD,MAP3K7,MYD88,RPS6KA5,RELA,RIPK1,CD40,ATF2
GO:BP	cellular response to molecule of bacterial origin	GO:0071219	3.89E-16	15.40996054	224	158	24	18017	IL8,CXCL1,SERPINE1,CXCL6,HMGB1,AKT1,MIF,CXCL10,TNF,IL10,CCL3,NOD2,RIPK2,IL18,IL6,TLR2,CEBPB,IL1B,CCL2,MYD88,RELA,IRF3,TNFAIP3,CD40
GO:BP	chemokine production	GO:0032602	8.10E-16	15.09154828	99	129	17	18017	IL6R,CXCL6,HMGB1,MIF,TLR7,TNF,IL10,TLR9,RIPK2,IL18,IL6,TLR2,TREM2,IL1B,TLR3,IL7,MYD88
GO:BP	defense response to virus	GO:0051607	1.46E-15	14.83487105	265	158	25	18017	IRF7,IRF1,OASL,CXCL10,BCL2L1,MX2,IRF5,TLR7,TLR9,IL6,IFIT1,IL15,IL23A,BECN1,IL1B,TLR3,STAT2,IFIT2,RELA,IRF3,STAT1,OAS2,TNFAIP3,BIRC2,CD40
GO:BP	regulation of NIK/NF-kappaB signaling	GO:1901222	1.69E-15	14.77332854	122	156	19	18017	HMGB1,NOD1,TLR7,TRAF2,TNF,NOD2,TLR9,IL18,EDN1,TLR2,IL23A,PRDX1,GREM1,IL1B,TLR3,TRADD,MAP3K7,RELA,BIRC2
GO:BP	cellular response to biotic stimulus	GO:0071216	4.70E-15	14.32813299	249	158	24	18017	IL8,CXCL1,SERPINE1,CXCL6,HMGB1,AKT1,MIF,CXCL10,TNF,IL10,CCL3,NOD2,RIPK2,IL18,IL6,TLR2,CEBPB,IL1B,CCL2,MYD88,RELA,IRF3,TNFAIP3,CD40
GO:BP	regulation of leukocyte migration	GO:0002685	7.55E-15	14.12230745	215	129	21	18017	IL8,VEGFA,IL6R,CCL20,SERPINE1,HMGB1,AKT1,MIF,CXCL10,THBS1,TNF,CCL3,EDN1,IL6,IL23A,TREM2,GREM1,PTK2,CCL2,CSF1,MYD88
GO:BP	regulation of chemokine production	GO:0032642	7.62E-15	14.11815194	92	129	16	18017	IL6R,CXCL6,HMGB1,MIF,TLR7,TNF,IL10,TLR9,RIPK2,IL6,TLR2,TREM2,IL1B,TLR3,IL7,MYD88
GO:BP	I-kappaB kinase/NF-kappaB signaling	GO:0007249	1.29E-14	13.88928588	290	158	25	18017	AKT1,HLA-DRB1,NOD1,TLR7,TRAF2,TNF,NOD2,TLR9,RIPK2,ROCK2,SQSTM1,TLR2,IL1B,TLR3,TRADD,MAP3K7,MYD88,RELA,IRF3,STAT1,RELB,TNFAIP3,BIRC2,RIPK1,CD40
GO:BP	positive regulation of JNK cascade	GO:0046330	2.43E-14	13.61505584	139	157	19	18017	GADD45G,HMGB1,MAP3K9,NOD1,DAXX,TRAF2,TNF,NOD2,TLR9,RIPK2,GADD45A,EDN1,MAP2K4,IL1B,TLR3,MAP3K7,MYD88,MAP3K5,RIPK1
GO:BP	regulation of stress-activated MAPK cascade	GO:0032872	2.49E-14	13.60446369	240	157	23	18017	VEGFA,GADD45G,HMGB1,MAP3K9,AKT1,NOD1,DAXX,TRAF2,TNF,NOD2,TLR9,RIPK2,GADD45A,EDN1,MAP2K4,PRDX1,IL1B,TLR3,MAP3K7,MYD88,MAP2K1,MAP3K5,RIPK1
GO:BP	NIK/NF-kappaB signaling	GO:0038061	2.63E-14	13.5796142	188	156	21	18017	HMGB1,AKT1,NOD1,TLR7,TRAF2,TNF,NOD2,TLR9,IL18,EDN1,TLR2,IL23A,PRDX1,GREM1,IL1B,TLR3,TRADD,MAP3K7,RELA,RELB,BIRC2
GO:BP	cellular response to interleukin-1	GO:0071347	2.75E-14	13.55988142	186	158	21	18017	IL8,IL1RN,IL1RAP,CCL20,NOD1,CCL11,CCL3,NOD2,RIPK2,EDN1,IL6,SQSTM1,CEBPB,IL1B,CCL2,MAP3K7,MYD88,RPS6KA5,RELA,CCL4,CD40
GO:BP	positive regulation of NF-kappaB	GO:0051092	3.24E-14	13.48879105	163	158	20	18017	IL1RAP,NOD1,TRAF2,TNF,NOD2,TLR9,RIPK2,IL18,TLR2,ITGB2,GREM1,IL1B,TLR3,TRADD,

	transcription factor activity								MAP3K7,MYD88,RPS6KA5,RELA,RIPK1,CD40
GO:BP	regulation of stress-activated protein kinase signaling cascade	GO:0070302	3.28E-14	13.48376201	243	157	23	18017	VEGFA,GADD45G,HMGB1,MAP3K9,AKT1,NOD1,DAXX,TRAF2,TNF,NOD2,TLR9,RIPK2,GADD45A,EDN1,MAP2K4,PRDX1,IL1B,TLR3,MAP3K7,MYD88,MAP2K1,MAP3K5,RIPK1
GO:BP	positive regulation of stress-activated MAPK cascade	GO:0032874	8.37E-14	13.07728309	172	157	20	18017	VEGFA,GADD45G,HMGB1,MAP3K9,NOD1,DAXX,TRAF2,TNF,NOD2,TLR9,RIPK2,GADD45A,EDN1,MAP2K4,IL1B,TLR3,MAP3K7,MYD88,MAP3K5,RIPK1
GO:BP	negative regulation of extrinsic apoptotic signaling pathway	GO:2001237	9.83E-14	13.00727386	107	157	17	18017	SERPINE1,TERT,AKT1,BCL2L1,THBS1,TRAF2,TNF,RAF1,GCLM,IL1B,TRADD,IL7,MCL1,RELA,TGFBR1,TNFAIP3,RIPK1
GO:BP	positive regulation of stress-activated protein kinase signaling cascade	GO:0070304	1.05E-13	12.97725448	174	157	20	18017	VEGFA,GADD45G,HMGB1,MAP3K9,NOD1,DAXX,TRAF2,TNF,NOD2,TLR9,RIPK2,GADD45A,EDN1,MAP2K4,IL1B,TLR3,MAP3K7,MYD88,MAP3K5,RIPK1
GO:BP	pattern recognition receptor signaling pathway	GO:0002221	2.07E-13	12.68449076	205	158	21	18017	HMGB1,IRF7,IRF1,NOD1,TLR7,NOD2,TLR9,RIPK2,MAP2K6,TLR2,ITGB2,TLR3,MAP3K7,MYD88,RELA,IRF3,TNFAIP3,MAP3K1,BIRC2,RIPK1,CD40
GO:BP	negative regulation of apoptotic signaling pathway	GO:2001234	2.41E-13	12.61868049	236	157	22	18017	PLAUR,MMP9,SERPINE1,TERT,AKT1,BID,MIF,BCL2L1,THBS1,TRAF2,TNF,SNAI1,RAF1,GCLM,IL1B,TRADD,IL7,MCL1,RELA,TGFBR1,TNFAIP3,RIPK1
GO:BP	mononuclear cell migration	GO:0071674	2.54E-13	12.59595659	96	153	16	18017	IL6R,CCL20,SERPINE1,HMGB1,CXCL10,THBS1,CCL11,TNF,CCL3,PDGFB,IL6,GREM1,PTK2,CCL2,CSF1,CCL4
GO:BP	regulation of JNK cascade	GO:0046328	3.55E-13	12.44933894	185	157	20	18017	GADD45G,HMGB1,MAP3K9,AKT1,NOD1,DAXX,TRAF2,TNF,NOD2,TLR9,RIPK2,GADD45A,EDN1,MAP2K4,IL1B,TLR3,MAP3K7,MYD88,MAP3K5,RIPK1
GO:BP	regulation of leukocyte chemotaxis	GO:0002688	4.37E-13	12.36000104	122	124	16	18017	IL8,VEGFA,IL6R,SERPINE1,HMGB1,MIF,CXCL10,THBS1,CCL3,EDN1,IL6,IL23A,GREM1,PTK2,CCL2,CSF1
GO:BP	response to interleukin-1	GO:0070555	5.50E-13	12.25986444	215	158	21	18017	IL8,IL1RN,IL1RAP,CCL20,NOD1,CCL11,CCL3,NOD2,RIPK2,EDN1,IL6,SQSTM1,CEBPB,IL1B,CCL2,MAP3K7,MYD88,RPS6KA5,RELA,CCL4,CD40
GO:BP	response to mechanical stimulus	GO:0009612	6.64E-13	12.17762244	217	158	21	18017	CHEK1,SLC2A1,IGFBP2,AKT1,IRF1,CXCL10,THBS1,TLR7,CXCR4,GADD45A,RAF1,EDN1,MAP2K4,IL1B,TLR3,MYD88,COL3A1,RELA,STAT1,MAP3K1,CD40
GO:BP	regulation of leukocyte proliferation	GO:0070663	8.63E-13	12.06394113	249	158	22	18017	BCL6,HMGB1,IGFBP2,HLA-DRB1,IRF1,MIF,IL10,TLR9,RIPK2,IL18,IL6,IL15,IL23A,

									GREM1,PTK2,CEBPB,IL1B,IL7,CSF1,MYD88,TNFAIP3,CD40
GO:BP	positive regulation of chemokine production	GO:0032722	1.13E-12	11.94756986	63	129	13	18017	IL6R,HMGB1,MIF,TLR7,TNF,TLR9,RIPK2,IL6,TLR2,IL1B,TLR3,IL7,MYD88
GO:BP	stress-activated MAPK cascade	GO:0051403	1.51E-12	11.82019677	289	157	23	18017	VEGFA,GADD45G,HMGB1,MAP3K9,AKT1,NOD1,DAXX,TRAF2,TNF,NOD2,TLR9,RIPK2,GADD45A,EDN1,MAP2K4,PRDX1,IL1B,TLR3,MAP3K7,MYD88,MAP2K1,MAP3K5,RIPK1
GO:BP	extrinsic apoptotic signaling pathway	GO:0097191	1.90E-12	11.7202381	230	157	21	18017	IL6R,SERPINE1,TERT,AKT1,BID,BCL2L1,THBS1,DAXX,TRAF2,TNF,RAF1,GCLM,IL1B,TLR3,TRADD,IL7,MCL1,RELA,TGFBR1,TNFAIP3,RIPK1
GO:BP	regulation of chemotaxis	GO:0050920	2.58E-12	11.58781402	226	124	19	18017	IL8,VEGFA,IL6R,SERPINE1,HMGB1,MIF,CXCL10,THBS1,CCL3,CXCR4,PDGFB,EDN1,IL6,IL23A,TREM2,GREM1,PTK2,CCL2,CSF1
GO:BP	interleukin-6 production	GO:0032635	3.48E-12	11.45880121	189	129	18	18017	IL1RAP,IL6R,HMGB1,NOD1,TLR7,TNF,IL10,NOD2,TLR9,RIPK2,IL18,IL6,TLR2,TREM2,CEBPB,IL1B,TLR3,MYD88
GO:BP	positive regulation of inflammatory response	GO:0050729	3.52E-12	11.45375418	160	129	17	18017	SERPINE1,TLR7,TNF,CCL3,NOD2,TLR9,IL18,IL6,TLR2,IL15,IL23A,TREM2,CEBPB,IL1B,TLR3,TRADD,MYD88
GO:BP	positive regulation of interleukin-8 production	GO:0032757	3.70E-12	11.43189283	57	157	13	18017	SERPINE1,HMGB1,TLR7,TNF,NOD2,TLR9,IL6,TLR2,IL1B,TLR3,MYD88,RELA,RIPK1
GO:BP	positive regulation of chemotaxis	GO:0050921	5.75E-12	11.24008359	143	124	16	18017	IL8,VEGFA,IL6R,SERPINE1,HMGB1,CXCL10,THBS1,CCL3,CXCR4,PDGFB,EDN1,IL6,IL23A,TREM2,PTK2,CSF1
GO:BP	JNK cascade	GO:0007254	6.14E-12	11.21200365	214	157	20	18017	GADD45G,HMGB1,MAP3K9,AKT1,NOD1,DAXX,TRAF2,TNF,NOD2,TLR9,RIPK2,GADD45A,EDN1,MAP2K4,IL1B,TLR3,MAP3K7,MYD88,MAP3K5,RIPK1
GO:BP	positive regulation of leukocyte migration	GO:0002687	6.44E-12	11.19140039	144	124	16	18017	IL8,VEGFA,IL6R,CCL20,SERPINE1,HMGB1,CXCL10,THBS1,TNF,CCL3,EDN1,IL6,IL23A,TREM2,PTK2,CSF1
GO:BP	regulation of extrinsic apoptotic signaling pathway	GO:2001236	6.88E-12	11.16261155	161	157	18	18017	SERPINE1,TERT,AKT1,BID,BCL2L1,THBS1,TRAF2,TNF,RAF1,GCLM,IL1B,TRADD,IL7,MCL1,RELA,TGFBR1,TNFAIP3,RIPK1
GO:BP	regulation of interleukin-12 production	GO:0032655	1.05E-11	10.98019209	61	158	13	18017	LTB,HMGB1,IRF1,THBS1,IRF5,IL10,TLR9,RIPK2,TLR2,IL23A,TLR3,RELA,CD40
GO:BP	interleukin-12 production	GO:0032615	1.64E-11	10.78414996	63	158	13	18017	LTB,HMGB1,IRF1,THBS1,IRF5,IL10,TLR9,RIPK2,TLR2,IL23A,TLR3,RELA,CD40
GO:BP	regulation of I-kappaB kinase/NF-kappaB signaling	GO:0043122	1.73E-11	10.76071644	255	158	21	18017	AKT1,HLA-DRB1,NOD1,TRAF2,TNF,NOD2,TLR9,RIPK2,SQSTM1,IL1B,TLR3,TRADD,MAP3K7,MYD88,RELA,IRF3,STAT1,TNFAIP3,BIRC2,RIPK1,CD40
GO:BP	regulation of interleukin-6 production	GO:0032675	1.93E-11	10.71402259	177	129	17	18017	IL1RAP,IL6R,HMGB1,NOD1,TLR7,TNF,IL10,NOD2,TLR9,RIPK2,IL6,TLR2,TREM2,CEBPB,IL1B,TLR3,MYD88
GO:BP	positive regulation of interleukin-6	GO:0032755	2.14E-11	10.6691742	99	129	14	18017	IL1RAP,IL6R,HMGB1,NOD1,TLR7,TNF,NOD2,

	production								TLR9,RIPK2,IL6,TLR2,IL1B,TLR3,MYD88
GO:BP	interleukin-8 production	GO:0032637	2.44E-11	10.6133955	102	157	15	18017	SERPINE1,HMGB1,NOD1,TLR7,TNF,IL10,NOD2,TLR9,IL6,TLR2,IL1B,TLR3,MYD88,RELA,RIPK1
GO:BP	regulation of type I interferon production	GO:0032479	2.56E-11	10.59246579	128	152	16	18017	HMGB1,IRF7,IRF1,IRF5,TLR7,IL10,TLR9,RIPK2,TLR2,TLR3,MYD88,RELA,IRF3,STAT1,RELB,TNFAIP3
GO:BP	cytokine production involved in immune response	GO:0002367	2.68E-11	10.57242675	108	120	14	18017	BCL6,MIF,TRAF2,TNF,IL10,NOD2,IL18,ATG5,IL6,TLR2,SMAD7,IL1B,TLR3,MAP3K7
GO:BP	granulocyte chemotaxis	GO:0071621	2.80E-11	10.55234019	130	124	15	18017	IL8,CXCL1,CCL20,CXCL6,CXCL10,THBS1,CCL11,CCL3,EDN1,ITGB2,IL23A,PTK2,IL1B,CCL2,CSF1
GO:BP	regulation of interferon-alpha production	GO:0032647	2.84E-11	10.54648774	29	144	10	18017	HMGB1,IRF7,IRF5,TLR7,IL10,TLR9,RIPK2,TLR3,IRF3,STAT1
GO:BP	type I interferon production	GO:0032606	3.28E-11	10.48413288	130	152	16	18017	HMGB1,IRF7,IRF1,IRF5,TLR7,IL10,TLR9,RIPK2,TLR2,TLR3,MYD88,RELA,IRF3,STAT1,RELB,TNFAIP3
GO:BP	granulocyte migration	GO:0097530	3.36E-11	10.47370783	154	153	17	18017	IL8,CXCL1,CCL20,CXCL6,CXCL10,THBS1,CCL11,CCL3,EDN1,ITGB2,IL23A,PTK2,IL1B,CCL2,CSF1,MYD88,CCL4
GO:BP	regulation of cytokine production involved in immune response	GO:0002718	3.68E-11	10.43451988	87	120	13	18017	BCL6,MIF,TRAF2,TNF,IL10,NOD2,IL18,ATG5,IL6,SMAD7,IL1B,TLR3,MAP3K7
GO:BP	interferon-alpha production	GO:0032607	6.21E-11	10.20714934	31	144	10	18017	HMGB1,IRF7,IRF5,TLR7,IL10,TLR9,RIPK2,TLR3,IRF3,STAT1
GO:BP	positive regulation of interleukin-12 production	GO:0032735	6.42E-11	10.19249141	40	158	11	18017	LTB,HMGB1,IRF1,IRF5,TLR9,RIPK2,TLR2,IL23A,TLR3,RELA,CD40
GO:BP	toll-like receptor signaling pathway	GO:0002224	6.43E-11	10.19164892	155	158	17	18017	HMGB1,IRF7,IRF1,TLR7,TLR9,RIPK2,TLR2,ITGB2,TLR3,MAP3K7,MYD88,IRF3,TNFAIP3,MAP3K1,BIRC2,RIPK1,CD40
GO:BP	positive regulation of cell-cell adhesion	GO:0022409	7.75E-11	10.11052936	284	119	19	18017	PLAUR,BCL6,HMGB1,IGFBP2,AKT1,ALOX5,TNF,IL10,NOD2,RIPK2,IL18,IL6,ITGB2,IL15,IL23A,SMAD7,IL1B,IL7,CCL2
GO:BP	activation of MAPK activity	GO:0000187	7.98E-11	10.09824267	158	157	17	18017	MAP3K9,NOD1,THBS1,DAXX,TNF,NOD2,CXCR4,RIPK2,MAP2K6,MAP2K4,SHC1,IL1B,MAP3K7,MAPKAPK5,MAP2K1,MAP3K5,RIPK1
GO:BP	positive regulation of type I interferon production	GO:0032481	9.23E-11	10.03495666	78	144	13	18017	HMGB1,IRF7,IRF1,IRF5,TLR7,TLR9,RIPK2,TLR2,TLR3,MYD88,RELA,IRF3,STAT1
GO:BP	regulation of mononuclear cell proliferation	GO:0032944	1.09E-10	9.962625094	230	129	18	18017	BCL6,HMGB1,IGFBP2,HLA-DRB1,IRF1,MIF,IL10,TLR9,RIPK2,IL18,IL6,IL15,IL23A,CEBPB,IL1B,IL7,CSF1,MYD88
GO:BP	positive regulation of I-kappaB kinase/NF-kappaB signaling	GO:0043123	1.30E-10	9.884723665	189	158	18	18017	AKT1,HLA-DRB1,NOD1,TRAF2,TNF,NOD2,TLR9,RIPK2,IL1B,TLR3,TRADD,MAP3K7,MYD88,RELA,IRF3,BIRC2,RIPK1,CD40
GO:BP	positive regulation of leukocyte chemotaxis	GO:0002690	1.52E-10	9.817997456	96	153	14	18017	IL8,VEGFA,IL6R,SERPINE1,HMGB1,CXCL10,THBS1,CCL3,EDN1,IL6,IL23A,PTK2,CSF1,CCL4

GO:BP	regulation of leukocyte differentiation	GO:1902105	1.58E-10	9.800378907	294	136	20	18017	BCL6,HMGB1,IRF7,HLA-DRB1,IRF1,TNF,CCL3,TLR9,RIPK2,IL18,IL15,IL23A,SMAD7,CEBPB,IL1B,TLR3,IL7,CSF1,GNAS,CREB1
GO:BP	positive regulation of interferon-alpha production	GO:0032727	1.60E-10	9.795861856	23	144	9	18017	HMGB1,IRF7,IRF5,TLR7,TLR9,RIPK2,TLR3,IRF3,STAT1
GO:BP	positive regulation of tumor necrosis factor production	GO:0032760	1.61E-10	9.792750281	94	157	14	18017	HMGB1,MIF,NOD1,THBS1,CCL3,NOD2,TLR9,RIPK2,IL6,TLR2,IL23A,TLR3,MYD88,RIPK1
GO:BP	regulation of interleukin-8 production	GO:0032677	1.61E-10	9.792750281	94	157	14	18017	SERPINE1,HMGB1,TLR7,TNF,IL10,NOD2,TLR9,IL6,TLR2,IL1B,TLR3,MYD88,RELA,RIPK1
GO:BP	positive regulation of interferon-beta production	GO:0032728	1.68E-10	9.775939296	34	143	10	18017	HMGB1,IRF7,IRF1,IRF5,TLR7,TLR9,RIPK2,TLR2,TLR3,IRF3
GO:BP	lipopolysaccharide-mediated signaling pathway	GO:0031663	1.72E-10	9.763496873	60	152	12	18017	AKT1,MIF,TNF,CCL3,RIPK2,IL18,TLR2,IL1B,CCL2,MYD88,IRF3,TNFAIP3
GO:BP	positive regulation of tumor necrosis factor superfamily cytokine production	GO:1903557	2.18E-10	9.661526743	96	157	14	18017	HMGB1,MIF,NOD1,THBS1,CCL3,NOD2,TLR9,RIPK2,IL6,TLR2,IL23A,TLR3,MYD88,RIPK1
GO:BP	regulation of response to cytokine stimulus	GO:0060759	2.40E-10	9.61967945	197	157	18	18017	IL1RN,IRF7,TRAF2,TNF,CXCR4,RIPK2,EDN1,IL6,TLR2,TREM2,TRADD,IL7,CSF1,IRF3,STAT1,TNFAIP3,BIRC2,RIPK1
GO:BP	regulation of smooth muscle cell proliferation	GO:0048660	3.21E-10	9.493351979	174	155	17	18017	MMP9,IL6R,TERT,AKT1,THBS1,TNF,IL10,IL18,PDGFB,EDN1,IL6,IL15,MYD88,PTGIR,STAT1,TNFAIP3,MAP3K5
GO:BP	smooth muscle cell proliferation	GO:0048659	3.88E-10	9.411196135	176	155	17	18017	MMP9,IL6R,TERT,AKT1,THBS1,TNF,IL10,IL18,PDGFB,EDN1,IL6,IL15,MYD88,PTGIR,STAT1,TNFAIP3,MAP3K5
GO:BP	positive regulation of smooth muscle cell proliferation	GO:0048661	4.98E-10	9.30282227	103	155	14	18017	MMP9,IL6R,TERT,AKT1,THBS1,TNF,IL10,IL18,PDGFB,EDN1,IL6,MYD88,STAT1,MAP3K5
GO:BP	monocyte chemotaxis	GO:0002548	6.28E-10	9.201721621	66	153	12	18017	IL6R,CCL20,SERPINE1,HMGB1,CXCL10,CCL11,CCL3,PDGFB,IL6,GREM1,CCL2,CCL4
GO:BP	regulation of production of molecular mediator of immune response	GO:0002700	6.54E-10	9.184188292	151	158	16	18017	BCL6,MIF,TRAF2,TNF,IL10,NOD2,TLR9,IL18,ATG5,IL6,SMAD7,IL1B,TLR3,MAP3K7,IL13RA2,CD40
GO:BP	I-kappaB phosphorylation	GO:0007252	7.50E-10	9.124710363	20	120	8	18017	AKT1,TLR7,TRAF2,TNF,TLR9,TLR2,TLR3,MAP3K7
GO:BP	positive regulation of leukocyte proliferation	GO:0070665	8.54E-10	9.06841753	157	129	15	18017	BCL6,HMGB1,IGFBP2,MIF,TLR9,RIPK2,IL18,IL6,IL15,IL23A,PTK2,IL1B,IL7,CSF1,MYD88
GO:BP	regulation of interferon-beta production	GO:0032648	8.63E-10	9.06389883	52	150	11	18017	HMGB1,IRF7,IRF1,IRF5,TLR7,TLR9,RIPK2,TLR2,TLR3,IRF3,RELB
GO:BP	regulation of cytokine-mediated signaling pathway	GO:0001959	9.99E-10	9.000613195	184	157	17	18017	IL1RN,IRF7,TRAF2,TNF,CXCR4,RIPK2,EDN1,IL6,TREM2,TRADD,IL7,CSF1,IRF3,STAT1,TNFAIP3,BIRC2,RIPK1
GO:BP	myeloid leukocyte differentiation	GO:0002573	1.00E-09	8.998728662	214	157	18	18017	VEGFA,MMP9,IRF7,HLA-DRB1,PARP1,TNF,CCL3,TLR2,IL15,IL23A,TREM2,CEBPB,TLR3,CSF1,GNAS,CREB1,RELB,RIPK1

GO:BP	muscle cell proliferation	GO:0033002	1.08E-09	8.96476521	247	157	19	18017	MMP9,IL6R,TERT,AKT1,THBS1,TNF,IL10,IL18,PDGFB,EDN1,IL6,IL15,MYD88,PTGIR,STAT1,TGFBR1,TNFAIP3,MAP3K5,RIPK1
GO:BP	regulation of lymphocyte proliferation	GO:0050670	1.27E-09	8.89698797	228	129	17	18017	BCL6,HMGB1,IGFBP2,HLA-DRB1,IRF1,MIF,IL10,TLR9,RIPK2,IL18,IL6,IL15,IL23A,CEBPB,IL1B,IL7,MYD88
GO:BP	interferon-beta production	GO:0032608	1.35E-09	8.870115298	54	150	11	18017	HMGB1,IRF7,IRF1,IRF5,TLR7,TLR9,RIPK2,TLR2,TLR3,IRF3,RELB
GO:BP	regulation of adaptive immune response	GO:0002819	2.62E-09	8.582189482	165	158	16	18017	BCL6,HMGB1,IRF7,IRF1,TRAF2,TNF,IL10,RIPK2,IL18,IL6,IL23A,SMAD7,IL1B,MAP3K7,TNFAIP3,CD40
GO:BP	regulation of peptidyl-tyrosine phosphorylation	GO:0050730	3.01E-09	8.522059712	266	117	17	18017	VEGFA,IL6R,IL11,MIF,ITGB3,TNF,RIPK2,IL18,PDGFB,IL6,ITGB2,IL15,IL23A,SHC1,TREM2,GREM1,IL7
GO:BP	response to interferon-gamma	GO:0034341	3.67E-09	8.434875729	198	158	17	18017	CCL20,IRF7,HLA-DRB1,IRF1,OASL,IRF5,CCL11,CCL3,EDN1,TLR2,TLR3,CCL2,IRF3,STAT1,OAS2,CCL4,CD40
GO:BP	regulation of tumor necrosis factor production	GO:0032680	4.13E-09	8.384494845	171	157	16	18017	HMGB1,MIF,NOD1,THBS1,IL10,CCL3,NOD2,TLR9,RIPK2,IL6,TLR2,IL23A,TLR3,MYD88,TNFAIP3,RIPK1
GO:BP	positive regulation of response to cytokine stimulus	GO:0060760	4.21E-09	8.376194072	57	157	11	18017	IRF7,TRAF2,CXCR4,RIPK2,EDN1,TLR2,TREM2,IL7,CSF1,IRF3,RIPK1
GO:BP	positive regulation of mononuclear cell proliferation	GO:0032946	4.24E-09	8.372920037	144	129	14	18017	BCL6,HMGB1,IGFBP2,MIF,TLR9,RIPK2,IL18,IL6,IL15,IL23A,IL1B,IL7,CSF1,MYD88
GO:BP	cellular response to interferon-gamma	GO:0071346	5.14E-09	8.28936624	178	153	16	18017	CCL20,IRF7,HLA-DRB1,IRF1,OASL,IRF5,CCL11,CCL3,EDN1,TLR2,TLR3,CCL2,IRF3,STAT1,OAS2,CCL4
GO:BP	regulation of nitric-oxide synthase biosynthetic process	GO:0051769	5.31E-09	8.274552979	21	144	8	18017	NOD2,TLR9,MAP2K6,EDN1,TLR2,MAP2K4,CCL2,STAT1
GO:BP	nitric-oxide synthase biosynthetic process	GO:0051767	5.31E-09	8.274552979	21	144	8	18017	NOD2,TLR9,MAP2K6,EDN1,TLR2,MAP2K4,CCL2,STAT1
GO:BP	regulation of tumor necrosis factor superfamily cytokine production	GO:1903555	5.40E-09	8.267730581	174	157	16	18017	HMGB1,MIF,NOD1,THBS1,IL10,CCL3,NOD2,TLR9,RIPK2,IL6,TLR2,IL23A,TLR3,MYD88,TNFAIP3,RIPK1
GO:BP	positive regulation of vasculature development	GO:1904018	6.88E-09	8.162380512	245	114	16	18017	IL8,VEGFA,IL6R,SERPINE1,TERT,HMGB1,ITGB8,THBS1,CCL11,IL10,CXCR4,PDGFB,ITGB2,GREM1,IL1B,TLR3
GO:BP	tumor necrosis factor production	GO:0032640	7.03E-09	8.153228443	177	157	16	18017	HMGB1,MIF,NOD1,THBS1,IL10,CCL3,NOD2,TLR9,RIPK2,IL6,TLR2,IL23A,TLR3,MYD88,TNFAIP3,RIPK1
GO:BP	neutrophil migration	GO:1990266	7.05E-09	8.152047727	126	153	14	18017	IL8,CXCL1,CCL20,CXCL6,CXCL10,CCL11,CCL3,EDN1,ITGB2,IL23A,IL1B,CCL2,MYD88,CCL4
GO:BP	regulation of leukocyte mediated immunity	GO:0002703	7.55E-09	8.122141344	207	158	17	18017	BCL6,CXCL6,HMGB1,TRAF2,TNF,IL10,NOD2,IL18,IL6,ITGB2,IL23A,SMAD7,IL1B,TLR3,MAP3K7,IL13RA2,CD40
GO:BP	positive regulation of ERK1 and ERK2 cascade	GO:0070374	7.63E-09	8.117401784	214	153	17	18017	CCL20,HMGB1,HLA-DRB1,MIF,NOD1,CCL11,TNF,CCL3,NOD2,RIPK2,PDGFB,SHC1,TREM2,

									CCL2,PDGFA,MAP2K1,CCL4
GO:BP	positive regulation of leukocyte cell-cell adhesion	GO:1903039	7.89E-09	8.103181083	240	137	17	18017	BCL6,HMGB1,IGFBP2,AKT1,ALOX5,TNF,NOD2,RIPK2,IL18,IL6,ITGB2,IL15,IL23A,IL1B,IL7,CCL2,RELA
GO:BP	macrophage activation	GO:0042116	7.97E-09	8.098729225	108	114	12	18017	HMGB1,MIF,THBS1,TLR7,TNF,IL10,CCL3,IL6,TLR2,ITGB2,TREM2,TLR3
GO:BP	mononuclear cell proliferation	GO:0032943	8.55E-09	8.067826902	297	129	18	18017	BCL6,HMGB1,IGFBP2,HLA-DRB1,IRF1,MIF,IL10,TLR9,RIPK2,IL18,IL6,IL15,IL23A,CEBPB,IL1B,IL7,CSF1,MYD88
GO:BP	neuroinflammatory response	GO:0150076	9.14E-09	8.039265065	83	114	11	18017	MMP9,TLR7,TNF,CCL3,IL18,IL6,TLR2,ITGB2,TREM2,IL1B,TLR3
GO:BP	cellular response to mechanical stimulus	GO:0071260	1.02E-08	7.991927579	80	158	12	18017	CHEK1,SLC2A1,AKT1,IRF1,TLR7,GADD45A,MAP2K4,IL1B,TLR3,MYD88,MAP3K1,CD40
GO:BP	neutrophil chemotaxis	GO:0030593	1.07E-08	7.97247216	106	119	12	18017	IL8,CXCL1,CCL20,CXCL6,CXCL10,CCL11,CCL3,EDN1,ITGB2,IL23A,IL1B,CCL2
GO:BP	tumor necrosis factor superfamily cytokine production	GO:0071706	1.08E-08	7.967204353	182	157	16	18017	HMGB1,MIF,NOD1,THBS1,IL10,CCL3,NOD2,TLR9,RIPK2,IL6,TLR2,IL23A,TLR3,MYD88,TNFAIP3,RIPK1
GO:BP	positive regulation of peptidyl-tyrosine phosphorylation	GO:0050731	1.87E-08	7.728253319	196	106	14	18017	VEGFA,IL6R,IL11,MIF,ITGB3,TNF,RIPK2,IL18,PDGFB,IL6,IL15,IL23A,TREM2,GREM1
GO:BP	chemokine-mediated signaling pathway	GO:0070098	1.94E-08	7.711264471	87	153	12	18017	IL8,CXCL1,CCL20,CXCL6,CXCL10,CCL11,CCL3,CXCR4,EDN1,TREM2,CCL2,CCL4
GO:BP	positive regulation of cytokine-mediated signaling pathway	GO:0001961	3.00E-08	7.522757936	50	157	10	18017	IRF7,TRAF2,CXCR4,RIPK2,EDN1,TREM2,IL7,CSF1,IRF3,RIPK1
GO:BP	type I interferon signaling pathway	GO:0060337	3.25E-08	7.48822372	95	146	12	18017	IRF7,IRF1,OASL,MX2,IRF5,IFIT1,STAT2,MYD88,IFIT2,IRF3,STAT1,OAS2
GO:BP	cellular response to type I interferon	GO:0071357	3.25E-08	7.48822372	95	146	12	18017	IRF7,IRF1,OASL,MX2,IRF5,IFIT1,STAT2,MYD88,IFIT2,IRF3,STAT1,OAS2
GO:BP	interleukin-1-mediated signaling pathway	GO:0070498	5.11E-08	7.291938884	105	137	12	18017	IL1RN,IL1RAP,NOD1,NOD2,RIPK2,IL6,SQSTM1,IL1B,MAP3K7,MYD88,RPS6KA5,RELA
GO:BP	response to type I interferon	GO:0034340	5.35E-08	7.272019501	99	146	12	18017	IRF7,IRF1,OASL,MX2,IRF5,IFIT1,STAT2,MYD88,IFIT2,IRF3,STAT1,OAS2
GO:BP	positive regulation of lymphocyte proliferation	GO:0050671	6.22E-08	7.206454912	143	158	14	18017	BCL6,HMGB1,IGFBP2,MIF,TLR9,RIPK2,IL18,IL6,IL15,IL23A,IL1B,IL7,MYD88,CD40
GO:BP	cellular response to chemokine	GO:1990869	6.41E-08	7.192858259	96	153	12	18017	IL8,CXCL1,CCL20,CXCL6,CXCL10,CCL11,CCL3,CXCR4,EDN1,TREM2,CCL2,CCL4
GO:BP	response to chemokine	GO:1990868	6.41E-08	7.192858259	96	153	12	18017	IL8,CXCL1,CCL20,CXCL6,CXCL10,CCL11,CCL3,CXCR4,EDN1,TREM2,CCL2,CCL4
GO:BP	lymphocyte proliferation	GO:0046651	7.42E-08	7.129500426	294	129	17	18017	BCL6,HMGB1,IGFBP2,HLA-DRB1,IRF1,MIF,IL10,TLR9,RIPK2,IL18,IL6,IL15,IL23A,CEBPB,IL1B,IL7,MYD88
GO:BP	regulation of cysteine-type endopeptidase activity	GO:2000116	8.26E-08	7.083143631	242	157	17	18017	BIRC5,VEGFA,PLAUR,MMP9,HMGB1,AKT1,BID,NOD1,THBS1,TRAF2,TNF,RIPK2,RAF1,TRADD,MAP3K5,BIRC2,RIPK1
GO:BP	positive regulation of JUN kinase activity	GO:0043507	8.39E-08	7.076126763	74	157	11	18017	MAP3K9,DAXX,TRAF2,TNF,TLR9,RIPK2,EDN1,MAP2K4,MAP3K7,MAP3K5,RIPK1
GO:BP	regulation of response to wounding	GO:1903034	1.03E-07	6.98809403	185	152	15	18017	PLAUR,SERPINE1,HMGB1,PLAU,ALOX5,THBS1,

									TNF,IL10,CXCR4,PDGFB,EDN1,PTK2,PDGFA, MAP2K1,TNFAIP3
GO:BP	regulation of adaptive immune response based on somatic recombination of immune receptors built from immunoglobulin superfamily domains	GO:0002822	1.19E-07	6.924962155	150	158	14	18017	BCL6,HMGB1,TRAF2,TNF,IL10,RIPK2,IL18,IL6, IL23A,SMAD7,IL1B,MAP3K7,TNFAIP3,CD40
GO:BP	cell-matrix adhesion	GO:0007160	1.34E-07	6.871752101	233	145	16	18017	VEGFA,BCL6,ITGB6,SERPINE1,PLAU,ITGB8, THBS1,ITGB5,ITGB3,ROCK2,ITGB2,GREM1, PTK2,CSF1,COL3A1,ITGA3
GO:BP	regulation of interferon-gamma production	GO:0032649	1.55E-07	6.810928209	107	114	11	18017	HMGB1,HLA-DRB1,TLR7,TNF,IL10,TLR9,RIPK2,IL18,IL23A,IL1B,TLR3
GO:BP	regulation of cysteine-type endopeptidase activity involved in apoptotic process	GO:0043281	1.66E-07	6.779348851	218	157	16	18017	BIRC5,VEGFA,PLAUR,MMP9,HMGB1,AKT1, BID,NOD1,THBS1,TRAF2,TNF,RAF1,TRADD, MAP3K5,BIRC2,RIPK1
GO:BP	positive regulation of angiogenesis	GO:0045766	1.77E-07	6.752219716	215	114	14	18017	IL8,VEGFA,SERPINE1,TERT,HMGB1,ITGB8,THBS1,CCL11,IL10,CXCR4,ITGB2,GREM1,IL1B,TLR3
GO:BP	positive regulation of leukocyte differentiation	GO:1902107	2.60E-07	6.584673518	160	157	14	18017	BCL6,HMGB1,HLA-DRB1,TNF,RIPK2,IL18,IL15, IL23A,IL1B,IL7,CSF1,GNAS,CREB1,RIPK1
GO:BP	interferon-gamma production	GO:0032609	5.41E-07	6.267084638	120	114	11	18017	HMGB1,HLA-DRB1,TLR7,TNF,IL10,TLR9,RIPK2,IL18,IL23A,IL1B,TLR3
GO:BP	glial cell activation	GO:0061900	5.84E-07	6.233308878	65	114	9	18017	TLR7,TNF,CCL3,IL6,TLR2,ITGB2,TREM2,IL1B, TLR3
GO:BP	response to reactive oxygen species	GO:0000302	6.12E-07	6.212971637	238	157	16	18017	MMP9,FANCC,AKT1,TRAF2,TNF,IL10,LDHA, EDN1,IL6,PRDX1,TXN,RELA,STAT1,TNFAIP3, MAP3K5,RIPK1
GO:BP	regulation of JUN kinase activity	GO:0043506	6.56E-07	6.18334697	89	157	11	18017	MAP3K9,DAXX,TRAF2,TNF,TLR9,RIPK2,EDN1,MAP2K4,MAP3K7,MAP3K5,RIPK1
GO:BP	extrinsic apoptotic signaling pathway via death domain receptors	GO:0008625	6.56E-07	6.18334697	89	157	11	18017	SERPINE1,BID,BCL2L1,THBS1,DAXX,TRAF2, TNF,RAF1,TRADD,TNFAIP3,RIPK1
GO:BP	positive regulation of hemopoiesis	GO:1903708	6.97E-07	6.15706744	205	157	15	18017	BCL6,HMGB1,HLA-DRB1,TNF,RIPK2,IL18,IL15, IL23A,IL1B,IL7,CSF1,GNAS,CREB1,STAT1,RIPK1
GO:BP	cytoplasmic pattern recognition receptor signaling pathway	GO:0002753	6.98E-07	6.156398973	68	156	10	18017	IRF7,NOD1,NOD2,RIPK2,MAP2K6,MAP3K7, RELA,IRF3,TNFAIP3,BIRC2
GO:BP	reactive oxygen species metabolic process	GO:0072593	7.32E-07	6.135665434	288	113	15	18017	FANCC,AKT1,ALOX5,THBS1,TNF,IL10, GADD45A,ROCK2,ATG5,PDGFB,EDN1,TLR2, ITGB2,PRDX1,IL1B
GO:BP	regulation of wound healing	GO:0061041	1.09E-06	5.962773301	152	152	13	18017	PLAUR,SERPINE1,HMGB1,PLAU,ALOX5,THBS1,TNF,CXCR4,PDGFB,EDN1,PTK2,PDGFA,TNFAIP3
GO:BP	negative regulation of signal transduction in absence of ligand	GO:1901099	1.12E-06	5.952322771	35	157	8	18017	TERT,AKT1,BCL2L1,TNF,IL1B,IL7,MCL1,RIPK1
GO:BP	negative regulation of extrinsic apoptotic signaling pathway in absence of ligand	GO:2001240	1.12E-06	5.952322771	35	157	8	18017	TERT,AKT1,BCL2L1,TNF,IL1B,IL7,MCL1,RIPK1
GO:BP	intrinsic apoptotic signaling pathway	GO:0097193	1.47E-06	5.833263204	295	155	17	18017	PLAUR,MMP9,AKT1,BID,MIF,BCL2L1,CHEK2,

									TRAF2,PARP1,TNF,SNAI1,BECN1,CEBPB, RAD9A,ATF4,MCL1,MAP3K5
GO:BP	MyD88-dependent toll-like receptor signaling pathway	GO:0002755	1.55E-06	5.810493878	37	154	8	18017	IRF7,IRF1,TLR7,TLR9,TLR2,MAP3K7,MYD88, MAP3K1
GO:BP	nucleotide-binding oligomerization domain containing signaling pathway	GO:0070423	1.71E-06	5.765866597	37	156	8	18017	NOD1,NOD2,RIPK2,MAP2K6,MAP3K7,RELA, TNFAIP3,BIRC2
GO:BP	regulation of T cell proliferation	GO:0042129	1.99E-06	5.701679522	174	113	12	18017	HMGB1,IGFBP2,HLA-DRB1,IRF1,IL10,RIPK2, IL18,IL6,IL15,IL23A,CEBPB,IL1B
GO:BP	nucleotide-binding domain, leucine rich repeat containing receptor signaling pathway	GO:0035872	2.16E-06	5.666384351	38	156	8	18017	NOD1,NOD2,RIPK2,MAP2K6,MAP3K7,RELA, TNFAIP3,BIRC2
GO:BP	epithelial cell apoptotic process	GO:1904019	2.33E-06	5.63264801	126	158	12	18017	SERPINE1,TERT,BID,BCL2L1,THBS1,TNF,IL10, IL6,CCL2,TNFAIP3,MAP3K5,CD40
GO:BP	regulation of phagocytosis	GO:0050764	2.36E-06	5.627705552	100	119	10	18017	C2,HMGB1,TNF,ATG5,TLR2,IL15,TREM2,ATG3, IL1B,CCL2
GO:BP	positive regulation of neuron death	GO:1901216	2.68E-06	5.571828111	100	159	11	18017	DAXX,PARP1,TNF,CCL3,ITGB2,MAP2K4,ELK1,ATF4,MCL1,MAP3K5,ATF2
GO:BP	cellular response to radiation	GO:0071478	3.59E-06	5.444442988	193	132	13	18017	CHEK1,MMP9,BLM,RAD51,BCL2L1,CHEK2, TIMP1,PARP1,ATR,GADD45A,ELK1,RAD9A,ATF4
GO:BP	T-helper cell differentiation	GO:0042093	3.77E-06	5.423470008	61	150	9	18017	BCL6,IL6R,HMGB1,RIPK2,IL18,IL6,IL23A, SMAD7,RELB
GO:BP	angiogenesis involved in wound healing	GO:0060055	3.93E-06	5.406055975	31	70	6	18017	VEGFA,SERPINE1,ALOX5,ITGB3,TNF,CXCR4
GO:BP	microglial cell activation	GO:0001774	3.97E-06	5.40141495	55	114	8	18017	TLR7,TNF,CCL3,IL6,TLR2,ITGB2,TREM2,TLR3
GO:BP	leukocyte activation involved in inflammatory response	GO:0002269	3.97E-06	5.40141495	55	114	8	18017	TLR7,TNF,CCL3,IL6,TLR2,ITGB2,TREM2,TLR3
GO:BP	positive regulation of T cell activation	GO:0050870	4.63E-06	5.334092144	219	119	13	18017	BCL6,HMGB1,IGFBP2,AKT1,NOD2,RIPK2,IL18, IL6,IL15,IL23A,IL1B,IL7,CCL2
GO:BP	regulation of mononuclear cell migration	GO:0071675	4.88E-06	5.311897964	52	124	8	18017	SERPINE1,HMGB1,CXCL10,THBS1,TNF,GREM1, PTK2,CSF1
GO:BP	CD4-positive, alpha-beta T cell differentiation involved in immune response	GO:0002294	5.08E-06	5.294542254	63	150	9	18017	BCL6,IL6R,HMGB1,RIPK2,IL18,IL6,IL23A, SMAD7,RELB
GO:BP	negative regulation of wound healing	GO:0061045	5.40E-06	5.267205931	78	83	8	18017	PLAUR,SERPINE1,PLAU,ALOX5,THBS1,TNF, PDGFB,EDN1
GO:BP	regulation of reactive oxygen species metabolic process	GO:2000377	5.63E-06	5.249421043	202	157	14	18017	AKT1,ALOX5,THBS1,TNF,IL10,GADD45A, ROCK2,ATG5,PDGFB,EDN1,ITGB2,IL1B,BIRC2, RIPK1
GO:BP	alpha-beta T cell activation involved in immune response	GO:0002287	5.86E-06	5.231792276	64	150	9	18017	BCL6,IL6R,HMGB1,RIPK2,IL18,IL6,IL23A, SMAD7,RELB
GO:BP	alpha-beta T cell differentiation involved in immune response	GO:0002293	5.86E-06	5.231792276	64	150	9	18017	BCL6,IL6R,HMGB1,RIPK2,IL18,IL6,IL23A, SMAD7,RELB
GO:BP	cellular response to reactive oxygen species	GO:0034614	6.94E-06	5.158689673	171	157	13	18017	MMP9,FANCC,AKT1,TRAF2,TNF,IL10,IL6, PRDX1,TXN,RELA,TNFAIP3,MAP3K5,RIPK1

GO:BP	response to acid chemical	GO:0001101	7.77E-06	5.109518507	139	159	12	18017	VEGFA,BCL2L1,TNF,COL1A2,EDN1,CFL1, GCLM,CEBPB,COL3A1,CREB1,RELA,ATF2
GO:BP	negative regulation of cysteine-type endopeptidase activity involved in apoptotic process	GO:0043154	8.75E-06	5.057858945	87	79	8	18017	BIRC5,VEGFA,PLAUR,MMP9,AKT1,THBS1,TNF,RAF1
GO:BP	regulation of endothelial cell proliferation	GO:0001936	9.54E-06	5.020638114	185	149	13	18017	VEGFA,HMGB1,AKT1,ALOX5,THBS1,CCL11, ITGB3,TNF,IL10,PDGFB,CCL2,STAT1,TGFBR1
GO:BP	regulation of lymphocyte mediated immunity	GO:0002706	9.54E-06	5.020614181	149	120	11	18017	BCL6,HMGB1,TRAF2,TNF,IL10,IL18,IL6,IL23A, SMAD7,IL1B,MAP3K7
GO:BP	regulation of peptidyl-serine phosphorylation	GO:0033135	9.70E-06	5.013148095	148	121	11	18017	VEGFA,IL11,AKT1,MIF,TNF,RIPK2,GADD45A, RAF1,IL6,SMAD7,TXN
GO:BP	regulation of extrinsic apoptotic signaling pathway in absence of ligand	GO:2001239	1.14E-05	4.942736043	46	157	8	18017	TERT,AKT1,BCL2L1,TNF,IL1B,IL7,MCL1,RIPK1
GO:BP	T cell proliferation	GO:0042098	1.22E-05	4.9153055	204	113	12	18017	HMGB1,IGFBP2,HLA-DRB1,IRF1,IL10,RIPK2, IL18,IL6,IL15,IL23A,CEBPB,IL1B
GO:BP	regulation of ossification	GO:0030278	1.51E-05	4.819732363	214	134	13	18017	IL6R,SMAD6,ALOX5,TNF,CCL3,IL6,SMAD7, GREM1,PTK2,CEBPB,CSF1,ATF4,GNAS
GO:BP	macrophage differentiation	GO:0030225	1.63E-05	4.78892187	48	157	8	18017	VEGFA,MMP9,HLA-DRB1,PARP1,TLR2,IL15, CSF1,RIPK1
GO:BP	positive regulation of apoptotic signaling pathway	GO:2001235	1.69E-05	4.772473322	184	157	13	18017	PLAUR,MMP9,BID,BCL2L1,THBS1,TRAF2,TNF,GZMB,BECN1,RAD9A,MCL1,TGFBR1,RIPK1
GO:BP	T cell differentiation involved in immune response	GO:0002292	1.71E-05	4.766305015	72	150	9	18017	BCL6,IL6R,HMGB1,RIPK2,IL18,IL6,IL23A, SMAD7,RELB
GO:BP	negative regulation of cysteine-type endopeptidase activity	GO:2000117	1.77E-05	4.751964698	95	79	8	18017	BIRC5,VEGFA,PLAUR,MMP9,AKT1,THBS1,TNF,RAF1
GO:BP	neuron apoptotic process	GO:0051402	1.82E-05	4.739224846	258	135	14	18017	BIRC5,TERT,BID,BCL2L1,PARP1,TNF,IL10, CCL3,MAP2K4,GCLM,CEBPB,CCL2,ATF4,MCL1
GO:BP	endothelial cell apoptotic process	GO:0072577	1.84E-05	4.735621469	69	158	9	18017	SERPINE1,TERT,THBS1,TNF,IL10,CCL2, TNFAIP3,MAP3K5,CD40
GO:BP	response to ketone	GO:1901654	1.94E-05	4.711604905	206	142	13	18017	CA9,AKT1,BCL2L1,THBS1,PARP1,PTGER2, ROCK2,EDN1,TLR2,ELK1,GNAS,RELA,IGFBP7
GO:BP	positive regulation of gliogenesis	GO:0014015	1.99E-05	4.700062134	80	137	9	18017	TNF,CCL3,CXCR4,IL6,TLR2,TREM2,IL1B,CSF1, RELA
GO:BP	positive regulation of interleukin-1 beta production	GO:0032731	2.17E-05	4.663717795	59	84	7	18017	HMGB1,NOD1,TNF,CCL3,NOD2,RIPK2,IL6
GO:BP	positive regulation of immune effector process	GO:0002699	2.18E-05	4.661332752	223	158	14	18017	MIF,TRAF2,TNF,NOD2,TLR9,RIPK2,IL18,IL6, ITGB2,IL23A,IL1B,MAP3K7,IL13RA2,CD40
GO:BP	negative regulation of response to wounding	GO:1903035	2.22E-05	4.653530624	93	83	8	18017	PLAUR,SERPINE1,PLAU,ALOX5,THBS1,TNF, PDGFB,EDN1
GO:BP	cytokine secretion	GO:0050663	2.25E-05	4.648602659	129	86	9	18017	ITGB6,HMGB1,MIF,TNF,IL10,NOD2,TLR9,IL6, TLR2
GO:BP	positive regulation of interferon-gamma	GO:0032729	2.25E-05	4.647733584	68	114	8	18017	TLR7,TNF,TLR9,RIPK2,IL18,IL23A,IL1B,TLR3

	production							
GO:BP	response to muramyl dipeptide	GO:0032495	2.39E-05	4.621279446	20	152	6	18017	NOD1,IRF5,NOD2,RIPK2,RELA,TNFAIP3
GO:BP	regulation of myeloid leukocyte differentiation	GO:0002761	2.55E-05	4.594290423	125	157	11	18017	IRF7,HLA-DRB1,TNF,CCL3,IL23A,CEBPB,TLR3,CSF1,GNAS,CREB1,RIPK1
GO:BP	negative regulation of neuron death	GO:1901215	2.67E-05	4.573643499	221	136	13	18017	BIRC5,TERT,AKT1,BCL2L1,TRAF2,IL10,MAP2K4,GCLM,CEBPB,CCL2,CSF1,ATF4,CREB1
GO:BP	cell adhesion mediated by integrin	GO:0033627	2.69E-05	4.570197453	72	110	8	18017	ITGB6,SERPINE1,PLAU,ITGB8,ITGB5,ITGB3,ITGB2,PTK2
GO:BP	endothelial cell proliferation	GO:0001935	2.75E-05	4.560277501	202	149	13	18017	VEGFA,HMGB1,AKT1,ALOX5,THBS1,CCL11,ITGB3,TNF,IL10,PDGFB,CCL2,STAT1,TGFBR1
GO:BP	alpha-beta T cell differentiation	GO:0046632	2.76E-05	4.558354267	108	105	9	18017	BCL6,IL6R,HMGB1,IRF1,RIPK2,IL18,IL6,IL23A,SMAD7
GO:BP	regulation of neuron apoptotic process	GO:0043523	2.80E-05	4.552193251	226	159	14	18017	BIRC5,TERT,BCL2L1,PARP1,TNF,IL10,CCL3,MAP2K4,GCLM,CEBPB,CCL2,ATF4,MCL1,ATF2
GO:BP	T cell differentiation	GO:0030217	2.97E-05	4.527831221	260	117	13	18017	BCL6,IL6R,HMGB1,IRF1,RIPK2,IL18,ATG5,IL6,IL15,IL23A,SMAD7,IL1B,IL7
GO:BP	vascular wound healing	GO:0061042	3.09E-05	4.509716616	21	70	5	18017	VEGFA,SERPINE1,ALOX5,TNF,CXCR4
GO:BP	regulation of neuroinflammatory response	GO:0150077	3.37E-05	4.472308977	47	113	7	18017	MMP9,TNF,CCL3,IL18,IL6,TREM2,IL1B
GO:BP	alpha-beta T cell activation	GO:0046631	3.39E-05	4.469445442	149	105	10	18017	BCL6,IL6R,HMGB1,IRF1,RIPK2,IL18,IL6,IL15,IL23A,SMAD7
GO:BP	activation of MAPKK activity	GO:0000186	3.68E-05	4.434071295	53	157	8	18017	MAP3K9,RIPK2,RAF1,MAP3K7,TGFBR1,MAP3K1,MAP3K5,RIPK1
GO:BP	regulation of kidney development	GO:0090183	3.98E-05	4.399903969	57	147	8	18017	VEGFA,CD133,MMP9,IL6R,PDGFB,GREM1,STAT1,PDGFA
GO:BP	endothelial cell migration	GO:0043542	4.15E-05	4.381813298	285	110	13	18017	VEGFA,HMGB1,AKT1,THBS1,ITGB3,TNF,GADD45A,ROCK2,PDGFB,EDN1,ITGB2,GREM1,PTK2
GO:BP	CD4-positive, alpha-beta T cell differentiation	GO:0043367	4.34E-05	4.362978365	80	105	8	18017	BCL6,IL6R,HMGB1,RIPK2,IL18,IL6,IL23A,SMAD7
GO:BP	positive chemotaxis	GO:0050918	4.53E-05	4.343849335	67	82	7	18017	IL8,VEGFA,HMGB1,MIF,CXCL10,CCL3,PDGFB
GO:BP	cellular response to ionizing radiation	GO:0071479	4.61E-05	4.336136906	69	123	8	18017	BLM,RAD51,BCL2L1,CHEK2,ATR,GADD45A,ELK1,RAD9A
GO:BP	response to amino acid	GO:0043200	4.69E-05	4.328656563	118	137	10	18017	BCL2L1,TNF,COL1A2,EDN1,CFL1,GCLM,CEBPB,COL3A1,CREB1,RELA
GO:BP	regulation of T cell mediated immunity	GO:0002709	4.78E-05	4.320756886	71	120	8	18017	HMGB1,TRAF2,IL18,IL6,IL23A,SMAD7,IL1B,MAP3K7
GO:BP	positive regulation of interleukin-1 production	GO:0032732	5.37E-05	4.270332288	67	84	7	18017	HMGB1,NOD1,TNF,CCL3,NOD2,RIPK2,IL6
GO:BP	receptor signaling pathway via JAK-STAT	GO:0007259	6.58E-05	4.181667977	169	158	12	18017	IL6R,TNF,IL10,GADD45A,IL18,IL6,IL15,IL23A,STAT2,CCL2,STAT1,CD40
GO:BP	tissue remodeling	GO:0048771	6.60E-05	4.180387608	184	117	11	18017	TNFRSF11B,TIMP1,ITGB3,IL18,ROCK2,ATG5,IL6,IL15,IL23A,GREM1,IL7
GO:BP	regulation of lymphocyte differentiation	GO:0045619	6.60E-05	4.180387608	184	117	11	18017	BCL6,HMGB1,IRF1,TLR9,RIPK2,IL18,IL15,IL23A,SMAD7,IL1B,IL7
GO:BP	cytokine biosynthetic process	GO:0042089	6.70E-05	4.173738065	69	129	8	18017	THBS1,TNF,IL10,IL18,IL6,IL1B,TLR3,MYD88

GO:BP	response to transforming growth factor beta	GO:0071559	6.82E-05	4.166118026	259	149	14	18017	SMAD6,THBS1,ITGB5,PARP1,COL1A2,ROCK2,EDN1,SMAD7,PTK2,MAP3K7,COL3A1,CREB1,ITGA3,TGFBR1
GO:BP	regulation of fatty acid transport	GO:2000191	7.19E-05	4.143457455	31	113	6	18017	AKT1,MIF,THBS1,MAP2K6,EDN1,IL1B
GO:BP	negative regulation of cell-cell adhesion	GO:0022408	7.21E-05	4.14223194	194	112	11	18017	VEGFA,BCL6,IL1RN,HMGB1,AKT1,HLA-DRB1,IRF1,IL10,SMAD7,PTK2,CEBPB
GO:BP	regulation of response to DNA damage stimulus	GO:2001020	7.28E-05	4.137996517	228	75	10	18017	CHEK1,RAD51,HMGB1,BID,MIF,BCL2L1,CHEK2,PARP1,ATR,SNAI1
GO:BP	regulation of interleukin-10 production	GO:0032653	7.33E-05	4.13469714	64	92	7	18017	HMGB1,HLA-DRB1,NOD2,TLR9,IL6,TLR2,IL23A
GO:BP	regulation of osteoclast differentiation	GO:0045670	8.00E-05	4.096662969	67	136	8	18017	TNF,CCL3,IL23A,CEBPB,TLR3,CSF1,GNAS,CREB1
GO:BP	cytokine metabolic process	GO:0042107	8.43E-05	4.074308015	71	129	8	18017	THBS1,TNF,IL10,IL18,IL6,IL1B,TLR3,MYD88
GO:BP	positive regulation of oxidoreductase activity	GO:0051353	9.15E-05	4.038353976	54	113	7	18017	TERT,AKT1,NOD1,TNF,NOD2,EDN1,IL1B
GO:BP	positive regulation of peptidyl-serine phosphorylation	GO:0033138	9.90E-05	4.004239763	111	84	8	18017	VEGFA,IL11,AKT1,MIF,TNF,RIPK2,RAF1,IL6
GO:BP	interleukin-10 production	GO:0032613	0.000101395	3.993982184	67	92	7	18017	HMGB1,HLA-DRB1,NOD2,TLR9,IL6,TLR2,IL23A
GO:BP	negative regulation of cell junction assembly	GO:1901889	0.000107014	3.970558154	33	113	6	18017	THBS1,TNF,ROCK2,TLR2,PTK2,IL1B
GO:BP	regulation of extrinsic apoptotic signaling pathway via death domain receptors	GO:1902041	0.000115294	3.938192092	61	157	8	18017	SERPINE1,BCL2L1,THBS1,TRAF2,RAF1,TRADD,TNFAIP3,RIPK1
GO:BP	negative regulation of extrinsic apoptotic signaling pathway via death domain receptors	GO:1902042	0.000121851	3.914169424	41	157	7	18017	SERPINE1,BCL2L1,TRAF2,RAF1,TRADD,TNFAIP3,RIPK1
GO:BP	regulation of intrinsic apoptotic signaling pathway	GO:2001242	0.000121923	3.913913851	169	135	11	18017	PLAUR,MMP9,AKT1,BID,MIF,BCL2L1,PARP1,SNAI1,BECN1,RAD9A,MCL1
GO:BP	regulation of anion transport	GO:0044070	0.000123489	3.908371548	114	157	10	18017	AKT1,MIF,THBS1,MAP2K6,EDN1,PRKG2,CEBPB,IL1B,ATF4,RIPK1
GO:BP	receptor signaling pathway via STAT	GO:0097696	0.000124509	3.904799436	179	158	12	18017	IL6R,TNF,IL10,GADD45A,IL18,IL6,IL15,IL23A,STAT2,CCL2,STAT1,CD40
GO:BP	response to gamma radiation	GO:0010332	0.000125076	3.902825137	57	66	6	18017	RAD51,CXCL10,BCL2L1,CHEK2,PARP1,ATR
GO:BP	nitric oxide metabolic process	GO:0046209	0.000125096	3.902756025	85	113	8	18017	AKT1,TNF,IL10,ROCK2,EDN1,TLR2,ITGB2,IL1B
GO:BP	T-helper 1 type immune response	GO:0042088	0.000125814	3.900270697	43	150	7	18017	HMGB1,HLA-DRB1,RIPK2,IL18,IL23A,IL1B,RELB
GO:BP	regulation of T cell cytokine production	GO:0002724	0.000126131	3.899178289	32	120	6	18017	TRAF2,IL18,IL6,SMAD7,IL1B,MAP3K7
GO:BP	regulation of T cell differentiation	GO:0045580	0.000131869	3.879856083	154	117	10	18017	BCL6,HMGB1,IRF1,RIPK2,IL18,IL15,IL23A,SMAD7,IL1B,IL7
GO:BP	response to ionizing radiation	GO:0010212	0.000136775	3.86399284	147	123	10	18017	BLM,RAD51,CXCL10,BCL2L1,CHEK2,PARP1,ATR,GADD45A,ELK1,RAD9A
GO:BP	positive regulation of interleukin-10 production	GO:0032733	0.000141652	3.848777148	42	92	6	18017	HMGB1,NOD2,TLR9,IL6,TLR2,IL23A
GO:BP	osteoclast differentiation	GO:0030316	0.000147393	3.831521683	101	136	9	18017	TNF,CCL3,IL23A,TREM2,CEBPB,TLR3,CSF1,GNAS,CREB1

GO:BP	regulation of gliogenesis	GO:0014013	0.00014752	3.831149609	133	137	10	18017	TNF,CCL3,CXCR4,IL6,TLR2,TREM2,IL1B,CSF1,CREB1,RELA
GO:BP	regulation of tissue remodeling	GO:0034103	0.000154142	3.812079569	93	106	8	18017	TNFRSF11B,ITGB3,IL18,ROCK2,IL6,IL15,IL23A,GREM1
GO:BP	temperature homeostasis	GO:0001659	0.000161442	3.791982646	175	134	11	18017	VEGFA,GADD45G,TNF,CXCR4,IL18,MAP2K6,IL15,CEBPB,IL1B,ATF4,GNAS
GO:BP	reactive nitrogen species metabolic process	GO:2001057	0.000164502	3.783827768	88	113	8	18017	AKT1,TNF,IL10,ROCK2,EDN1,TLR2,ITGB2,IL1B
GO:BP	regulation of interleukin-1 production	GO:0032652	0.000170685	3.767804814	119	84	8	18017	HMGB1,NOD1,TNF,IL10,CCL3,NOD2,RIPK2,IL6
GO:BP	positive regulation of vascular associated smooth muscle cell proliferation	GO:1904707	0.000174256	3.758811203	48	83	6	18017	MMP9,TERT,TNF,IL10,PDGFB,EDN1
GO:BP	regulation of myeloid cell differentiation	GO:0045637	0.0001759	3.754733763	265	157	14	18017	HMGB1,IRF7,HLA-DRB1,THBS1,TNF,CCL3,IL23A,CEBPB,TLR3,CSF1,GNAS,CREB1,STAT1,RIPK1
GO:BP	regulation of endothelial cell apoptotic process	GO:2000351	0.000178051	3.749456258	64	158	8	18017	SERPINE1,TERT,THBS1,TNF,IL10,CCL2,TNFAIP3,CD40
GO:BP	positive regulation of cytokine production involved in immune response	GO:0002720	0.000203778	3.690842457	57	120	7	18017	MIF,TRAF2,NOD2,IL18,IL6,IL1B,MAP3K7
GO:BP	connective tissue development	GO:0061448	0.000215988	3.665570271	266	159	14	18017	IL6R,ITGB8,TIMP1,SNAI1,PDGFB,EDN1,SERPINH1,SMAD7,GREM1,CSF1,GNAS,RELA,TGFBR1,ATF2
GO:BP	negative regulation of blood coagulation	GO:0030195	0.000224001	3.649750975	50	83	6	18017	PLAUR,SERPINE1,PLAU,THBS1,PDGFB,EDN1
GO:BP	macrophage migration	GO:1905517	0.000225278	3.647281158	56	124	7	18017	MIF,THBS1,CCL3,TREM2,PTK2,CCL2,CSF1
GO:BP	transforming growth factor beta receptor signaling pathway	GO:0007179	0.000245534	3.609888523	202	149	12	18017	SMAD6,THBS1,ITGB5,PARP1,COL1A2,SMAD7,PTK2,MAP3K7,COL3A1,CREB1,ITGA3,TGFBR1
GO:BP	CD4-positive, alpha-beta T cell activation	GO:0035710	0.000252863	3.597114275	100	105	8	18017	BCL6,IL6R,HMGB1,RIPK2,IL18,IL6,IL23A,SMAD7
GO:BP	negative regulation of hemostasis	GO:1900047	0.000252938	3.596985601	51	83	6	18017	PLAUR,SERPINE1,PLAU,THBS1,PDGFB,EDN1
GO:BP	regulation of epithelial cell differentiation	GO:0030856	0.000254001	3.595164632	171	113	10	18017	VEGFA,CD133,MMP9,SERPINE1,KEAP1,TNF,ROCK2,MAFG,CEBPB,IL1B
GO:BP	positive regulation of epithelial cell migration	GO:0010634	0.000255069	3.593342152	177	83	9	18017	VEGFA,MMP9,HMGB1,AKT1,THBS1,ITGB3,ROCK2,PDGFB,EDN1
GO:BP	interleukin-1 production	GO:0032612	0.000264972	3.576800051	130	113	9	18017	HMGB1,NOD1,TNF,IL10,CCL3,NOD2,RIPK2,IL6,IL1B
GO:BP	regulation of endothelial cell migration	GO:0010594	0.000280658	3.551823046	237	83	10	18017	VEGFA,HMGB1,AKT1,THBS1,ITGB3,TNF,GADD45A,ROCK2,PDGFB,EDN1
GO:BP	regulation of immunoglobulin production	GO:0002637	0.000288672	3.539595657	68	158	8	18017	BCL6,TRAF2,TNF,IL10,TLR9,IL6,IL13RA2,CD40
GO:BP	regulation of cellular response to oxidative stress	GO:1900407	0.00029732	3.526775938	95	157	9	18017	AKT1,ALOX5,PARP1,TNF,IL10,TXN,ATF4,MCL1,RIPK1
GO:BP	negative regulation of endopeptidase activity	GO:0010951	0.000326351	3.486314772	258	98	11	18017	BIRC5,VEGFA,PLAUR,MMP9,SERPINE1,AKT1,THBS1,TIMP1,TNF,RAF1,SERPINH1
GO:BP	osteoblast differentiation	GO:0001649	0.00032842	3.483571029	231	134	12	18017	IL6R,AKT1,SMAD6,TNF,CCL3,SNAI1,IL6,GREM1,PTK2,CEBPB,ATF4,GNAS

GO:BP	apoptotic mitochondrial changes	GO:0008637	0.000333921	3.476356032	125	159	10	18017	PLAUR,MMP9,AKT1,BID,BCL2L1,GZMB,ATG3,GCLM,IFIT2,ATF2
GO:BP	positive regulation of endothelial cell migration	GO:0010595	0.000347432	3.459130145	132	83	8	18017	VEGFA,HMGB1,AKT1,THBS1,ITGB3,ROCK2,PDGFB,EDN1
GO:BP	regulation of release of cytochrome c from mitochondria	GO:0090199	0.000354609	3.45025054	48	48	5	18017	PLAUR,MMP9,AKT1,BID,BCL2L1
GO:BP	positive regulation of T cell cytokine production	GO:0002726	0.000359384	3.444441513	20	120	5	18017	TRAF2,IL18,IL6,IL1B,MAP3K7
GO:BP	cellular response to transforming growth factor beta stimulus	GO:0071560	0.000388636	3.410456502	253	149	13	18017	SMAD6,THBS1,ITGB5,PARP1,COL1A2,EDN1,SMAD7,PTK2,MAP3K7,COL3A1,CREB1,ITGA3,TGFBR1
GO:BP	protein autophosphorylation	GO:0046777	0.000389733	3.409232763	240	157	13	18017	VEGFA,MAP3K9,AKT1,CHEK2,ATR,PDGFB,MKNK1,PRKG2,GREM1,PTK2,MAPKAPK5,PDGFA,RIPK1
GO:BP	negative regulation of intrinsic apoptotic signaling pathway	GO:2001243	0.000398417	3.399661852	100	75	7	18017	PLAUR,MMP9,AKT1,BID,MIF,BCL2L1,SNAI1
GO:BP	telomere maintenance via telomere lengthening	GO:0010833	0.000404375	3.39321614	81	138	8	18017	TERT,RAD51,PARP1,ATR,DKC1,MAPKAPK5,TERF1,PARN
GO:BP	regulation of cell-matrix adhesion	GO:0001952	0.000421132	3.375582267	125	124	9	18017	VEGFA,BCL6,SERPINE1,PLAU,THBS1,ROCK2,GREM1,PTK2,CSF1
GO:BP	TRIF-dependent toll-like receptor signaling pathway	GO:0035666	0.000429827	3.366706764	30	158	6	18017	IRF7,TLR3,IRF3,BIRC2,RIPK1,CD40
GO:BP	positive regulation of DNA metabolic process	GO:0051054	0.000466779	3.330888706	202	158	12	18017	RAD51,HMGB1,AKT1,PARP1,ATR,DKC1,PDGFB,IL6,GREM1,MAPKAPK5,PARN,CD40
GO:BP	positive regulation of cytokine biosynthetic process	GO:0042108	0.00048391	3.315235104	37	129	6	18017	THBS1,TNF,IL6,IL1B,TLR3,MYD88
GO:BP	negative regulation of coagulation	GO:0050819	0.000498571	3.302272924	57	83	6	18017	PLAUR,SERPINE1,PLAU,THBS1,PDGFB,EDN1
GO:BP	regulation of nitric oxide biosynthetic process	GO:0045428	0.00051622	3.287164942	69	113	7	18017	AKT1,TNF,IL10,ROCK2,EDN1,ITGB2,IL1B
GO:BP	T cell activation involved in immune response	GO:0002286	0.000530668	3.275176981	110	105	8	18017	BCL6,IL6R,HMGB1,RIPK2,IL18,IL6,IL23A,SMAD7
GO:BP	positive regulation of adaptive immune response based on somatic recombination of immune receptors built from immunoglobulin superfamily domains	GO:0002824	0.000533531	3.272840149	101	158	9	18017	TRAF2,TNF,RIPK2,IL18,IL6,IL23A,IL1B,MAP3K7,CD40
GO:BP	negative regulation of peptidase activity	GO:0010466	0.000534469	3.272077216	271	98	11	18017	BIRC5,VEGFA,PLAUR,MMP9,SERPINE1,AKT1,THBS1,TIMP1,TNF,RAF1,SERPINH1
GO:BP	regulation of toll-like receptor signaling pathway	GO:0034121	0.000567363	3.246138909	75	156	8	18017	HMGB1,IRF7,IRF1,TLR9,TLR2,TLR3,TNFAIP3,BIRC2
GO:BP	positive regulation of leukocyte mediated immunity	GO:0002705	0.000576439	3.239246504	134	120	9	18017	TRAF2,TNF,NOD2,IL18,IL6,ITGB2,IL23A,IL1B,MAP3K7
GO:BP	extrinsic apoptotic signaling pathway in absence of ligand	GO:0097192	0.000595847	3.224865459	75	157	8	18017	TERT,AKT1,BCL2L1,TNF,IL1B,IL7,MCL1,RIPK1

GO:BP	signal transduction in absence of ligand	GO:0038034	0.000595847	3.224865459	75	157	8	18017	TERT,AKT1,BCL2L1,TNF,IL1B,IL7,MCL1,RIPK1
GO:BP	positive regulation of myeloid cell differentiation	GO:0045639	0.000598531	3.222913567	103	157	9	18017	HMGB1,HLA-DRB1,TNF,IL23A,CSF1,GNAS,CREB1,STAT1,RIPK1
GO:BP	cell aging	GO:0007569	0.000604649	3.21849682	121	66	7	18017	CHEK1,BCL6,SERPINE1,TERT,MIF,CHEK2,ATR
GO:BP	integrin-mediated signaling pathway	GO:0007229	0.000625157	3.204011168	112	145	9	18017	ITGB6,ITGB8,TIMP1,ITGB5,ITGB3,ITGB2,PTK2,COL3A1,ITGA3
GO:BP	regulation of response to oxidative stress	GO:1902882	0.000650401	3.186819103	104	157	9	18017	AKT1,ALOX5,PARP1,TNF,IL10,TXN,ATF4,MCL1,RIPK1
GO:BP	positive regulation of production of molecular mediator of immune response	GO:0002702	0.000686412	3.163414865	104	158	9	18017	MIF,TRAF2,NOD2,TLR9,IL18,IL6,IL1B,MAP3K7,CD40
GO:BP	regulation of epithelial cell apoptotic process	GO:1904035	0.000686412	3.163414865	104	158	9	18017	SERPINE1,TERT,THBS1,TNF,IL10,IL6,CCL2,TNFAIP3,CD40
GO:BP	positive regulation of T cell proliferation	GO:0042102	0.000703017	3.153034466	106	113	8	18017	HMGB1,IGFBP2,RIPK2,IL18,IL6,IL15,IL23A,IL1B
GO:BP	regulation of CD4-positive, alpha-beta T cell differentiation	GO:0043370	0.000710977	3.148144698	48	105	6	18017	BCL6,HMGB1,RIPK2,IL18,IL23A,SMAD7
GO:BP	macrophage chemotaxis	GO:0048246	0.000723758	3.140406904	41	124	6	18017	MIF,THBS1,CCL3,PTK2,CCL2,CSF1
GO:BP	positive regulation of reactive oxygen species metabolic process	GO:2000379	0.000755895	3.121538397	107	113	8	18017	AKT1,THBS1,TNF,GADD45A,PDGFB,EDN1,ITGB2,IL1B
GO:BP	receptor metabolic process	GO:0043112	0.000764193	3.11679701	196	111	10	18017	IL8,VEGFA,MX2,ITGB3,TNF,IL10,EDN1,ITGB2,GREM1,BECN1
GO:BP	programmed necrotic cell death	GO:0097300	0.000765436	3.116091162	53	157	7	18017	TRAF2,TNF,TLR3,IRF3,MAP3K5,BIRC2,RIPK1
GO:BP	T cell cytokine production	GO:0002369	0.000799364	3.097255198	43	120	6	18017	TRAF2,IL18,IL6,SMAD7,IL1B,MAP3K7
GO:BP	positive regulation of adaptive immune response	GO:0002821	0.000808284	3.09243612	106	158	9	18017	TRAF2,TNF,RIPK2,IL18,IL6,IL23A,IL1B,MAP3K7,CD40
GO:BP	T cell mediated immunity	GO:0002456	0.000829594	3.08113414	102	120	8	18017	HMGB1,TRAF2,IL18,IL6,IL23A,SMAD7,IL1B,MAP3K7
GO:BP	homeostasis of number of cells	GO:0048872	0.000833618	3.079032847	265	152	13	18017	VEGFA,BCL6,CXCL6,HMGB1,FANCC,AKT1,MIF,IL6,PRDX1,IL7,CSF1,STAT1,TNFAIP3
GO:BP	regulation of cytokine biosynthetic process	GO:0042035	0.00084117	3.075116414	65	129	7	18017	THBS1,TNF,IL10,IL6,IL1B,TLR3,MYD88
GO:BP	regulation of reactive oxygen species biosynthetic process	GO:1903426	0.000871938	3.059514396	109	113	8	18017	AKT1,ALOX5,TNF,IL10,ROCK2,EDN1,ITGB2,IL1B
GO:BP	regulation of interleukin-17 production	GO:0032660	0.000914267	3.038926998	41	129	6	18017	NOD2,IL18,IL6,IL15,IL23A,MYD88
GO:BP	interleukin-1 beta production	GO:0032611	0.000932728	3.030245114	112	152	9	18017	HMGB1,NOD1,TNF,CCL3,NOD2,RIPK2,IL6,IL1B,TNFAIP3
GO:BP	MyD88-independent toll-like receptor signaling pathway	GO:0002756	0.000945769	3.024214944	34	158	6	18017	IRF7,TLR3,IRF3,BIRC2,RIPK1,CD40
GO:BP	regulation of cell junction assembly	GO:1901888	0.000946793	3.023744939	197	113	10	18017	VEGFA,IL1RAP,THBS1,TNF,SNAI1,ROCK2,TLR2,GREM1,PTK2,IL1B
GO:BP	tissue homeostasis	GO:0001894	0.000947553	3.02339652	268	152	13	18017	TNFRSF11B,VEGFA,CD133,SLC2A1,ITGB3,NOD2,TLR9,IL6,PRDX1,IL7,CSF1,GNAS,TNFAIP3
GO:BP	tumor necrosis factor-mediated signaling pathway	GO:0033209	0.000967598	3.014304909	177	158	11	18017	TNFRSF11B,LTB,TRAF2,TNF,TRADD,RELA,STAT1,TNFAIP3,BIRC2,RIPK1,CD40
GO:BP	regulation of macrophage migration	GO:1905521	0.000970348	3.013072304	43	124	6	18017	MIF,THBS1,CCL3,TREM2,PTK2,CSF1
GO:BP	leukocyte apoptotic process	GO:0071887	0.000972593	3.012068798	109	157	9	18017	BCL6,IRF7,AKT1,MIF,IL10,NOD2,IL6,IRF3,RIPK1

GO:BP	positive regulation of receptor signaling pathway via JAK-STAT	GO:0046427	0.000992034	3.003473396	93	92	7	18017	IL6R,TNF,IL10,IL18,IL6,IL15,IL23A
GO:BP	release of cytochrome c from mitochondria	GO:0001836	0.001014341	2.993815814	59	48	5	18017	PLAUR,MMP9,AKT1,BID,BCL2L1
GO:BP	regulation of interleukin-1 beta production	GO:0032651	0.001068422	2.971257315	103	84	7	18017	HMGB1,NOD1,TNF,CCL3,NOD2,RIPK2,IL6
GO:BP	interferon-gamma-mediated signaling pathway	GO:0060333	0.001087846	2.963432428	87	146	8	18017	IRF7,HLA-DRB1,IRF1,OASL,IRF5,IRF3,STAT1,OAS2
GO:BP	regulation of osteoblast differentiation	GO:0045667	0.001140125	2.943047444	130	134	9	18017	IL6R,SMAD6,TNF,IL6,GREM1,PTK2,CEBPB,ATF4,GNAS
GO:BP	chronic inflammatory response	GO:0002544	0.00116676	2.933018387	20	152	5	18017	THBS1,CCL11,TNF,IL10,TNFAIP3
GO:BP	response to nutrient	GO:0007584	0.001209272	2.917475934	181	158	11	18017	C2,TNFRSF11B,IGFBP2,CXCL10,NOD2,LDHA,IL15,GCLM,RELA,STAT1,CD40
GO:BP	positive regulation of receptor signaling pathway via STAT	GO:1904894	0.001232749	2.90912524	96	92	7	18017	IL6R,TNF,IL10,IL18,IL6,IL15,IL23A
GO:BP	positive regulation of pri-miRNA transcription by RNA polymerase II	GO:1902895	0.001303436	2.88491033	41	137	6	18017	TERT,SMAD6,TNF,IL10,PDGFB,RELA
GO:BP	positive regulation of T cell mediated immunity	GO:0002711	0.001377679	2.860851943	47	120	6	18017	TRAF2,IL18,IL6,IL23A,IL1B,MAP3K7
GO:BP	nitric oxide biosynthetic process	GO:0006809	0.00143624	2.842773055	80	113	7	18017	AKT1,TNF,IL10,ROCK2,EDN1,ITGB2,IL1B
GO:BP	fibrinolysis	GO:0042730	0.001438802	2.841999046	26	49	4	18017	PLAUR,SERPINE1,PLAU,THBS1
GO:BP	positive regulation of leukocyte adhesion to vascular endothelial cell	GO:1904996	0.001483458	2.828724827	23	137	5	18017	ALOX5,TNF,IL6,ITGB2,RELA
GO:BP	regulation of nuclease activity	GO:0032069	0.001601572	2.795453405	22	146	5	18017	HMGB1,AKT1,OASL,TERF1,OAS2
GO:BP	positive regulation of myeloid leukocyte differentiation	GO:0002763	0.001621573	2.790063622	59	157	7	18017	HLA-DRB1,TNF,IL23A,CSF1,GNAS,CREB1,RIPK1
GO:BP	regulation of symbiotic process	GO:0043903	0.001666155	2.778284676	235	153	12	18017	IL8,CXCL6,HLA-DRB1,OASL,TNF,CCL3,CXCR4,IFIT1,CFL1,STAT1,OAS2,CCL4
GO:BP	lymphocyte activation involved in immune response	GO:0002285	0.001671748	2.776829306	187	158	11	18017	BCL6,IL6R,HMGB1,IL10,RIPK2,IL18,IL6,IL23A,SMAD7,RELB,CD40
GO:BP	positive regulation of macrophage migration	GO:1905523	0.001737962	2.759959632	26	124	5	18017	THBS1,CCL3,TREM2,PTK2,CSF1
GO:BP	positive regulation of endothelial cell proliferation	GO:0001938	0.001805917	2.743302328	114	82	7	18017	VEGFA,HMGB1,AKT1,CCL11,ITGB3,IL10,PDGFB
GO:BP	positive regulation of nitric-oxide synthase activity	GO:0051000	0.0018491	2.733039492	22	62	4	18017	TERT,AKT1,NOD1,TNF
GO:BP	interleukin-17 production	GO:0032620	0.00184965	2.732910394	46	129	6	18017	NOD2,IL18,IL6,IL15,IL23A,MYD88
GO:BP	regulation of receptor signaling pathway via JAK-STAT	GO:0046425	0.001856963	2.73119674	148	92	8	18017	IL6R,TNF,IL10,GADD45A,IL18,IL6,IL15,IL23A
GO:BP	positive regulation of kidney development	GO:0090184	0.001971236	2.705261273	41	147	6	18017	VEGFA,CD133,IL6R,PDGFB,GREM1,PDGFA
GO:BP	cellular response to inorganic substance	GO:0071241	0.002043484	2.689628656	222	136	11	18017	MMP9,BLM,RAD51,AKT1,DAXX,TRAF2,PARP1,

									EDN1,MEF2A,ATF4,CREB1
GO:BP	type 2 immune response	GO:0042092	0.00206803	2.684443194	39	84	5	18017	BCL6,IL10,NOD2,IL18,IL6
GO:BP	protein kinase B signaling	GO:0043491	0.002231584	2.651386685	278	158	13	18017	AKT1,THBS1,TNF,CCL3,IL18,PDGFB,PTK2,IL1B, CCL2,TXN,PDGFA,TGFBR1,CD40
GO:BP	response to corticosteroid	GO:0031960	0.002299721	2.638324912	167	84	8	18017	IL1RN,HMGB1,IGFBP2,PARP1,TNF,IL10,EDN1, IL6
GO:BP	interaction with host	GO:0051701	0.002405662	2.618765467	215	89	9	18017	IL8,ITGB6,HLA-DRB1,BCL2L1,ITGB5,ITGB3, CXCR4,ATG5,IFIT1
GO:BP	apoptotic cell clearance	GO:0043277	0.002420391	2.616114531	52	119	6	18017	C2,HMGB1,THBS1,ITGB3,TREM2,CCL2
GO:BP	activation of JUN kinase activity	GO:0007257	0.002490446	2.603722909	40	157	6	18017	MAP3K9,DAXX,RIPK2,MAP2K4,MAP3K5,RIPK1
GO:BP	positive regulation of ion transport	GO:0043270	0.002582461	2.587966283	291	153	13	18017	AKT1,MIF,CXCL10,CCL3,MAP2K6,PDGFB,EDN1,TREM2,CEBPB,IL1B,CCL2,ATF4, CCL4
GO:BP	cold-induced thermogenesis	GO:0106106	0.00269718	2.569089993	144	134	9	18017	VEGFA,GADD45G,CXCR4,IL18,MAP2K6,IL15, CEBPB,ATF4,GNAS
GO:BP	regulation of cold-induced thermogenesis	GO:0120161	0.00269718	2.569089993	144	134	9	18017	VEGFA,GADD45G,CXCR4,IL18,MAP2K6,IL15, CEBPB,ATF4,GNAS
GO:BP	intrinsic apoptotic signaling pathway in response to DNA damage	GO:0008630	0.002735526	2.562959185	106	135	8	18017	BID,MIF,BCL2L1,CHEK2,TNF,SNAI1,RAD9A, MCL1
GO:BP	positive regulation of osteoclast differentiation	GO:0045672	0.002746073	2.561287865	26	136	5	18017	TNF,IL23A,CSF1,GNAS,CREB1
GO:BP	positive regulation of monooxygenase activity	GO:0032770	0.002759018	2.559245537	31	113	5	18017	TERT,AKT1,NOD1,TNF,IL1B
GO:BP	regulation of protein modification by small protein conjugation or removal	GO:1903320	0.00279166	2.55413746	242	156	12	18017	AKT1,DAXX,NOD2,RIPK2,ATG5,SQSTM1, LIMK1,SMAD7,RELA,TGFBR1,TNFAIP3,BIRC2
GO:BP	alpha-beta T cell proliferation	GO:0046633	0.002847387	2.545553473	38	92	5	18017	IRF1,RIPK2,IL18,IL15,IL23A
GO:BP	regulation of receptor signaling pathway via STAT	GO:1904892	0.002901019	2.5374494	157	92	8	18017	IL6R,TNF,IL10,GADD45A,IL18,IL6,IL15,IL23A
GO:BP	signal transduction in response to DNA damage	GO:0042770	0.002919396	2.534706991	134	75	7	18017	CHEK1,BID,MIF,CHEK2,ATR,GADD45A,SNAI1
GO:BP	positive regulation of chromosome organization	GO:2001252	0.003062511	2.513922331	183	138	10	18017	VEGFA,BCL6,ATR,DKC1,BECN1,IL1B, MAPKAPK5,TERF1,RPS6KA5,PARN
GO:BP	regulation of granulocyte chemotaxis	GO:0071622	0.003080708	2.511349446	52	124	6	18017	IL8,THBS1,EDN1,IL23A,PTK2,CSF1
GO:BP	reactive oxygen species biosynthetic process	GO:1903409	0.003343112	2.475849014	130	113	8	18017	AKT1,ALOX5,TNF,IL10,ROCK2,EDN1,ITGB2, IL1B
GO:BP	regulation of glucose transmembrane transport	GO:0010827	0.003362202	2.473376139	82	125	7	18017	SLC2A1,TERT,AKT1,TNF,EDN1,IL1B,MEF2A
GO:BP	cellular response to gamma radiation	GO:0071480	0.003398776	2.468677502	30	122	5	18017	RAD51,BCL2L1,CHEK2,ATR,ELK1
GO:BP	regulation of alpha-beta T cell activation	GO:0046634	0.00348092	2.458306012	98	105	7	18017	BCL6,HMGB1,IRF1,RIPK2,IL18,IL23A,SMAD7
GO:BP	cellular response to acid chemical	GO:0071229	0.003574239	2.446816412	79	131	7	18017	VEGFA,BCL2L1,TNF,COL1A2,GCLM,CEBPB, COL3A1
GO:BP	regulation of production of small RNA involved in gene silencing by RNA	GO:0070920	0.003651192	2.437565328	24	157	5	18017	TERT,TNF,IL6,MAP2K1,RIPK1

GO:BP	regulation of DNA recombination	GO:0000018	0.003668032	2.435566888	105	63	6	18017	CHEK1,BCL6,BLM,RAD51,PARP1,IL10
GO:BP	positive regulation of mononuclear cell migration	GO:0071677	0.00374035	2.427087795	26	62	4	18017	SERPINE1,HMGB1,CXCL10,TNF
GO:BP	regulation of macrophage activation	GO:0043030	0.003808775	2.419214659	64	104	6	18017	MIF,THBS1,IL10,CCL3,IL6,TREM2
GO:BP	necrotic cell death	GO:0070265	0.003899643	2.408975157	67	157	7	18017	TRAF2,TNF,TLR3,IRF3,MAP3K5,BIRC2,RIPK1
GO:BP	regulation of CD4-positive, alpha-beta T cell activation	GO:2000514	0.004028472	2.394859654	64	105	6	18017	BCL6,HMGB1,RIPK2,IL18,IL23A,SMAD7
GO:BP	regulation of alpha-beta T cell differentiation	GO:0046637	0.004028472	2.394859654	64	105	6	18017	BCL6,HMGB1,RIPK2,IL18,IL23A,SMAD7
GO:BP	positive regulation of tyrosine phosphorylation of STAT protein	GO:0042531	0.004048985	2.392653879	73	92	6	18017	IL6R,TNF,IL18,IL6,IL15,IL23A
GO:BP	response to UV	GO:0009411	0.00407712	2.389646547	148	137	9	18017	CHEK1,MMP9,AKT1,TIMP1,PARP1,ATR,HMGN1,ATF4,RELA
GO:BP	regulation of T-helper cell differentiation	GO:0045622	0.0041548	2.381449916	36	105	5	18017	BCL6,RIPK2,IL18,IL23A,SMAD7
GO:BP	regulation of lipid localization	GO:1905952	0.004210385	2.375678191	181	84	8	18017	AKT1,MIF,THBS1,ITGB3,TNF,MAP2K6,EDN1,IL6
GO:BP	regulation of blood coagulation	GO:0030193	0.00438982	2.357553247	82	83	6	18017	PLAUR,SERPINE1,PLAU,THBS1,PDGFB,EDN1
GO:BP	negative regulation of cell activation	GO:0050866	0.004483842	2.348349698	215	152	11	18017	BCL6,HMGB1,HLA-DRB1,IRF1,IL10,PDGFB, SMAD7,CEBPB,IL13RA2,PDGFA,TNFAIP3
GO:BP	acute-phase response	GO:0006953	0.004560493	2.340988177	49	141	6	18017	IL6R,TNF,IL6,CEBPB,IL1B,CD163
GO:BP	regulation of hemostasis	GO:1900046	0.004714585	2.326556523	83	83	6	18017	PLAUR,SERPINE1,PLAU,THBS1,PDGFB,EDN1
GO:BP	regulation of pri-miRNA transcription by RNA polymerase II	GO:1902893	0.004905225	2.309341073	51	137	6	18017	TERT,SMAD6,TNF,IL10,PDGFB,RELA
GO:BP	adaptive thermogenesis	GO:1990845	0.004974881	2.303217305	155	134	9	18017	VEGFA,GADD45G,CXCR4,IL18,MAP2K6,IL15, CEBPB,ATF4,GNAS
GO:BP	regulation of protein ubiquitination	GO:0031396	0.005044216	2.297206365	212	156	11	18017	AKT1,DAXX,NOD2,RIPK2,ATG5,SQSTM1, LIMK1,SMAD7,TGFBR1,TNFAIP3,BIRC2
GO:BP	heterotypic cell-cell adhesion	GO:0034113	0.005124249	2.290369787	62	113	6	18017	IL1RN,ITGB3,TNF,IL10,ITGB2,IL1B
GO:BP	vascular associated smooth muscle cell proliferation	GO:1990874	0.005422991	2.265761131	85	83	6	18017	MMP9,TERT,TNF,IL10,PDGFB,EDN1
GO:BP	regulation of vascular associated smooth muscle cell proliferation	GO:1904705	0.005422991	2.265761131	85	83	6	18017	MMP9,TERT,TNF,IL10,PDGFB,EDN1
GO:BP	pri-miRNA transcription by RNA polymerase II	GO:0061614	0.005510602	2.258800981	52	137	6	18017	TERT,SMAD6,TNF,IL10,PDGFB,RELA
GO:BP	regulation of pattern recognition receptor signaling pathway	GO:0062207	0.005620822	2.250200135	101	156	8	18017	HMGB1,IRF7,IRF1,TLR9,TLR2,TLR3,TNFAIP3, BIRC2
GO:BP	cell death in response to oxidative stress	GO:0036473	0.005895473	2.229481381	101	157	8	18017	AKT1,PARP1,IL10,TXN,ATF4,MCL1,MAP3K5, RIPK1
GO:BP	regulation of viral process	GO:0050792	0.005973662	2.223759349	220	153	11	18017	IL8,HLA-DRB1,OASL,TNF,CCL3,CXCR4,IFIT1, CFL1,STAT1,OAS2,CCL4
GO:BP	negative regulation of leukocyte cell-cell adhesion	GO:1903038	0.006068607	2.216911004	142	112	8	18017	BCL6,HMGB1,AKT1,HLA-DRB1,IRF1,IL10, SMAD7,CEBPB
GO:BP	inflammatory response to antigenic	GO:0002437	0.006511376	2.18632722	65	63	5	18017	IL1RN,HMGB1,HLA-DRB1,TNF,IL10

	stimulus								
GO:BP	positive regulation of lymphocyte mediated immunity	GO:0002708	0.006658092	2.176650232	102	158	8	18017	TRAF2,TNF,IL18,IL6,IL23A,IL1B,MAP3K7,CD40
GO:BP	fatty acid transport	GO:0015908	0.007455271	2.127536584	102	113	7	18017	SLC2A1,AKT1,MIF,THBS1,MAP2K6,EDN1,IL1B
GO:BP	multi-multicellular organism process	GO:0044706	0.007556659	2.121670155	238	145	11	18017	VEGFA,SLC2A1,MMP9,IGFBP2,AKT1,TIMP1, EDN1,IL1B,GNAS,IGFBP7,ITGA3
GO:BP	regulation of coagulation	GO:0050818	0.007580078	2.120326351	90	83	6	18017	PLAUR,SERPINE1,PLAU,THBS1,PDGFB,EDN1
GO:BP	negative regulation of DNA replication	GO:0008156	0.008222259	2.085008836	34	128	5	18017	BCL6,BLM,CHEK2,ATR,TERF1
GO:BP	detection of external biotic stimulus	GO:0098581	0.008328374	2.079439797	23	86	4	18017	HLA-DRB1,NOD1,NOD2,TLR2
GO:BP	intracellular receptor signaling pathway	GO:0030522	0.008364882	2.077540196	269	156	12	18017	IRF7,NOD1,DAXX,PARP1,NOD2,RIPK2,MAP2K6,MAP3K7,RELA,IRF3,TNFAIP3,BIRC2
GO:BP	peptide hormone secretion	GO:0030072	0.008761549	2.057419116	267	84	9	18017	BIRC5,SLC2A1,IL1RN,HLA-DRB1,ALOX5,TNF, RAF1,EDN1,IL6
GO:BP	positive regulation of endopeptidase activity	GO:0010950	0.008904635	2.050383881	181	157	10	18017	HMGB1,BID,NOD1,TRAF2,TNF,RIPK2,ROCK2, TRADD,MAP3K5,RIPK1
GO:BP	regulation of mitochondrion organization	GO:0010821	0.009247737	2.033964546	190	118	9	18017	PLAUR,MMP9,AKT1,BID,BCL2L1,SQSTM1, GZMB,TREM2,STAT2
GO:BP	telomere maintenance	GO:0000723	0.00959499	2.017955461	163	138	9	18017	BLM,TERT,RAD51,PARP1,ATR,DKC1, MAPKAPK5,TERF1,PARN
GO:BP	regulation of antigen processing and presentation	GO:0002577	0.009848327	2.006637525	20	104	4	18017	NOD1,THBS1,NOD2,TREM2
GO:BP	anoikis	GO:0043276	0.010673942	1.971675145	34	135	5	18017	AKT1,CHEK2,PTK2,MAP3K7,MCL1
GO:BP	negative regulation of vasculature development	GO:1901343	0.010944761	1.960793712	211	82	8	18017	SERPINE1,CXCL10,ALOX5,THBS1,TNF, GADD45A,ROCK2,PDGFB
GO:BP	regulation of signal transduction by p53 class mediator	GO:1901796	0.011403116	1.942976439	181	127	9	18017	CHEK1,BLM,AKT1,MIF,CHEK2,ATR,SNAI1, RAD9A,MAPKAPK5
GO:BP	regulation of defense response to virus	GO:0050688	0.011420049	1.942332015	79	156	7	18017	IFIT1,IL15,IL23A,IL1B,STAT1,TNFAIP3,BIRC2
GO:BP	T cell selection	GO:0045058	0.011452819	1.941087597	50	92	5	18017	IL6R,ATG5,IL6,IL15,IL23A
GO:BP	positive regulation of phagocytosis	GO:0050766	0.011940868	1.9229641	68	119	6	18017	C2,TNF,IL15,TREM2,IL1B,CCL2
GO:BP	regulation of tyrosine phosphorylation of STAT protein	GO:0042509	0.012123168	1.916383887	88	92	6	18017	IL6R,TNF,IL18,IL6,IL15,IL23A
GO:BP	myeloid cell apoptotic process	GO:0033028	0.012139362	1.915804142	33	143	5	18017	IRF7,MIF,NOD2,IL6,IRF3
GO:BP	positive regulation of lymphocyte differentiation	GO:0045621	0.012141174	1.915739334	106	117	7	18017	BCL6,RIPK2,IL18,IL15,IL23A,IL1B,IL7
GO:BP	positive regulation of anion transport	GO:1903793	0.012623026	1.898836534	62	132	6	18017	MIF,MAP2K6,EDN1,CEBPB,IL1B,ATF4
GO:BP	female pregnancy	GO:0007565	0.013220668	1.878746596	205	145	10	18017	VEGFA,SLC2A1,MMP9,IGFBP2,AKT1,TIMP1, IL1B,GNAS,IGFBP7,ITGA3
GO:BP	response to hydrogen peroxide	GO:0042542	0.013231587	1.878388072	149	157	9	18017	IL10,LDHA,IL6,TXN,RELA,STAT1,TNFAIP3, MAP3K5,RIPK1
GO:BP	response to glucocorticoid	GO:0051384	0.013301759	1.876090916	150	84	7	18017	IL1RN,HMGB1,IGFBP2,TNF,IL10,EDN1,IL6
GO:BP	cartilage development	GO:0051216	0.013541843	1.868322228	200	149	10	18017	ITGB8,TIMP1,SNAI1,EDN1,SERPINH1,SMAD7,

									GREM1,GNAS,RELA,TGFBR1
GO:BP	regulation of intrinsic apoptotic signaling pathway in response to DNA damage	GO:1902229	0.013611972	1.866078951	39	123	5	18017	BID,MIF,BCL2L1,SNAI1,RAD9A
GO:BP	positive regulation of icosanoid secretion	GO:0032305	0.013702485	1.863200669	20	113	4	18017	MIF,MAP2K6,EDN1,IL1B
GO:BP	prostaglandin transport	GO:0015732	0.013702485	1.863200669	20	113	4	18017	MIF,MAP2K6,EDN1,IL1B
GO:BP	positive regulation of T-helper 1 type immune response	GO:0002827	0.013702485	1.863200669	20	113	4	18017	RIPK2,IL18,IL23A,IL1B
GO:BP	insulin secretion	GO:0030073	0.01375515	1.861534677	223	134	10	18017	BIRC5,SLC2A1,IL1RN,HLA-DRB1,ALOX5,TNF, RAF1,IL6,IL1B,GNAS
GO:BP	tyrosine phosphorylation of STAT protein	GO:0007260	0.013814685	1.859659017	90	92	6	18017	IL6R,TNF,IL18,IL6,IL15,IL23A
GO:BP	positive regulation of epithelial cell proliferation	GO:0050679	0.013911323	1.856631562	218	82	8	18017	VEGFA,HMGB1,AKT1,CCL11,ITGB3,IL10,NOD2,PDGFB
GO:BP	regulation of oxidative stress-induced cell death	GO:1903201	0.014081797	1.851341915	81	157	7	18017	AKT1,PARP1,IL10,TXN,ATF4,MCL1,RIPK1
GO:BP	positive regulation of response to biotic stimulus	GO:0002833	0.014375209	1.842385819	246	150	11	18017	HMGB1,IRF7,MIF,NOD1,RIPK2,RAF1,MAP3K7, RPS6KA5,RELA,IRF3,RELB
GO:BP	positive regulation of cysteine-type endopeptidase activity	GO:2001056	0.014748689	1.831246579	151	157	9	18017	HMGB1,BID,NOD1,TRAF2,TNF,RIPK2,TRADD, MAP3K5,RIPK1
GO:BP	negative regulation of production of molecular mediator of immune response	GO:0002701	0.014783891	1.830211242	35	140	5	18017	BCL6,TNF,IL10,SMAD7,IL13RA2
GO:BP	positive regulation of p38MAPK cascade	GO:1900745	0.015362605	1.813535139	32	155	5	18017	VEGFA,GADD45G,GADD45A,IL1B,MAP3K5
GO:BP	regulation of organic acid transport	GO:0032890	0.015710703	1.803804389	75	113	6	18017	AKT1,MIF,THBS1,MAP2K6,EDN1,IL1B
GO:BP	regulation of telomere maintenance via telomere lengthening	GO:1904356	0.016302532	1.78774493	62	138	6	18017	PARP1,ATR,DKC1,MAPKAPK5,TERF1,PARN
GO:BP	regulation of oxidoreductase activity	GO:0051341	0.016543945	1.781360933	115	113	7	18017	TERT,AKT1,NOD1,TNF,NOD2,EDN1,IL1B
GO:BP	negative regulation of intrinsic apoptotic signaling pathway in response to DNA damage	GO:1902230	0.016670848	1.778042311	31	75	4	18017	BID,MIF,BCL2L1,SNAI1
GO:BP	defense response to Gram-negative bacterium	GO:0050829	0.017773056	1.750237885	94	92	6	18017	IL6R,SERPINE1,CXCL6,TLR9,IL6,IL23A
GO:BP	telomere organization	GO:0032200	0.017902386	1.747089083	176	138	9	18017	BLM,TERT,RAD51,PARP1,ATR,DKC1, MAPKAPK5,TERF1,PARN
GO:BP	negative regulation of cytokine production involved in immune response	GO:0002719	0.018449	1.734027159	23	105	4	18017	BCL6,TNF,IL10,SMAD7
GO:BP	regulation of hormone secretion	GO:0046883	0.018480276	1.733291555	279	136	11	18017	BIRC5,SLC2A1,IL11,HLA-DRB1,ALOX5,TNF, EDN1,IL6,IL1B,GNAS,CREB1
GO:BP	positive regulation of cardiac muscle hypertrophy	GO:0010613	0.018958932	1.722186136	41	125	5	18017	PARP1,ROCK2,EDN1,PTK2,MEF2A
GO:BP	receptor biosynthetic process	GO:0032800	0.018976148	1.721791948	29	83	4	18017	ITGB3,TNF,IL10,EDN1
GO:BP	regulation of blood vessel endothelial cell migration	GO:0043535	0.019542092	1.709028942	163	82	7	18017	VEGFA,HMGB1,AKT1,THBS1,TNF,GADD45A, PDGFB

GO:BP	regulation of leukocyte adhesion to vascular endothelial cell	GO:1904994	0.020192127	1.694817931	38	137	5	18017	ALOX5,TNF,IL6,ITGB2,RELA
GO:BP	response to toxic substance	GO:0009636	0.020229266	1.69401988	250	153	11	18017	PTGS1,RAD51,FANCC,TNF,CCL3,TLR2,PRDX1,TXNRD1,TXN,ATF4,CCL4
GO:BP	positive regulation of nitric oxide biosynthetic process	GO:0045429	0.020652241	1.685032806	46	113	5	18017	AKT1,TNF,EDN1,ITGB2,IL1B
GO:BP	regulation of cell-substrate adhesion	GO:0010810	0.020925505	1.679324046	216	145	10	18017	VEGFA,BCL6,SERPINE1,PLAU,THBS1,ROCK2,GREM1,PTK2,CSF1,ITGA3
GO:BP	positive regulation of activated T cell proliferation	GO:0042104	0.02127394	1.672152077	27	92	4	18017	HMGB1,IGFBP2,IL18,IL23A
GO:BP	viral genome replication	GO:0019079	0.021320937	1.671193711	129	146	8	18017	IL8,OASL,TNF,ROCK2,ATG5,IFIT1,CCL2,OAS2
GO:BP	positive regulation of muscle hypertrophy	GO:0014742	0.021401966	1.669546324	42	125	5	18017	PARP1,ROCK2,EDN1,PTK2,MEF2A
GO:BP	negative regulation of neuron apoptotic process	GO:0043524	0.021990398	1.657766909	159	119	8	18017	BIRC5,TERT,BCL2L1,IL10,MAP2K4,GCLM,CEBPB,CCL2
GO:BP	positive regulation of peptidase activity	GO:0010952	0.022460903	1.648572796	201	157	10	18017	HMGB1,BID,NOD1,TRAF2,TNF,RIPK2,ROCK2,TRADD,MAP3K5,RIPK1
GO:BP	negative regulation of DNA-dependent DNA replication	GO:2000104	0.022461666	1.648558036	20	128	4	18017	BCL6,BLM,CHEK2,TERF1
GO:BP	positive regulation of protein localization to membrane	GO:1905477	0.022535958	1.647123984	131	104	7	18017	AKT1,BID,TNF,SQSTM1,ITGB2,GZMB,TREM2
GO:BP	positive regulation of nitric oxide metabolic process	GO:1904407	0.022995835	1.638350807	47	113	5	18017	AKT1,TNF,EDN1,ITGB2,IL1B
GO:BP	placenta development	GO:0001890	0.023530816	1.628363014	161	156	9	18017	AKT1,ITGB8,IL10,SNAI1,PDGFB,PTK2,CEBPB,MAP2K1,BIRC2
GO:BP	platelet activation	GO:0030168	0.023577125	1.627509154	159	158	9	18017	ITGB3,COL1A2,RAF1,PDGFB,IL6,COL3A1,GNAS,PDGFA,CD40
GO:BP	negative regulation of phagocytosis	GO:0050765	0.02375126	1.624313346	24	107	4	18017	HMGB1,ATG5,TLR2,ATG3
GO:BP	response to testosterone	GO:0033574	0.024012467	1.619563223	44	122	5	18017	CA9,THBS1,ROCK2,EDN1,ELK1
GO:BP	negative regulation of T cell activation	GO:0050868	0.024280156	1.614748532	123	112	7	18017	BCL6,HMGB1,HLA-DRB1,IRF1,IL10,SMAD7,CEBPB
GO:BP	regulation of innate immune response	GO:0045088	0.024430763	1.612062965	299	156	12	18017	HMGB1,IRF7,IRF1,RAF1,MAP3K7,RPS6KA5,RELA,IRF3,STAT1,RELB,TNFAIP3,BIRC2
GO:BP	positive regulation of fatty acid transport	GO:2000193	0.024682474	1.607611311	23	113	4	18017	MIF,MAP2K6,EDN1,IL1B
GO:BP	regulation of icosanoid secretion	GO:0032303	0.024682474	1.607611311	23	113	4	18017	MIF,MAP2K6,EDN1,IL1B
GO:BP	regulation of type 2 immune response	GO:0002828	0.026180467	1.582022612	31	84	4	18017	BCL6,NOD2,IL18,IL6
GO:BP	cellular response to amino acid stimulus	GO:0071230	0.026681857	1.573783943	71	131	6	18017	BCL2L1,TNF,COL1A2,GCLM,CEBPB,COL3A1
GO:BP	negative regulation of protein modification by small protein conjugation or removal	GO:1903321	0.028494007	1.545246466	93	152	7	18017	AKT1,ATG5,SQSTM1,LIMK1,SMAD7,RELA,TNFAIP3
GO:BP	negative regulation of lipid localization	GO:1905953	0.029086391	1.536310157	66	84	5	18017	AKT1,THBS1,ITGB3,TNF,IL6
GO:BP	response to hepatocyte growth factor	GO:0035728	0.02938066	1.531938459	20	137	4	18017	IL10,GCLM,CREB1,RELA

GO:BP	positive regulation of developmental growth	GO:0048639	0.029424007	1.53129819	190	136	9	18017	VEGFA,AKT1,CXCR4,EDN1,LIMK1,SMAD7,IL7,CSF1,CREB1
GO:BP	regulation of membrane protein ectodomain proteolysis	GO:0051043	0.029476018	1.530531194	24	113	4	18017	TIMP1,TNF,IL10,IL1B
GO:BP	glucose transmembrane transport	GO:1904659	0.030298257	1.518582353	114	125	7	18017	SLC2A1,TERT,AKT1,TNF,EDN1,IL1B,MEF2A
GO:BP	positive regulation of DNA biosynthetic process	GO:2000573	0.030425693	1.516759518	69	138	6	18017	ATR,DKC1,PDGFB,GREM1,MAPKAPK5,PARN
GO:BP	telomere maintenance via telomerase	GO:0007004	0.030425693	1.516759518	69	138	6	18017	TERT,ATR,DKC1,MAPKAPK5,TERF1,PARN
GO:BP	positive regulation of toll-like receptor signaling pathway	GO:0034123	0.030520713	1.515405321	24	114	4	18017	HMGB1,TLR9,TLR2,TLR3
GO:BP	regulation of transforming growth factor beta production	GO:0071634	0.031644357	1.499703724	36	159	5	18017	ITGB6,ITGB8,THBS1,CREB1,ATF2
GO:BP	blood vessel endothelial cell migration	GO:0043534	0.031807074	1.497476283	188	106	8	18017	VEGFA,HMGB1,AKT1,THBS1,TNF,GADD45A,PDGFB,GREM1
GO:BP	regulation of monocyte chemotaxis	GO:0090025	0.031905522	1.496134148	26	106	4	18017	SERPINE1,HMGB1,CXCL10,GREM1
GO:BP	regulation of transcription from RNA polymerase II promoter in response to stress	GO:0043618	0.031994822	1.494920305	119	8	3	18017	CHEK1,CA9,VEGFA
GO:BP	signal transduction by p53 class mediator	GO:0072331	0.032068003	1.49392808	268	75	8	18017	CHEK1,BLM,AKT1,MIF,CHEK2,ATR,GADD45A,SNAI1
GO:BP	lymphocyte chemotaxis	GO:0048247	0.032281339	1.491048465	63	153	6	18017	CCL20,CXCL10,CCL11,CCL3,CCL2,CCL4
GO:BP	regulation of lymphocyte migration	GO:2000401	0.032281339	1.491048465	63	153	6	18017	CCL20,AKT1,CXCL10,CCL3,CCL2,CCL4
GO:BP	Rho protein signal transduction	GO:0007266	0.033208336	1.478752885	138	145	8	18017	BCL6,COL1A2,ROCK2,RAF1,CFL1,LIMK1,COL3A1,ITGA3
GO:BP	positive regulation of neuron apoptotic process	GO:0043525	0.033296899	1.477596205	61	159	6	18017	TNF,CCL3,MAP2K4,ATF4,MCL1,ATF2
GO:BP	response to alcohol	GO:0097305	0.033847348	1.470475359	259	156	11	18017	BLM,RAD51,AKT1,BCL2L1,PARP1,CCL3,PTGER2,GNAS,IGFBP7,TGFBR1,BIRC2
GO:BP	regulation of nitric-oxide synthase activity	GO:0050999	0.034520032	1.461928807	51	113	5	18017	TERT,AKT1,NOD1,TNF,IL1B
GO:BP	regulation of cytokine secretion	GO:0050707	0.034688825	1.459810414	113	86	6	18017	MIF,TNF,IL10,TLR9,IL6,TLR2
GO:BP	establishment of endothelial barrier	GO:0061028	0.035216365	1.453255477	45	129	5	18017	VEGFA,TNF,ROCK2,IL1B,MYD88
GO:BP	regulation of leukocyte apoptotic process	GO:2000106	0.035681061	1.447562243	85	68	5	18017	BCL6,IRF7,MIF,IL10,NOD2
GO:BP	RNA-dependent DNA biosynthetic process	GO:0006278	0.035897236	1.444938984	71	138	6	18017	TERT,ATR,DKC1,MAPKAPK5,TERF1,PARN
GO:BP	hexose transmembrane transport	GO:0008645	0.03589755	1.444935186	117	125	7	18017	SLC2A1,TERT,AKT1,TNF,EDN1,IL1B,MEF2A
GO:BP	cellular response to UV	GO:0034644	0.036496127	1.437753225	88	66	5	18017	CHEK1,MMP9,TIMP1,PARP1,ATR
GO:BP	regulation of DNA-templated transcription in response to stress	GO:0043620	0.037081493	1.430842792	125	8	3	18017	CHEK1,CA9,VEGFA
GO:BP	regulation of tumor necrosis factor-mediated signaling pathway	GO:0010803	0.037376708	1.427398952	63	157	6	18017	TRAF2,TNF,TRADD,TNFAIP3,BIRC2,RIPK1
GO:BP	positive regulation of protein kinase B	GO:0051897	0.038025795	1.419921698	179	149	9	18017	THBS1,TNF,CCL3,IL18,PDGFB,PTK2,TXN,

	signaling								PDGFA,TGFBR1
GO:BP	regulation of B cell proliferation	GO:0030888	0.03874689	1.411763152	63	158	6	18017	BCL6,MIF,IL10,TLR9,IL7,CD40
GO:BP	monosaccharide transmembrane transport	GO:0015749	0.040085356	1.397014254	119	125	7	18017	SLC2A1,TERT,AKT1,TNF,EDN1,IL1B,MEF2A
GO:BP	regulation of heterotypic cell-cell adhesion	GO:0034114	0.041071348	1.386461047	26	113	4	18017	IL1RN,TNF,IL10,IL1B
GO:BP	transforming growth factor beta production	GO:0071604	0.04153736	1.381561107	38	159	5	18017	ITGB6,ITGB8,THBS1,CREB1,ATF2
GO:BP	T-helper 17 cell differentiation	GO:0072539	0.041713377	1.37972465	28	105	4	18017	IL6R,IL6,IL23A,SMAD7
GO:BP	regulation of protein localization to membrane	GO:1905475	0.041718624	1.379670022	199	104	8	18017	AKT1,BID,BCL2L1,TNF,SQSTM1,ITGB2,GZMB,TREM2
GO:BP	regulation of defense response to virus by host	GO:0050691	0.043223095	1.364284136	40	152	5	18017	IL15,IL23A,IL1B,STAT1,TNFAIP3
GO:BP	interleukin-2 production	GO:0032623	0.044429122	1.352332271	67	152	6	18017	IL1RAP,TRAF2,RIPK2,IL1B,MAP3K7,TNFAIP3
GO:BP	carbohydrate transmembrane transport	GO:0034219	0.044668625	1.349997413	121	125	7	18017	SLC2A1,TERT,AKT1,TNF,EDN1,IL1B,MEF2A
GO:BP	negative regulation of angiogenesis	GO:0016525	0.046423496	1.333262158	196	78	7	18017	SERPINE1,CXCL10,ALOX5,THBS1,TNF,GADD45A,ROCK2
GO:BP	detection of biotic stimulus	GO:0009595	0.047141951	1.326592452	35	86	4	18017	HLA-DRB1,NOD1,NOD2,TLR2
GO:BP	positive regulation of cysteine-type endopeptidase activity involved in apoptotic process	GO:0043280	0.047706802	1.321419699	134	157	8	18017	HMGB1,BID,NOD1,TRAF2,TNF,TRADD,MAP3K5,RIPK1
GO:BP	regulation of T-helper 1 type immune response	GO:0002825	0.047981606	1.318925224	27	113	4	18017	RIPK2,IL18,IL23A,IL1B
GO:BP	astrocyte activation	GO:0048143	0.047981606	1.318925224	27	113	4	18017	TNF,IL6,TREM2,IL1B
GO:BP	regulation of DNA biosynthetic process	GO:2000278	0.048414168	1.315027524	111	138	7	18017	ATR,DKC1,PDGFB,GREM1,MAPKAPK5,TERF1,PARN
GO:BP	negative regulation of blood vessel morphogenesis	GO:2000181	0.049554893	1.304913458	198	78	7	18017	SERPINE1,CXCL10,ALOX5,THBS1,TNF,GADD45A,ROCK2
GO:BP	positive regulation of cytokine production involved in inflammatory response	GO:1900017	0.049687776	1.30375044	24	129	4	18017	TNF,NOD2,IL6,MYD88
GO:CC	integrin complex	GO:0008305	3.44E-05	4.463311175	31	145	6	18956	ITGB6,ITGB8,ITGB5,ITGB3,ITGB2,ITGA3
GO:CC	protein complex involved in cell adhesion	GO:0098636	8.82E-05	4.054475142	36	145	6	18956	ITGB6,ITGB8,ITGB5,ITGB3,ITGB2,ITGA3
GO:CC	PML body	GO:0016605	0.000112497	3.948858626	102	85	7	18956	BLM,TERT,RAD51,DAXX,CHEK2,ATR,SQSTM1
GO:CC	plasma membrane signaling receptor complex	GO:0098802	0.000297859	3.525988833	290	158	13	18956	IL6R,ITGB6,ITGB8,TRAF2,ITGB5,ITGB3,IL6,TLR2,ITGB2,ITGA3,TGFBR1,BIRC2,CD40
GO:CC	chromosome, telomeric region	GO:0000781	0.00045188	3.344976521	162	66	7	18956	CHEK1,BLM,TERT,RAD51,CHEK2,PARP1,ATR
GO:CC	platelet alpha granule	GO:0031091	0.000768582	3.114309821	90	82	6	18956	VEGFA,SERPINE1,THBS1,TIMP1,ITGB3,PDGFB
GO:CC	phagocytic vesicle	GO:0045335	0.001082218	2.965685418	141	86	7	18956	NOD1,TLR7,ITGB5,NOD2,TLR9,ATG5,TLR2
GO:CC	platelet alpha granule lumen	GO:0031093	0.00294831	2.530426901	66	82	5	18956	VEGFA,SERPINE1,THBS1,TIMP1,PDGFB
GO:CC	condensed chromosome	GO:0000793	0.007009122	2.154336361	221	30	5	18956	BIRC5,CHEK1,BLM,RAD51,HMGB1

GO:CC	replication fork	GO:0005657	0.011459951	1.94081724	70	18	3	18956	CHEK1,BCL6,BLM
GO:CC	ficolin-1-rich granule	GO:0101002	0.018742964	1.72716173	124	64	5	18956	MMP9,HMGB1,MIF,ALOX5,FTH1
GO:CC	ficolin-1-rich granule lumen	GO:1904813	0.018742964	1.72716173	124	64	5	18956	MMP9,HMGB1,MIF,ALOX5,FTH1
GO:CC	microvillus membrane	GO:0031528	0.021182703	1.674018618	27	9	2	18956	CA9,CD133
KEGG	TNF signaling pathway	KEGG:04668	1.03E-25	24.98626188	112	159	31	7963	CXCL1,MMP9,CCL20,CXCL6,AKT1,IRF1,CXCL10,TRAF2,TNF,NOD2,MAP2K6,EDN1,IL6,IL15,MAP2K4,CEBPB,IL1B,TRADD,CCL2,MAP3K7,CSF1,RPS6KA5,ATF4,CREB1,RELA,MAP2K1,TNFAIP3,MAP3K5,BIRC2,RIPK1,ATF2
KEGG	Toll-like receptor signaling pathway	KEGG:04620	8.25E-18	17.08354789	102	158	24	7963	IL8,IRF7,AKT1,CXCL10,IRF5,TLR7,TNF,CCL3,TLR9,MAP2K6,IL6,TLR2,MAP2K4,IL1B,TLR3,MAP3K7,MYD88,RELA,IRF3,STAT1,MAP2K1,CCL4,RIPK1,CD40
KEGG	Rheumatoid arthritis	KEGG:05323	3.81E-15	14.41914719	88	124	19	7963	IL8,VEGFA,CXCL1,LTB,CCL20,CXCL6,IL11,HLA-DRB1,TNF,CCL3,IL18,IL6,TLR2,ITGB2,IL15,IL23A,IL1B,CCL2,CSF1
KEGG	PD-L1 expression and PD-1 checkpoint pathway in cancer	KEGG:05235	4.81E-15	2.382621678	89	151	9	7963	AKT1,TLR9,RAF1,MAP2K6,TLR2,MYD88,RELA,STAT1,MAP2K1
KEGG	Hepatitis B	KEGG:05161	6.58E-15	14.18178776	162	159	26	7963	BIRC5,IL8,MMP9,IRF7,AKT1,BID,TNF,RAF1,MAP2K6,IL6,TLR2,MAP2K4,TLR3,STAT2,MAP3K7,ELK1,MYD88,ATF4,CREB1,RELA,IRF3,STAT1,TGFBR1,MAP2K1,MAP3K1,ATF2
KEGG	Human cytomegalovirus infection	KEGG:05163	3.14E-14	13.50358609	223	159	29	7963	IL8,VEGFA,IL6R,AKT1,BID,TRAF2,ITGB3,TNF,CCL3,CXCR4,PTGER2,ROCK2,RAF1,MAP2K6,IL6,PTK2,IL1B,TRADD,CCL2,ELK1,ATF4,GNAS,CREB1,RELA,IRF3,MAP2K1,CCL4,RIPK1,ATF2
KEGG	NF-kappa B signaling pathway	KEGG:04064	3.63E-14	13.43999474	102	158	21	7963	IL8,CXCL1,GADD45G,LTB,PLAU,BCL2L1,TRAF2,PARP1,TNF,GADD45A,IL1B,TRADD,MAP3K7,MYD88,RELA,RELB,TNFAIP3,CCL4,BIRC2,RIPK1,CD40
KEGG	NOD-like receptor signaling pathway	KEGG:04621	4.49E-13	12.34757126	177	157	25	7963	IL8,CXCL1,IRF7,NOD1,BCL2L1,TRAF2,TNF,NOD2,RIPK2,IL18,ATG5,IL6,IL1B,STAT2,CCL2,MAP3K7,TXN,MYD88,RELA,IRF3,STAT1,OAS2,TNFAIP3,BIRC2,RIPK1
KEGG	Influenza A	KEGG:05164	5.18E-12	11.28603286	168	151	23	7963	IL8,IRF7,AKT1,HLA-DRB1,BID,CXCL10,MX2,TLR7,TNF,IL18,RAF1,IL6,IL1B,TLR3,TRADD,STAT2,CCL2,MYD88,RELA,IRF3,STAT1,OAS2,MAP2K1
KEGG	MAPK signaling pathway	KEGG:04010	7.24E-12	11.1404447	294	159	30	7963	VEGFA,IL1RAP,GADD45G,AKT1,DAXX,TRAF2,TNF,GADD45A,RAF1,MAP2K6,PDGFB,MKNK1,MAP2K4,IL1B,TRADD,MAP3K7,ELK1,CSF1,MAPKAPK5,MYD88,RPS6KA5,ATF4,RELA,PDGFA,TGFBR1,RELB,MAP2K1,MAP3K1,MAP3K5,ATF2
KEGG	Epstein-Barr virus infection	KEGG:05169	7.44E-12	11.12842833	198	158	25	7963	GADD45G,IRF7,AKT1,HLA-DRB1,BID,CXCL10,TRAF2,TNF,GADD45A,MAP2K6,IL6,TLR2,MAP2K4,TRADD,STAT2,MAP3K7,MYD88,RELA,IRF3,STAT1,OAS2,RELB,TNFAIP3,RIPK1,CD40

KEGG	Cytokine-cytokine receptor interaction	KEGG:04060	3.40E-11	10.46911173	292	158	29	7963	IL8,TNFRSF11B,CXCL1,IL1RN,IL1RAP,IL6R,LTB,CCL20,CXCL6,IL11,CXCL10,CCL11,TNF,IL10,CCL3,CXCR4,IL18,IL6,IL15,IL23A,INHBE,IL1B,IL7,CCL2,CSF1,IL13RA2,TGFBR1,CCL4,CD40
KEGG	IL-17 signaling pathway	KEGG:04657	9.46E-11	10.02411792	92	152	17	7963	IL8,CXCL1,MMP9,CCL20,CXCL6,CXCL10,CCL11,TRAF2,TNF,IL6,CEBPB,IL1B,TRADD,CCL2,MAP3K7,RELA,TNFAIP3
KEGG	Apoptosis	KEGG:04210	1.39E-10	9.855624426	136	157	20	7963	BIRC5,GADD45G,AKT1,BID,BCL2L1,DAXX,TRAF2,PARP1,TNF,GADD45A,RAF1,GZMB,TRADD,ATF4,MCL1,RELA,MAP2K1,MAP3K5,BIRC2,RIPK1
KEGG	Fluid shear stress and atherosclerosis	KEGG:05418	1.45E-10	9.839856693	138	155	20	7963	VEGFA,MMP9,AKT1,KEAP1,ITGB3,TNF,MAP2K6,PDGFB,EDN1,SQSTM1,MAP2K4,PTK2,IL1B,CCL2,MAP3K7,TXN,MEF2A,RELA,PDGFA,MAP3K5
KEGG	Yersinia infection	KEGG:05135	2.52E-10	9.598431057	129	151	19	7963	IL8,AKT1,TRAF2,TNF,IL10,IL18,ROCK2,MAP2K6,IL6,LIMK1,MAP2K4,PTK2,IL1B,CCL2,MAP3K7,MYD88,RELA,IRF3,MAP2K1
KEGG	Pertussis	KEGG:05133	3.29E-10	9.482933407	76	143	15	7963	IL8,C2,CXCL6,IRF1,NOD1,TNF,IL10,IL6,ITGB2,CFL1,IL23A,IL1B,MYD88,RELA,IRF3
KEGG	Tuberculosis	KEGG:05152	3.77E-10	9.423453905	175	144	21	7963	AKT1,HLA-DRB1,BID,TNF,IL10,NOD2,TLR9,RIPK2,IL18,RAF1,IL6,TLR2,ITGB2,IL23A,CEBPB,IL1B,TRADD,MYD88,CREB1,RELA,STAT1
KEGG	Malaria	KEGG:05144	6.06E-10	9.217395919	49	158	13	7963	IL8,THBS1,TNF,IL10,TLR9,IL18,IL6,TLR2,ITGB2,IL1B,CCL2,MYD88,CD40
KEGG	Kaposi sarcoma-associated herpesvirus infection	KEGG:05167	8.42E-10	9.074606555	193	151	22	7963	IL8,VEGFA,CXCL1,IRF7,AKT1,BID,TRAF2,RAF1,MAP2K6,PDGFB,IL6,MAP2K4,ATG3,BECN1,TLR3,TRADD,STAT2,CREB1,RELA,IRF3,STAT1,MAP2K1
KEGG	Measles	KEGG:05162	1.11E-09	8.954736664	139	152	19	7963	IRF7,AKT1,BID,BCL2L1,MX2,TLR7,TLR9,IL6,TLR2,IL1B,TRADD,STAT2,MAP3K7,MYD88,RELA,IRF3,STAT1,OAS2,TNFAIP3
KEGG	Osteoclast differentiation	KEGG:04380	1.46E-09	8.835536986	125	151	18	7963	TNFRSF11B,AKT1,TRAF2,ITGB3,TNF,MAP2K6,SQSTM1,TREM2,IL1B,STAT2,MAP3K7,CSF1,CREB1,RELA,STAT1,TGFBR1,RELB,MAP2K1
KEGG	Viral protein interaction with cytokine and cytokine receptor	KEGG:04061	1.91E-09	8.720038776	98	124	15	7963	IL8,CXCL1,IL6R,CCL20,CXCL6,CXCL10,CCL11,TNF,IL10,CCL3,CXCR4,IL18,IL6,CCL2,CSF1
KEGG	Salmonella infection	KEGG:05132	1.93E-09	8.715033665	213	157	23	7963	IL8,AKT1,NOD1,TRAF2,TNF,TLR9,RIPK2,IL18,ROCK2,RAF1,MAP2K6,IL6,TLR2,MAP2K4,IL1B,TRADD,MAP3K7,TXN,MYD88,RELA,MAP2K1,BIRC2,RIPK1
KEGG	Human T-cell leukemia virus 1 infection	KEGG:05166	3.36E-09	8.473724408	216	159	23	7963	CHEK1,SLC2A1,TERT,AKT1,HLA-DRB1,BCL2L1,CHEK2,TNF,ATR,IL6,ITGB2,IL15,MAP2K4,ELK1,ATF4,CREB1,RELA,TGFBR1,RELB,MAP2K1,MAP3K1,CD40,ATF2
KEGG	Chagas disease	KEGG:05142	3.91E-09	8.407967602	101	149	16	7963	IL8,SERPINE1,AKT1,TNF,IL10,CCL3,TLR9,IL6,TLR2,MAP2K4,IL1B,CCL2,MYD88,GNAS,RELA,TGFBR1

KEGG	Human immunodeficiency virus 1 infection	KEGG:05170	6.58E-08	7.181558679	210	157	21	7963	CHEK1,AKT1,BID,BCL2L1,TRAF2,TNF,ATR,CXCR4,RAF1,MAP2K6,TLR2,CFL1,LIMK1,PTK2,TRADD,MAP3K7,MYD88,RELA,IRF3,MAP2K1,RIPK1
KEGG	Hepatitis C	KEGG:05160	1.32E-07	6.880553937	157	157	18	7963	IRF7,AKT1,BID,CXCL10,MX2,TRAF2,TNF,RAF1,IFIT1,TLR3,TRADD,STAT2,RELA,IRF3,STAT1,OAS2,MAP2K1,RIPK1
KEGG	Amoebiasis	KEGG:05146	1.39E-07	6.857197152	101	137	14	7963	IL8,CXCL1,TNF,IL10,COL1A2,IL6,TLR2,ITGB2,PRDX1,PTK2,IL1B,COL3A1,GNAS,RELA
KEGG	Chemokine signaling pathway	KEGG:04062	2.95E-07	6.530652093	190	153	19	7963	IL8,CXCL1,CCL20,CXCL6,AKT1,CXCL10,CCL11,CCL3,CXCR4,ROCK2,RAF1,SHC1,PTK2,STAT2,CCL2,RELA,STAT1,MAP2K1,CCL4
KEGG	AGE-RAGE signaling pathway in diabetic complications	KEGG:04933	3.68E-07	6.433686133	100	149	14	7963	IL8,VEGFA,SERPINE1,AKT1,TNF,COL1A2,EDN1,IL6,IL1B,CCL2,COL3A1,RELA,STAT1,TGFBR1
KEGG	Relaxin signaling pathway	KEGG:04926	3.87E-07	6.412581892	128	159	16	7963	VEGFA,MMP9,AKT1,COL1A2,RAF1,EDN1,MAP2K4,SHC1,COL3A1,ATF4,GNAS,CREB1,RELA,TGFBR1,MAP2K1,ATF2
KEGG	RIG-I-like receptor signaling pathway	KEGG:04622	8.54E-07	6.068599985	70	157	12	7963	IL8,IRF7,CXCL10,TRAF2,TNF,ATG5,TRADD,MAP3K7,RELA,IRF3,MAP3K1,RIPK1
KEGG	Shigellosis	KEGG:05131	8.72E-07	6.059715894	242	157	21	7963	IL8,AKT1,NOD1,BCL2L1,TRAF2,TNF,RIPK2,IL18,ROCK2,ATG5,SQSTM1,PTK2,BECN1,IL1B,TRADD,MAP3K7,MYD88,RPS6KA5,RELA,IRF3,RIPK1
KEGG	Inflammatory bowel disease	KEGG:05321	1.01E-06	5.99506856	62	144	11	7963	HLA-DRB1,TNF,IL10,NOD2,IL18,IL6,TLR2,IL23A,IL1B,RELA,STAT1
KEGG	p53 signaling pathway	KEGG:04115	1.59E-06	5.797959283	73	73	9	7963	CHEK1,GADD45G,SERPINE1,BID,BCL2L1,THBS1,CHEK2,ATR,GADD45A
KEGG	Toxoplasmosis	KEGG:05145	2.46E-06	5.608209947	109	158	14	7963	AKT1,HLA-DRB1,ALOX5,BCL2L1,TNF,IL10,MAP2K6,TLR2,MAP3K7,MYD88,RELA,STAT1,BIRC2,CD40
KEGG	Cellular senescence	KEGG:04218	3.26E-06	5.486884578	156	151	16	7963	IL8,CHEK1,GADD45G,SERPINE1,AKT1,CHEK2,ATR,GADD45A,RAF1,MAP2K6,IL6,SQSTM1,RAD9A,RELA,TGFBR1,MAP2K1
KEGG	Legionellosis	KEGG:05134	3.37E-06	5.472284068	57	137	10	7963	IL8,CXCL1,TNF,IL18,IL6,TLR2,ITGB2,IL1B,MYD88,RELA
KEGG	JAK-STAT signaling pathway	KEGG:04630	3.80E-06	5.419876145	162	147	16	7963	IL6R,IL11,AKT1,BCL2L1,IL10,RAF1,PDGFB,IL6,IL15,IL23A,IL7,STAT2,MCL1,IL13RA2,STAT1,PDGFA
KEGG	Leishmaniasis	KEGG:05140	5.15E-06	5.28792632	72	144	11	7963	HLA-DRB1,TNF,IL10,TLR2,ITGB2,IL1B,MAP3K7,ELK1,MYD88,RELA,STAT1
KEGG	Focal adhesion	KEGG:04510	5.63E-06	5.249395442	200	156	18	7963	VEGFA,ITGB6,AKT1,ITGB8,THBS1,ITGB5,ITGB3,COL1A2,ROCK2,RAF1,PDGFB,SHC1,PTK2,ELK1,ITGA3,PDGFA,MAP2K1,BIRC2
KEGG	Pancreatic cancer	KEGG:05212	1.49E-05	4.82537334	76	151	11	7963	VEGFA,GADD45G,RAD51,AKT1,BCL2L1,

									GADD45A,RAF1,RELA,STAT1,TGFBR1,MAP2K1
KEGG	Proteoglycans in cancer	KEGG:05205	2.36E-05	4.626782151	205	86	13	7963	VEGFA,PLAUR,MMP9,PLAU,AKT1,THBS1,ITGB5,ITGB3,TNF,COL1A2,ROCK2,RAF1,TLR2
KEGG	Necroptosis	KEGG:04217	4.52E-05	4.344983127	159	157	15	7963	HMGB1,BID,TRAF2,PARP1,TNF,FTH1,SQSTM1,IL1B,TLR3,TRADD,STAT2,STAT1,TNFAIP3,BIRC2,RIPK1
KEGG	C-type lectin receptor signaling pathway	KEGG:04625	4.76E-05	4.322391608	104	150	12	7963	AKT1,IRF1,TNF,IL10,RAF1,IL6,IL23A,IL1B,STAT2,RELA,STAT1,RELB
KEGG	Growth hormone synthesis, secretion and action	KEGG:04935	5.31E-05	4.275237396	118	159	13	7963	AKT1,RAF1,MAP2K6,MAP2K4,SHC1,PTK2,ATF4,GNAS,CREB1,STAT1,MAP2K1,MAP3K1,ATF2
KEGG	HIF-1 signaling pathway	KEGG:04066	5.54E-05	4.256657269	109	95	10	7963	VEGFA,SLC2A1,IL6R,SERPINE1,AKT1,TIMP1,LDHA,EDN1,IL6,MKNK1
KEGG	Transcriptional misregulation in cancer	KEGG:05202	0.000101186	3.99488097	191	158	16	7963	IL8,CD133,BCL6,MMP9,GADD45G,PLAU,BCL2L1,GADD45A,IL6,GZMB,PTK2,CEBPB,RELA,PDGFA,BIRC2,CD40
KEGG	African trypanosomiasis	KEGG:05143	0.000133506	3.874498721	36	129	7	7963	TNF,IL10,TLR9,IL18,IL6,IL1B,MYD88
KEGG	EGFR tyrosine kinase inhibitor resistance	KEGG:01521	0.000199237	3.700629155	79	151	10	7963	VEGFA,IL6R,AKT1,BCL2L1,RAF1,PDGFB,IL6,SHC1,PDGFA,MAP2K1
KEGG	Cytosolic DNA-sensing pathway	KEGG:04623	0.000282549	3.548906265	62	157	9	7963	IRF7,CXCL10,IL18,IL6,IL1B,RELA,IRF3,CCL4,RIPK1
KEGG	Hematopoietic cell lineage	KEGG:04640	0.000752637	3.123414553	95	145	10	7963	IL6R,IL11,HLA-DRB1,ITGB3,TNF,IL6,IL1B,IL7,CSF1,ITGA3
KEGG	Bladder cancer	KEGG:05219	0.000954682	3.020141241	41	151	7	7963	IL8,VEGFA,MMP9,THBS1,RAF1,RPS6KA5,MAP2K1
KEGG	Regulation of actin cytoskeleton	KEGG:04810	0.001020201	2.991314245	212	151	15	7963	ITGB6,ITGB8,ITGB5,ITGB3,CXCR4,ROCK2,RAF1,PDGFB,ITGB2,CFL1,LIMK1,PTK2,ITGA3,PDGFA,MAP2K1
KEGG	Chronic myeloid leukemia	KEGG:05220	0.001145174	2.941128555	76	151	9	7963	GADD45G,AKT1,BCL2L1,GADD45A,RAF1,SHC1,RELA,TGFBR1,MAP2K1
KEGG	Prostate cancer	KEGG:05215	0.001299295	2.886292378	97	151	10	7963	MMP9,PLAU,AKT1,RAF1,PDGFB,ATF4,CREB1,RELA,PDGFA,MAP2K1
KEGG	Complement and coagulation cascades	KEGG:04610	0.002195218	2.658522384	85	33	5	7963	CFB,C2,PLAUR,SERPINE1,PLAU
KEGG	Hypertrophic cardiomyopathy	KEGG:05410	0.003956374	2.402702618	90	84	7	7963	ITGB6,ITGB8,ITGB5,ITGB3,TNF,EDN1,IL6
KEGG	Asthma	KEGG:05310	0.005178188	2.285822194	27	63	4	7963	HLA-DRB1,CCL11,TNF,IL10
KEGG	Hepatocellular carcinoma	KEGG:05225	0.006563754	2.182847692	166	151	12	7963	GADD45G,TERT,AKT1,BCL2L1,KEAP1,GADD45A,RAF1,SHC1,TXNRD1,ELK1,TGFBR1,MAP2K1
KEGG	Small cell lung cancer	KEGG:05222	0.006956069	2.157636126	92	156	9	7963	GADD45G,AKT1,BCL2L1,TRAF2,GADD45A,PTK2,RELA,ITGA3,BIRC2
KEGG	ECM-receptor interaction	KEGG:04512	0.007141745	2.146195686	88	65	6	7963	ITGB6,ITGB8,THBS1,ITGB5,ITGB3,COL1A2
KEGG	Glioma	KEGG:05214	0.007601226	2.119116348	75	151	8	7963	GADD45G,AKT1,GADD45A,RAF1,PDGFB,SHC1,PDGFA,MAP2K1
KEGG	Sphingolipid signaling pathway	KEGG:04071	0.009588183	2.018263698	119	155	10	7963	AKT1,BID,TRAF2,TNF,ROCK2,RAF1,TRADD,RELA,MAP2K1,MAP3K5
KEGG	Neurotrophin signaling pathway	KEGG:04722	0.009588183	2.018263698	119	155	10	7963	AKT1,RIPK2,RAF1,SHC1,RPS6KA5,ATF4,RELA,

									MAP2K1,MAP3K1,MAP3K5
KEGG	Th17 cell differentiation	KEGG:04659	0.012708067	1.89592049	104	149	9	7963	IL1RAP,IL6R,HLA-DRB1,IL6,IL23A,IL1B,RELA,STAT1,TGFBR1
KEGG	Intestinal immune network for IgA production	KEGG:04672	0.013409862	1.872575697	45	90	5	7963	HLA-DRB1,IL10,CXCR4,IL6,IL15
KEGG	Fc epsilon RI signaling pathway	KEGG:04664	0.013759518	1.861396772	67	96	6	7963	AKT1,ALOX5,TNF,RAF1,MAP2K6,MAP2K4
KEGG	Non-alcoholic fatty liver disease	KEGG:04932	0.014744401	1.831372859	150	155	11	7963	IL8,IL6R,AKT1,BID,TRAF2,TNF,IL6,IL1B,ATF4,RELA,MAP3K5
KEGG	Graft-versus-host disease	KEGG:05332	0.015186764	1.818534762	37	113	5	7963	HLA-DRB1,TNF,IL6,GZMB,IL1B
KEGG	Autophagy - animal	KEGG:04140	0.018974671	1.721825753	136	120	9	7963	HMGB1,AKT1,BCL2L1,RAF1,ATG5,SQSTM1,ATG3,BECN1,MAP3K7
KEGG	Platelet activation	KEGG:04611	0.028619666	1.543335438	124	139	9	7963	PTGS1,AKT1,ITGB3,COL1A2,ROCK2,PRKG2,COL3A1,GNAS,PTGIR
KEGG	Prolactin signaling pathway	KEGG:04917	0.032159792	1.492686763	70	151	7	7963	AKT1,IRF1,RAF1,SHC1,RELA,STAT1,MAP2K1
KEGG	Apoptosis - multiple species	KEGG:04215	0.033780669	1.471331755	32	156	5	7963	BIRC5,BID,BCL2L1,BECN1,BIRC2
KEGG	Pathogenic Escherichia coli infection	KEGG:05130	0.037356045	1.427639107	192	157	12	7963	IL8,TRAF2,TNF,IL18,ROCK2,IL6,IL1B,TRADD,MAP3K7,MYD88,RELA,RIPK1
KEGG	Melanoma	KEGG:05218	0.038291051	1.416902709	72	151	7	7963	GADD45G,AKT1,GADD45A,RAF1,PDGFB,PDGFA,MAP2K1
KEGG	GnRH signaling pathway	KEGG:04912	0.039304099	1.405562154	93	154	8	7963	RAF1,MAP2K6,MAP2K4,ELK1,ATF4,GNAS,MAP2K1,MAP3K1
KEGG	FoxO signaling pathway	KEGG:04068	0.039861766	1.399443464	130	84	7	7963	BCL6,GADD45G,AKT1,IL10,GADD45A,RAF1,IL6
KEGG	Allograft rejection	KEGG:05330	0.047948957	1.319220839	34	158	5	7963	HLA-DRB1,TNF,IL10,GZMB,CD40
REAC	Interleukin-4 and Interleukin-13 signaling	REAC:R-HSA-6785807	7.22E-19	18.1412219	110	144	23	10627	BIRC5,IL8,VEGFA,BCL6,MMP9,IL6R,AKT1,ALOX5,BCL2L1,CCL11,TIMP1,TNF,IL10,COL1A2,IL18,IL6,ITGB2,IL23A,IL1B,CCL2,MCL1,IL13RA2,STAT1
REAC	Toll-like Receptor Cascades	REAC:R-HSA-168898	7.32E-17	16.13566796	152	159	25	10627	HMGB1,IRF7,NOD1,TLR7,NOD2,TLR9,RIPK2,MAP2K6,TLR2,ITGB2,MAP2K4,TLR3,MAP3K7,ELK1,MEF2A,MYD88,RPS6KA5,CREB1,RELA,IRF3,MAP2K1,MAP3K1,BIRC2,RIPK1,ATF2
REAC	Toll Like Receptor 4 (TLR4) Cascade	REAC:R-HSA-166016	3.29E-15	14.48240022	126	159	22	10627	HMGB1,IRF7,NOD1,NOD2,RIPK2,MAP2K6,TLR2,ITGB2,MAP2K4,MAP3K7,ELK1,MEF2A,MYD88,RPS6KA5,CREB1,RELA,IRF3,MAP2K1,MAP3K1,BIRC2,RIPK1,ATF2
REAC	Interleukin-10 signaling	REAC:R-HSA-6783783	1.05E-14	13.97981958	45	153	15	10627	IL8,CXCL1,IL1RN,CCL20,CXCL10,TIMP1,TNF,IL10,CCL3,IL18,IL6,IL1B,CCL2,CSF1,CCL4
REAC	Toll Like Receptor 7/8 (TLR7/8) Cascade	REAC:R-HSA-168181	1.91E-14	13.71915904	91	159	19	10627	HMGB1,IRF7,NOD1,TLR7,NOD2,TLR9,RIPK2,MAP2K6,MAP2K4,MAP3K7,ELK1,MEF2A,MYD88,RPS6KA5,CREB1,RELA,MAP2K1,MAP3K1,ATF2
REAC	MyD88 dependent cascade initiated on endosome	REAC:R-HSA-975155	1.91E-14	13.71915904	91	159	19	10627	HMGB1,IRF7,NOD1,TLR7,NOD2,TLR9,RIPK2,MAP2K6,MAP2K4,MAP3K7,ELK1,MEF2A,MYD88,RPS6KA5,CREB1,RELA,MAP2K1,MAP3K1,ATF2
REAC	Toll Like Receptor 3 (TLR3) Cascade	REAC:R-HSA-	2.38E-14	13.62419602	92	159	19	10627	HMGB1,IRF7,NOD1,NOD2,RIPK2,MAP2K6,

		168164						MAP2K4,TLR3,MAP3K7,ELK1,MEF2A,RPS6KA5,CREB1,RELA,IRF3,MAP2K1,BIRC2,RIPK1,ATF2
REAC	Toll Like Receptor 9 (TLR9) Cascade	REAC:R-HSA-168138	4.50E-14	13.34647584	95	159	19	10627	HMGB1,IRF7,NOD1,TLR7,NOD2,TLR9,RIPK2,MAP2K6,MAP2K4,MAP3K7,ELK1,MEF2A,MYD88,RPS6KA5,CREB1,RELA,MAP2K1,MAP3K1,ATF2
REAC	TRAF6 mediated induction of NFkB and MAP kinases upon TLR7/8 or 9 activation	REAC:R-HSA-975138	2.99E-13	12.52462872	90	159	18	10627	HMGB1,NOD1,TLR7,NOD2,TLR9,RIPK2,MAP2K6,MAP2K4,MAP3K7,ELK1,MEF2A,MYD88,RPS6KA5,CREB1,RELA,MAP2K1,MAP3K1,ATF2
REAC	TRIF(TICAM1)-mediated TLR4 signaling	REAC:R-HSA-937061	9.99E-13	12.0003561	96	159	18	10627	HMGB1,IRF7,NOD1,NOD2,RIPK2,MAP2K6,MAP2K4,MAP3K7,ELK1,MEF2A,RPS6KA5,CREB1,RELA,IRF3,MAP2K1,BIRC2,RIPK1,ATF2
REAC	MyD88-independent TLR4 cascade	REAC:R-HSA-166166	9.99E-13	12.0003561	96	159	18	10627	HMGB1,IRF7,NOD1,NOD2,RIPK2,MAP2K6,MAP2K4,MAP3K7,ELK1,MEF2A,RPS6KA5,CREB1,RELA,IRF3,MAP2K1,BIRC2,RIPK1,ATF2
REAC	Toll Like Receptor TLR6:TLR2 Cascade	REAC:R-HSA-168188	1.16E-11	10.93561669	94	159	17	10627	HMGB1,NOD1,NOD2,RIPK2,MAP2K6,TLR2,MAP2K4,MAP3K7,ELK1,MEF2A,MYD88,RPS6KA5,CREB1,RELA,MAP2K1,MAP3K1,ATF2
REAC	MyD88:MAL(TIRAP) cascade initiated on plasma membrane	REAC:R-HSA-166058	1.16E-11	10.93561669	94	159	17	10627	HMGB1,NOD1,NOD2,RIPK2,MAP2K6,TLR2,MAP2K4,MAP3K7,ELK1,MEF2A,MYD88,RPS6KA5,CREB1,RELA,MAP2K1,MAP3K1,ATF2
REAC	Toll Like Receptor TLR1:TLR2 Cascade	REAC:R-HSA-168179	2.00E-11	10.69829704	97	159	17	10627	HMGB1,NOD1,NOD2,RIPK2,MAP2K6,TLR2,MAP2K4,MAP3K7,ELK1,MEF2A,MYD88,RPS6KA5,CREB1,RELA,MAP2K1,MAP3K1,ATF2
REAC	Toll Like Receptor 2 (TLR2) Cascade	REAC:R-HSA-181438	2.00E-11	10.69829704	97	159	17	10627	HMGB1,NOD1,NOD2,RIPK2,MAP2K6,TLR2,MAP2K4,MAP3K7,ELK1,MEF2A,MYD88,RPS6KA5,CREB1,RELA,MAP2K1,MAP3K1,ATF2
REAC	Toll Like Receptor 10 (TLR10) Cascade	REAC:R-HSA-168142	2.92E-11	10.53463038	84	159	16	10627	HMGB1,NOD1,NOD2,RIPK2,MAP2K6,MAP2K4,MAP3K7,ELK1,MEF2A,MYD88,RPS6KA5,CREB1,RELA,MAP2K1,MAP3K1,ATF2
REAC	Toll Like Receptor 5 (TLR5) Cascade	REAC:R-HSA-168176	2.92E-11	10.53463038	84	159	16	10627	HMGB1,NOD1,NOD2,RIPK2,MAP2K6,MAP2K4,MAP3K7,ELK1,MEF2A,MYD88,RPS6KA5,CREB1,RELA,MAP2K1,MAP3K1,ATF2
REAC	MyD88 cascade initiated on plasma membrane	REAC:R-HSA-975871	2.92E-11	10.53463038	84	159	16	10627	HMGB1,NOD1,NOD2,RIPK2,MAP2K6,MAP2K4,MAP3K7,ELK1,MEF2A,MYD88,RPS6KA5,CREB1,RELA,MAP2K1,MAP3K1,ATF2
REAC	MAP kinase activation	REAC:R-HSA-450294	4.27E-08	7.369141985	63	159	12	10627	NOD1,NOD2,RIPK2,MAP2K6,MAP2K4,MAP3K7,ELK1,MEF2A,RPS6KA5,CREB1,MAP2K1,ATF2
REAC	Interleukin-17 signaling	REAC:R-HSA-448424	1.85E-07	6.732808681	71	159	12	10627	NOD1,NOD2,RIPK2,MAP2K6,MAP2K4,MAP3K7,ELK1,MEF2A,RPS6KA5,CREB1,MAP2K1,ATF2
REAC	Interleukin-1 family signaling	REAC:R-HSA-446652	3.50E-07	6.455670789	138	151	15	10627	IL1RN,HMGB1,NOD1,ALOX5,NOD2,RIPK2,IL18,MAP2K6,SQSTM1,MAP2K4,IL1B,MAP3K7,MYD88,RELA,MAP2K1
REAC	Interleukin-1 signaling	REAC:R-HSA-9020702	5.95E-07	6.225300963	101	151	13	10627	IL1RN,HMGB1,NOD1,NOD2,RIPK2,MAP2K6,SQSTM1,MAP2K4,IL1B,MAP3K7,MYD88,RELA,MAP2K1

REAC	Chemokine receptors bind chemokines	REAC:R-HSA-380108	1.12E-06	5.950427815	57	70	8	10627	IL8,CXCL1,CCL20,CXCL6,CXCL10,CCL11,CCL3,CXCR4
REAC	Nucleotide-binding domain, leucine rich repeat containing receptor (NLR) signaling pathways	REAC:R-HSA-168643	2.15E-06	5.666685988	55	156	10	10627	NOD1,BCL2L1,NOD2,RIPK2,MAP2K6,MAP3K7,TXN,RELA,TNFAIP3,BIRC2
REAC	Interferon alpha/beta signaling	REAC:R-HSA-909733	8.33E-06	5.079127418	67	146	10	10627	IRF7,IRF1,OASL,MX2,IRF5,IFIT1,STAT2,IFIT2,IRF3,OAS2
REAC	TNFR1-induced NFkappaB signaling pathway	REAC:R-HSA-5357956	7.67E-05	4.11508233	30	157	7	10627	TRAF2,TNF,TRADD,MAP3K7,TNFAIP3,BIRC2,RIPK1
REAC	NOD1/2 Signaling Pathway	REAC:R-HSA-168638	0.000279693	3.553318043	36	156	7	10627	NOD1,NOD2,RIPK2,MAP2K6,MAP3K7,TNFAIP3,BIRC2
REAC	Integrin cell surface interactions	REAC:R-HSA-216083	0.000735951	3.13315122	84	145	9	10627	ITGB6,ITGB8,THBS1,ITGB5,ITGB3,COL1A2,ITGB2,COL3A1,ITGA3
REAC	DDX58/IFIH1-mediated induction of interferon-alpha/beta	REAC:R-HSA-168928	0.000759611	3.119408859	78	157	9	10627	HMGB1,IRF7,TRAF2,ATG5,RELA,IRF3,TNFAIP3,MAP3K1,RIPK1
REAC	TNF signaling	REAC:R-HSA-75893	0.000876224	3.057384608	42	157	7	10627	TRAF2,TNF,TRADD,MAP3K7,TNFAIP3,BIRC2,RIPK1
REAC	TAK1 activates NFkB by phosphorylation and activation of IKKs complex	REAC:R-HSA-445989	0.001055759	2.976435272	32	137	6	10627	HMGB1,NOD1,NOD2,RIPK2,MAP3K7,RELA
REAC	JNK (c-Jun kinases) phosphorylation and activation mediated by activated human TAK1	REAC:R-HSA-450321	0.001422907	2.846823403	22	120	5	10627	NOD1,NOD2,RIPK2,MAP2K4,MAP3K7
REAC	activated TAK1 mediates p38 MAPK activation	REAC:R-HSA-450302	0.001801807	2.744291748	23	120	5	10627	NOD1,NOD2,RIPK2,MAP2K6,MAP3K7
REAC	Regulation of TNFR1 signaling	REAC:R-HSA-5357905	0.002325486	2.633486364	32	157	6	10627	TRAF2,TNF,TRADD,TNFAIP3,BIRC2,RIPK1
REAC	Death Receptor Signalling	REAC:R-HSA-73887	0.002533713	2.596242563	140	157	11	10627	TRAF2,TNF,RIPK2,SQSTM1,TRADD,MAP3K7,MYD88,RELA,TNFAIP3,BIRC2,RIPK1
REAC	ZBP1(DAI) mediated induction of type I IFNs	REAC:R-HSA-1606322	0.00414133	2.382860172	21	157	5	10627	TLR3,MYD88,RELA,IRF3,RIPK1
REAC	Interferon Signaling	REAC:R-HSA-913531	0.004764992	2.3219378	192	146	12	10627	IRF7,HLA-DRB1,IRF1,OASL,MX2,IRF5,IFIT1,STAT2,IFIT2,IRF3,STAT1,OAS2
REAC	Platelet activation, signaling and aggregation	REAC:R-HSA-76002	0.005160725	2.287289292	258	110	12	10627	VEGFA,SERPINE1,AKT1,THBS1,TIMP1,ITGB3,COL1A2,RAF1,PDGFB,CFL1,SHC1,PTK2
REAC	Non-integrin membrane-ECM interactions	REAC:R-HSA-3000171	0.005223041	2.282076535	58	147	7	10627	THBS1,ITGB5,ITGB3,COL1A2,PDGFB,COL3A1,PDGFA
REAC	Syndecan interactions	REAC:R-HSA-3000170	0.005256781	2.279280104	26	131	5	10627	THBS1,ITGB5,ITGB3,COL1A2,COL3A1
REAC	Extracellular matrix organization	REAC:R-HSA-1474244	0.005769402	2.238869187	298	147	15	10627	MMP9,ITGB6,SERPINE1,ITGB8,THBS1,TIMP1,ITGB5,ITGB3,COL1A2,PDGFB,ITGB2,SERPINH1,

									COL3A1,ITGA3,PDGFA
REAC	Peptide ligand-binding receptors	REAC:R-HSA-375276	0.007153676	2.145470727	194	83	9	10627	IL8,CXCL1,CCL20,CXCL6,CXCL10,CCL11,CCL3,CXCR4,EDN1
REAC	ATF4 activates genes in response to endoplasmic reticulum stress	REAC:R-HSA-380994	0.008219648	2.085146801	27	138	5	10627	IL8,CEBPB,CCL2,ATF4,PARN
REAC	Platelet Aggregation (Plug Formation)	REAC:R-HSA-76009	0.015472717	1.810433407	38	110	5	10627	AKT1,ITGB3,COL1A2,SHC1,PTK2
REAC	PERK regulates gene expression	REAC:R-HSA-381042	0.01946145	1.710824797	32	138	5	10627	IL8,CEBPB,CCL2,ATF4,PARN
REAC	Molecules associated with elastic fibres	REAC:R-HSA-2129379	0.021014488	1.677481188	37	61	4	10627	ITGB6,ITGB8,ITGB5,ITGB3
REAC	Interferon gamma signaling	REAC:R-HSA-877300	0.02346433	1.629591834	87	52	5	10627	IRF7,HLA-DRB1,IRF1,OASL,IRF5
REAC	Presynaptic phase of homologous DNA pairing and strand exchange	REAC:R-HSA-5693616	0.030015401	1.522655845	39	123	5	10627	CHEK1,BLM,RAD51,ATR,RAD9A
REAC	MAPK targets/ Nuclear events mediated by MAP kinases	REAC:R-HSA-450282	0.032589323	1.486924656	31	159	5	10627	ELK1,MEF2A,RPS6KA5,CREB1,ATF2
REAC	ECM proteoglycans	REAC:R-HSA-3000178	0.033904041	1.469748532	75	65	5	10627	ITGB6,SERPINE1,ITGB5,ITGB3,COL1A2
REAC	Platelet degranulation	REAC:R-HSA-114608	0.035068866	1.455078277	125	91	7	10627	VEGFA,SERPINE1,THBS1,TIMP1,ITGB3,PDGFB,CFL1
REAC	Elastic fibre formation	REAC:R-HSA-1566948	0.041917348	1.377606202	44	61	4	10627	ITGB6,ITGB8,ITGB5,ITGB3
REAC	Homologous DNA Pairing and Strand Exchange	REAC:R-HSA-5693579	0.043135143	1.365168756	42	123	5	10627	CHEK1,BLM,RAD51,ATR,RAD9A
REAC	Response to elevated platelet cytosolic Ca2+	REAC:R-HSA-76005	0.044879519	1.34795181	130	91	7	10627	VEGFA,SERPINE1,THBS1,TIMP1,ITGB3,PDGFB,CFL1
REAC	Regulation of TP53 Activity	REAC:R-HSA-5633007	0.046116721	1.336141581	160	127	9	10627	CHEK1,BLM,AKT1,DAXX,CHEK2,ATR,MAP2K6,RAD9A,MAPKAPK5
REAC	Cellular Senescence	REAC:R-HSA-2559583	0.046297639	1.334441157	194	155	11	10627	IL8,MAP2K6,IL6,MAP2K4,CEBPB,TXN,MAPKAPK5,TERF1,RELA,IGFBP7,MAP3K5
WP	p38 MAPK Signaling Pathway	WP:WP400	1.54E-23	22.81294106	34	159	20	7474	MAP3K9,DAXX,TRAF2,MAP2K6,MKNK1,MAP2K4,HMGN1,SHC1,TRADD,MAP3K7,ELK1,MAPKAPK5,RPS6KA5,CREB1,STAT1,TGFBR1,MAP3K1,MAP3K5,RIPK1,ATF2
WP	Toll-like Receptor Signaling Pathway	WP:WP75	8.00E-17	16.09689112	104	158	24	7474	IL8,IRF7,AKT1,CXCL10,IRF5,TLR7,TNF,CCL3,TLR9,MAP2K6,IL6,TLR2,MAP2K4,IL1B,TLR3,MAP3K7,MYD88,RELA,IRF3,STAT1,MAP2K1,CCL4,RIPK1,CD40
WP	Regulation of toll-like receptor signaling pathway	WP:WP1449	1.65E-16	15.78369122	145	158	27	7474	IL8,IRF7,AKT1,SMAD6,CXCL10,IRF5,TLR7,TNF,CCL3,TLR9,MAP2K6,IL6,SQSTM1,TLR2,MAP2K4,IL1B,TLR3,MAP3K7,MYD88,RELA,IRF3,STAT1,MAP2K1,TNFAIP3,CCL4,RIPK1,CD40

WP	Lung fibrosis	WP:WP3624	9.98E-16	15.00072448	63	153	19	7474	IL8,MMP9,TERT,PLAU,CCL11,TIMP1,TNF,CCL3,PDGFB,EDN1,IL6,SMAD7,GREM1,CEBPB,IL1B,CCL2,PARN,PDGFA,CCL4
WP	Hepatitis B infection	WP:WP4666	1.14E-14	13.94297198	154	159	26	7474	BIRC5,IL8,MMP9,IRF7,AKT1,BID,TNF,RAF1,MAP2K6,IL6,TLR2,MAP2K4,TLR3,STAT2,MAP3K7,ELK1,MYD88,ATF4,CREB1,RELA,IRF3,STAT1,TGFBR1,MAP2K1,MAP3K1,ATF2
WP	Senescence and Autophagy in Cancer	WP:WP615	2.35E-13	12.62810688	108	151	21	7474	IL8,CXCL1,IL6R,SERPINE1,PLAU,IRF7,IRF1,THBS1,IRF5,CCL3,RAF1,ATG5,IL6,SQSTM1,ATG3,BECN1,CEBPB,IL1B,COL3A1,IGFBP7,MAP2K1
WP	Apoptosis	WP:WP254	1.42E-11	10.84673924	86	157	18	7474	BIRC5,IRF7,AKT1,IRF1,BID,BCL2L1,IRF5,TRAF2,TNF,GZMB,MAP2K4,TRADD,MCL1,RELA,IRF3,MAP3K1,BIRC2,RIPK1
WP	TNF alpha Signaling Pathway	WP:WP231	7.28E-11	10.13787387	94	157	18	7474	AKT1,BID,BCL2L1,TRAF2,TNF,RAF1,MAP2K6,IL6,MAP2K4,TRADD,CCL2,MAP3K7,TXN,TNFAIP3,MAP3K1,MAP3K5,BIRC2,RIPK1
WP	Cytokines and Inflammatory Response	WP:WP530	9.38E-11	10.02758054	26	147	11	7474	CXCL1,IL11,HLA-DRB1,TNF,IL10,IL6,IL15,IL1B,IL7,CSF1,PDGFA
WP	miRNAs involvement in the immune response in sepsis	WP:WP4329	1.63E-10	9.787042343	63	153	15	7474	IL8,IRF7,IRF1,IRF5,TLR7,TNF,IL10,CCL3,IL6,GZMB,MAP3K7,MYD88,RELA,RELB,CCL4
WP	IL-18 signaling pathway	WP:WP4754	1.24E-09	8.90718841	279	153	27	7474	IL8,TNFRSF11B,VEGFA,MMP9,LTB,CCL20,IRF1,BID,BCL2L1,TIMP1,PARP1,TNF,IL10,COL1A2,CCL3,IL18,IL6,CEBPB,IL1B,CCL2,MAP3K7,MEF2A,MYD88,COL3A1,RELA,TNFAIP3,CCL4
WP	Structural Pathway of Interleukin 1 (IL-1)	WP:WP2637	2.69E-09	8.571013239	50	159	13	7474	IL1RAP,IRF7,MAP2K6,MKNK1,MAP2K4,MAP3K7,ELK1,MYD88,RPS6KA5,RELA,MAP2K1,MAP3K1,ATF2
WP	TNF related weak inducer of apoptosis (TWEAK) Signaling Pathway	WP:WP2036	4.16E-09	8.381286563	42	157	12	7474	MMP9,AKT1,TRAF2,TNF,RAF1,IL6,CCL2,MAP3K7,RELA,RELB,BIRC2,RIPK1
WP	Viral Acute Myocarditis	WP:WP4298	9.65E-09	8.015411121	87	144	15	7474	MMP9,AKT1,BID,BCL2L1,PARP1,TNF,IL10,NOD2,CXCR4,EDN1,IL6,ITGB2,TLR3,CREB1,STAT1
WP	IL-1 signaling pathway	WP:WP195	1.63E-08	7.788011587	57	159	13	7474	IL1RAP,AKT1,MAP2K6,SQSTM1,MAP2K4,IL1B,CCL2,MAP3K7,MYD88,RELA,MAP2K1,MAP3K1,ATF2
WP	Photodynamic therapy-induced HIF-1 survival signaling	WP:WP3614	2.13E-08	7.671419102	37	83	9	7474	BIRC5,VEGFA,SLC2A1,SERPINE1,IGFBP2,BID,BCL2L1,LDHA,EDN1
WP	MAPK Signaling Pathway	WP:WP382	5.03E-08	7.29870053	249	159	24	7474	AKT1,DAXX,TRAF2,TNF,GADD45A,RAF1,MAP2K6,PDGFB,MKNK1,MAP2K4,IL1B,MAP3K7,ELK1,MAPKAPK5,RPS6KA5,ATF4,RELA,PDGFA,TGFBR1,RELB,MAP2K1,MAP3K1,MAP3K5,ATF2
WP	IL-6 signaling pathway	WP:WP364	7.01E-08	7.154258064	43	151	11	7474	IL6R,AKT1,IRF1,BCL2L1,TIMP1,IL6,MAP2K4,SHC1,MAP3K7,STAT1,MAP2K1
WP	Signal transduction through IL1R	WP:WP4496	1.62E-07	6.789427751	35	154	10	7474	IL1RN,IL1RAP,TNF,MAP2K6,IL6,IL1B,MAP3K7,MYD88,RELA,MAP3K1
WP	Photodynamic therapy-induced NF-kB survival signaling	WP:WP3617	1.84E-07	6.734378479	35	156	10	7474	BIRC5,IL8,VEGFA,MMP9,TNF,IL6,IL1B,RELA,RELB,BIRC2
WP	Leptin signaling pathway	WP:WP2034	3.80E-07	6.420202025	76	151	13	7474	IL1RN,AKT1,BCL2L1,ROCK2,RAF1,SHC1,PTK2,

									IL1B,ELK1,CREB1,RELA,STAT1,MAP2K1
WP	Novel intracellular components of RIG-I-like receptor (RLR) pathway	WP:WP3865	4.64E-07	6.333314569	61	157	12	7474	IL8,IRF7,CXCL10,TRAF2,TNF,ATG5,TRADD, MAP3K7,RELA,IRF3,MAP3K1,RIPK1
WP	Photodynamic therapy-induced AP-1 survival signaling.	WP:WP3611	8.73E-07	6.058855329	51	159	11	7474	BID,BCL2L1,TRAF2,TNF,MAP2K6,IL6,MAP2K4,ELK1,MCL1,MAP3K5,ATF2
WP	Toll-like Receptor Signaling related to MyD88	WP:WP3858	1.05E-06	5.978462293	32	150	9	7474	IRF7,TLR7,TLR9,TLR2,TLR3,MYD88,RELA,IRF3,RELB
WP	RANKL/RANK (Receptor activator of NFKB (ligand)) Signaling Pathway	WP:WP2018	1.18E-06	5.926530452	55	151	11	7474	TNFRSF11B,AKT1,TRAF2,MAP2K6,SQSTM1, PTK2,MAP3K7,RELA,STAT1,RELB,MAP2K1
WP	Gastrin Signaling Pathway	WP:WP4659	1.93E-06	5.714299408	114	159	15	7474	BIRC5,IL8,VEGFA,SERPINE1,AKT1,BCL2L1, RAF1,SHC1,PTK2,ELK1,CREB1,RELA,MAP2K1, BIRC2,ATF2
WP	TGF-beta Signaling Pathway	WP:WP366	2.31E-06	5.635844776	133	159	16	7474	TERT,AKT1,THBS1,ITGB3,COL1A2,RAF1, MAP2K6,MAP2K4,SHC1,SMAD7,PTK2,MAP3K7, MEF2A,TGFBR1,MAP2K1,ATF2
WP	Oncostatin M Signaling Pathway	WP:WP2374	8.79E-06	5.056252011	66	151	11	7474	VEGFA,SERPINE1,AKT1,RAF1,SHC1,CEBPB, CCL2,CREB1,RELA,STAT1,MAP2K1
WP	Fibrin Complement Receptor 3 Signaling Pathway	WP:WP4136	9.30E-06	5.031337648	42	143	9	7474	AKT1,CXCL10,TNF,IL6,ITGB2,TLR3,CCL2, MYD88,IRF3
WP	PDGF Pathway	WP:WP2526	1.12E-05	4.949893534	40	154	9	7474	RAF1,PDGFB,MAP2K4,SHC1,ELK1,STAT1, PDGFA,MAP2K1,MAP3K1
WP	ATM Signaling Pathway	WP:WP2516	1.48E-05	4.82992252	40	159	9	7474	CHEK1,RAD51,BID,CHEK2,GADD45A,RAD9A, CREB1,RIPK1,ATF2
WP	Integrin-mediated Cell Adhesion	WP:WP185	1.67E-05	4.77811965	103	151	13	7474	ITGB6,AKT1,ITGB8,ITGB5,ITGB3,ROCK2,RAF1,MAP2K6,ITGB2,SHC1,PTK2,ITGA3,MAP2K1
WP	TLR4 Signaling and Tolerance	WP:WP3851	1.68E-05	4.775660208	30	157	8	7474	IL8,IRF7,TNF,IL6,MAP3K7,MYD88,IRF3,RIPK1
WP	IL1 and megakaryocytes in obesity	WP:WP2865	1.92E-05	4.715921343	25	129	7	7474	MMP9,TIMP1,IL18,TLR2,IL1B,CCL2,MYD88
WP	Focal Adhesion	WP:WP306	2.19E-05	4.660167779	201	156	18	7474	VEGFA,ITGB6,AKT1,ITGB8,THBS1,ITGB5,ITGB3,COL1A2,ROCK2,RAF1,PDGFB,SHC1,PTK2,ELK1,ITGA3,PDGFA,MAP2K1,BIRC2
WP	Cardiac Hypertrophic Response	WP:WP2795	2.59E-05	4.586791159	57	154	10	7474	AKT1,TNF,RAF1,MAP2K6,MAP2K4,MAP3K7, MEF2A,TGFBR1,MAP2K1,MAP3K1
WP	Non-genomic actions of 1,25 dihydroxyvitamin D3	WP:WP4341	2.63E-05	4.580684773	70	158	11	7474	IL8,TNF,NOD2,IL6,TLR2,STAT2,CCL2,STAT1, OAS2,RELB,CD40
WP	Host-pathogen interaction of human corona viruses - Interferon induction	WP:WP4880	3.77E-05	4.423772106	33	157	8	7474	TLR7,STAT2,MAP3K7,MYD88,IRF3,STAT1,OAS2,RIPK1
WP	Spinal Cord Injury	WP:WP2431	4.18E-05	4.378782651	118	119	12	7474	IL8,CXCL1,MMP9,LTB,MIF,CXCL10,TNF, GADD45A,ROCK2,IL6,IL1B,CCL2
WP	Corticotropin-releasing hormone signaling pathway	WP:WP2355	4.25E-05	4.371971113	91	155	12	7474	IL8,AKT1,PARP1,IL18,RAF1,PTK2,ELK1,GNAS, CREB1,RELA,MAP2K1,MAP3K5
WP	Cytosolic DNA-sensing pathway	WP:WP4655	4.42E-05	4.35430728	74	157	11	7474	IRF7,CXCL10,IL18,ATG5,IL6,IL1B,TRADD,RELA,IRF3,CCL4,RIPK1
WP	Integrated Breast Cancer Pathway	WP:WP1984	4.69E-05	4.328406326	154	149	15	7474	CHEK1,VEGFA,BLM,RAD51,AKT1,BID,SMAD6,CHEK2,ATR,GADD45A,SMAD7,TRADD,CREB1,STAT1,TGFBR1

WP	DNA IR-Double Strand Breaks (DSBs) and cellular response via ATM	WP:WP3959	5.87E-05	4.231005674	55	66	7	7474	CHEK1,BLM,RAD51,BID,CHEK2,PARP1,ATR
WP	Development and heterogeneity of the ILC family	WP:WP3893	6.26E-05	4.203294873	32	117	7	7474	TNF,IL18,IL6,IL15,IL23A,IL1B,IL7
WP	Hepatitis C and Hepatocellular Carcinoma	WP:WP3646	8.72E-05	4.059342117	50	48	6	7474	BIRC5,IL8,VEGFA,IL6R,AKT1,BCL2L1
WP	Selenium Micronutrient Network	WP:WP15	9.51E-05	4.021792441	91	137	11	7474	PTGS1,SERPINE1,ALOX5,TNF,IL6,PRDX1,IL1B, TXNRD1,CCL2,TXN,RELA
WP	LTF danger signal response pathway	WP:WP4478	1.00E-04	4.000001121	20	129	6	7474	IL8,TNF,IL6,TLR2,IL1B,MYD88
WP	Apoptosis-related network due to altered Notch3 in ovarian cancer	WP:WP2864	0.000135097	3.869354743	54	110	8	7474	BIRC5,AKT1,THBS1,TNF,RIPK2,SQSTM1,SMAD7,PTK2
WP	Type I Interferon Induction and Signaling During SARS-CoV-2 Infection	WP:WP4868	0.000136831	3.863814744	29	146	7	7474	TLR7,STAT2,MAP3K7,MYD88,IRF3,STAT1,OAS2
WP	Chemokine signaling pathway	WP:WP3929	0.000161535	3.791733816	165	153	15	7474	CCL20,AKT1,CXCL10,CCL11,CCL3,CXCR4, ROCK2,RAF1,SHC1,PTK2,STAT2,RELA,STAT1, MAP2K1,CCL4
WP	Pancreatic adenocarcinoma pathway	WP:WP4263	0.000178784	3.747670179	88	151	11	7474	VEGFA,GADD45G,RAD51,AKT1,BCL2L1, GADD45A,RAF1,RELA,STAT1,TGFBR1,MAP2K1
WP	PDGFR-beta pathway	WP:WP3972	0.000196171	3.707364381	29	154	7	7474	RAF1,MAP2K4,SHC1,ELK1,STAT1,MAP2K1, MAP3K1
WP	Interleukin-11 Signaling Pathway	WP:WP2332	0.000294972	3.530219295	44	151	8	7474	BIRC5,IL11,AKT1,RAF1,CREB1,RELA,STAT1, MAP2K1
WP	T-Cell antigen Receptor (TCR) Signaling Pathway	WP:WP69	0.000416909	3.379958457	91	159	11	7474	AKT1,RIPK2,RAF1,IL6,SHC1,IL1B,MAP3K7, CREB1,RELA,MAP2K1,ATF2
WP	Apoptosis Modulation and Signaling	WP:WP1772	0.000457594	3.339519383	93	157	11	7474	BIRC5,TNFRSF11B,BID,BCL2L1,DAXX,TRADD,MYD88,MCL1,MAP3K5,BIRC2,RIPK1
WP	EBV LMP1 signaling	WP:WP262	0.000466216	3.331412931	24	137	6	7474	IL8,CCL20,TNF,TRADD,MAP3K7,RELA
WP	Thymic Stromal LymphoPoietin (TSLP) Signaling Pathway	WP:WP2203	0.000497184	3.303482573	47	151	8	7474	IL8,AKT1,CCL11,IL6,RELA,STAT1,RELB,MAP2K1
WP	DNA Damage Response	WP:WP707	0.000504038	3.297536888	69	136	9	7474	CHEK1,GADD45G,RAD51,BID,CHEK2,ATR, GADD45A,RAD9A,CREB1
WP	Complement and Coagulation Cascades	WP:WP558	0.000691128	3.16044181	59	33	5	7474	CFB,C2,PLAUR,SERPINE1,PLAU
WP	EGFR Tyrosine Kinase Inhibitor Resistance	WP:WP4806	0.000862542	3.064219512	84	151	10	7474	VEGFA,IL6R,AKT1,BCL2L1,RAF1,PDGFB,IL6, SHC1,PDGFA,MAP2K1
WP	B Cell Receptor Signaling Pathway	WP:WP23	0.000868309	3.061325944	98	159	11	7474	BCL6,AKT1,RAF1,MAP2K6,SHC1,MAP3K7,ELK1,CREB1,RELA,MAP2K1,ATF2
WP	Neovascularisation processes	WP:WP4331	0.000947057	3.023624033	37	150	7	7474	MMP9,AKT1,CXCR4,PDGFB,RELA,TGFBR1,RELB
WP	Brain-Derived Neurotrophic Factor (BDNF) signaling pathway	WP:WP2380	0.000998576	3.000619009	144	154	13	7474	AKT1,RAF1,SQSTM1,CFL1,SHC1,ELK1,MEF2A, RPS6KA5,CREB1,RELA,STAT1,MAP2K1,MAP3K1
WP	Host-pathogen interaction of human corona viruses - MAPK signaling	WP:WP4877	0.00114777	2.94014496	36	159	7	7474	MAP3K9,RAF1,MAP2K6,MAP2K4,MAP2K1, MAP3K1,ATF2
WP	AGE/RAGE pathway	WP:WP2324	0.001248023	2.90377729	66	159	9	7474	MMP9,AKT1,RAF1,SHC1,MYD88,RELA,STAT1,MAP2K1,ATF2
WP	Oxidative Damage	WP:WP3941	0.00160474	2.794595267	41	96	6	7474	C2,MAP3K9,TRAF2,TNF,GADD45A,MAP2K4

WP	Allograft Rejection	WP:WP2328	0.001962759	2.707133094	88	158	10	7474	IL8,C2,VEGFA,HLA-DRB1,TNF,IL10,GZMB,IL1B,STAT1,CD40
WP	Bladder Cancer	WP:WP2828	0.002019436	2.694769882	41	151	7	7474	IL8,VEGFA,MMP9,THBS1,RAF1,RPS6KA5,MAP2K1
WP	Angiopoietin Like Protein 8 Regulatory Pathway	WP:WP3915	0.002090961	2.679654146	131	155	12	7474	SLC2A1,MAP3K9,AKT1,RAF1,MAP2K6,MAP2K4,SHC1,MAP3K7,RPS6KA5,MAP2K1,MAP3K1,MAP3K5
WP	TGF-beta Receptor Signaling	WP:WP560	0.002278647	2.642323001	58	149	8	7474	ITGB6,SERPINE1,SMAD6,THBS1,TNF,SMAD7,STAT1,TGFBR1
WP	IL-4 Signaling Pathway	WP:WP395	0.002449064	2.610999911	55	159	8	7474	BIRC5,AKT1,SHC1,CEBPB,ELK1,RELA,STAT1,ATF2
WP	Prolactin Signaling Pathway	WP:WP2037	0.002653591	2.576166	76	151	9	7474	AKT1,IRF1,RAF1,SHC1,PTK2,ELK1,RELA,STAT1,MAP2K1
WP	Angiogenesis	WP:WP1539	0.002865761	2.542760078	24	110	5	7474	VEGFA,MMP9,AKT1,PDGFB,PTK2
WP	Nonalcoholic fatty liver disease	WP:WP4396	0.003139191	2.503182327	159	155	13	7474	IL8,IL6R,AKT1,BID,TRAF2,TNF,IL6,SMAD7,IL1B,CCL2,ATF4,RELA,MAP3K5
WP	Insulin Signaling	WP:WP481	0.003356305	2.474138568	160	155	13	7474	SLC2A1,MAP3K9,AKT1,RAF1,MAP2K6,MAP2K4,SHC1,MAP3K7,ELK1,RPS6KA5,MAP2K1,MAP3K1,MAP3K5
WP	Fas Ligand (FasL) pathway and Stress induction of Heat Shock Proteins (HSP) regulation	WP:WP314	0.003716281	2.429891471	44	154	7	7474	DAXX,PARP1,TNF,RIPK2,MAP2K4,MAP3K7,MAP3K1
WP	Host-pathogen interaction of human corona viruses - apoptosis	WP:WP4864	0.003754292	2.425471906	22	62	4	7474	AKT1,BID,BCL2L1,TNF
WP	TGF-beta Receptor Signalling in Skeletal Dysplasias	WP:WP4816	0.003757675	2.425080729	62	149	8	7474	ITGB6,SERPINE1,SMAD6,THBS1,TNF,SMAD7,STAT1,TGFBR1
WP	miRNA Regulation of DNA Damage Response	WP:WP1530	0.004107353	2.386437921	93	73	7	7474	CHEK1,GADD45G,RAD51,BID,CHEK2,ATR,GADD45A
WP	Integrated Cancer Pathway	WP:WP1971	0.004509839	2.345838969	45	155	7	7474	CHEK1,BLM,AKT1,CHEK2,ATR,STAT1,MAP3K5
WP	Small cell lung cancer	WP:WP4658	0.004553915	2.341615053	98	156	10	7474	GADD45G,AKT1,BID,BCL2L1,TRAF2,GADD45A,PTK2,RELA,ITGA3,BIRC2
WP	Differentiation Pathway	WP:WP2848	0.00494469	2.305860895	48	147	7	7474	VEGFA,IL6R,IL11,PDGFB,IL6,CSF1,PDGFA
WP	Hereditary leiomyomatosis and renal cell carcinoma pathway	WP:WP4206	0.005652717	2.247742773	20	76	4	7474	VEGFA,SLC2A1,KEAP1,LDHA
WP	MAPK Cascade	WP:WP422	0.006487926	2.187894102	33	154	6	7474	RAF1,MAP2K6,MAP2K4,ELK1,MAP2K1,MAP3K1
WP	Amyotrophic lateral sclerosis (ALS)	WP:WP2447	0.006692321	2.174423241	38	81	5	7474	BID,BCL2L1,DAXX,TNF,MAP2K6
WP	Association Between Physico-Chemical Features and Toxicity Associated Pathways	WP:WP3680	0.008165705	2.088006334	68	151	8	7474	AKT1,ROCK2,RAF1,MAP2K4,SHC1,PTK2,ELK1,MAP2K1
WP	Type II interferon signaling (IFNG)	WP:WP619	0.008753495	2.057818499	37	144	6	7474	IRF1,CXCL10,IL1B,STAT2,IFIT2,STAT1
WP	p53 transcriptional gene network	WP:WP4963	0.008849269	2.053092582	72	73	6	7474	SLC2A1,SERPINE1,FANCC,THBS1,IRF5,GADD45A
WP	Vitamin D in inflammatory diseases	WP:WP4482	0.009229194	2.034836223	22	154	5	7474	TNF,MAP2K6,IL6,RELA,MAP3K1
WP	DNA IR-damage and cellular response via ATR	WP:WP4016	0.009723363	2.012183511	81	66	6	7474	CHEK1,BCL6,RAD51,CHEK2,PARP1,ATR
WP	Netrin-UNC5B signaling Pathway	WP:WP4747	0.009978247	2.000945754	52	151	7	7474	AKT1,TNF,IL10,RAF1,PTK2,CCL2,MAP2K1
WP	Estrogen signaling pathway	WP:WP712	0.010561764	1.97626356	23	151	5	7474	AKT1,ELK1,GNAS,CREB1,MAP2K1

WP	Nucleotide-binding Oligomerization Domain (NOD) pathway	WP:WP1433	0.012055884	1.918800948	41	137	6	7474	NOD1,NOD2,RIPK2,IL18,IL1B,RELA
WP	NRF2 pathway	WP:WP2884	0.014907711	1.826589049	145	121	10	7474	SLC2A1,KEAP1,FTH1,PDGFB,SQSTM1,MAFG,PRDX1,GCLM,TXNRD1,TXN
WP	IL-7 Signaling Pathway	WP:WP205	0.016141297	1.79206157	25	151	5	7474	AKT1,BCL2L1,IL7,STAT1,MAP2K1
WP	Complement Activation	WP:WP545	0.01646954	1.783318523	22	6	2	7474	CFB,C2
WP	EGF/EGFR Signaling Pathway	WP:WP437	0.016982983	1.769986017	163	154	12	7474	AKT1,RAF1,CFL1,SHC1,PTK2,ELK1,MEF2A,RPS6KA5,CREB1,STAT1,MAP2K1,MAP3K1
WP	IL-5 Signaling Pathway	WP:WP127	0.017914567	1.746793682	40	151	6	7474	AKT1,RAF1,SHC1,ELK1,STAT1,MAP2K1
WP	EPO Receptor Signaling	WP:WP581	0.019661376	1.706386102	26	151	5	7474	AKT1,RAF1,SHC1,STAT1,MAP2K1
WP	Human Complement System	WP:WP2806	0.0204195	1.689954894	99	88	7	7474	CFB,C2,PLAUR,THBS1,ITGB3,TLR2,ITGB2
WP	FGFR3 signalling in chondrocyte proliferation and terminal differentiation	WP:WP4767	0.02373992	1.624520754	27	151	5	7474	SNAI1,RAF1,ATG5,STAT1,MAP2K1
WP	Adipogenesis	WP:WP236	0.025563686	1.592376525	130	144	10	7474	SERPINE1,MIF,TNF,GADD45A,IL6,CEBPB,STAT2,MEF2A,CREB1,STAT1
WP	Mechanoregulation and pathology of YAP/TAZ via Hippo and non-Hippo mechanisms	WP:WP4534	0.02804026	1.55221797	47	88	5	7474	ITGB6,ITGB8,ITGB5,ITGB3,ITGB2
WP	Androgen receptor signaling pathway	WP:WP138	0.028127215	1.550873267	89	137	8	7474	AKT1,DAXX,ROCK2,PRDX1,PTK2,RAD9A,CREB1,RELA
WP	Vitamin D Receptor Pathway	WP:WP2877	0.032048345	1.494194387	182	52	7	7474	CA9,TNFRSF11B,BCL6,HLA-DRB1,ALOX5,MX2,IRF5
WP	Endochondral Ossification	WP:WP474	0.037086871	1.430779803	65	37	4	7474	VEGFA,MMP9,PLAU,AKT1
WP	Endochondral Ossification with Skeletal Dysplasias	WP:WP4808	0.037086871	1.430779803	65	37	4	7474	VEGFA,MMP9,PLAU,AKT1
WP	MicroRNAs in cardiomyocyte hypertrophy	WP:WP1544	0.039798356	1.400134867	101	96	7	7474	AKT1,TNF,ROCK2,RAF1,MAP2K6,EDN1,MAP2K4
WP	Resistin as a regulator of inflammation	WP:WP4481	0.040383579	1.393795197	33	137	5	7474	IL8,AKT1,TNF,IL6,RELA
WP	Regulation of Apoptosis by Parathyroid Hormone-related Protein	WP:WP3872	0.046982607	1.328062888	22	48	3	7474	AKT1,BID,BCL2L1
WP	Folate Metabolism	WP:WP176	0.047416093	1.32407423	73	137	7	7474	SERPINE1,TNF,IL6,IL1B,CCL2,CSF1,RELA
MIRNA	hsa-miR-146a-5p	MIRNA:hsa-miR-146a-5p	1.24E-07	6.90653791	200	89	13	14834	IL8,PLAUR,IL1RAP,IRF7,MIF,OASL,MX2,CXCR4,IL6,SQSTM1,TLR2,ITGB2,IFIT1
MIRNA	hsa-miR-451a	MIRNA:hsa-miR-451a	0.000443866	3.352748419	31	154	6	14834	MMP9,IL6R,AKT1,MIF,IL6,MAP3K1
MIRNA	hsa-miR-4677-3p	MIRNA:hsa-miR-4677-3p	0.016151904	1.791776279	74	2	2	14834	BIRC5,IL8
MIRNA	hsa-miR-143-3p	MIRNA:hsa-miR-143-3p	0.02263012	1.645313144	228	131	10	14834	MMP9,SERPINE1,TERT,AKT1,TNF,PDGFB,TLR2,LIMK1,MAP3K7,COL3A1
HP	Joint swelling	HP:0001386	0.004406848	2.3558719	35	84	7	4322	TNFRSF11B,IL1RN,HLA-DRB1,MIF,CHEK2,NOD2,IL6

ABSTRACT(IN KOREAN)

상피성 난소암에 호르몬 수용체 발현 패턴에 따른 종양 침윤 림프구의 임상적 의의 및 상피성 난소암과 재발성 난소암에서 호르몬 수용체 발현 패턴의 변화에 따른 임상적 의의

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한관희

호르몬 수용체 발현 양식은 종종 특정 림프구의 종양 침윤과 관련이 있다. 구체적으로, 특수한 호르몬 수용체 발현을 하는 특정 종양침윤 림프구(TIL)의 유무는 유방암과 관련되어 있다고 전해지지만 상피성 난소암(EOC)과 관련해서는 밝혀진 바가 없었다. 따라서 우리는 호르몬 수용체 발현과 상피성 난소암에서의 종양침윤 림프구와의 연관성을 조사하였다. 조직 미세배열 분석이나 전체 조직 단면 분석법을 이용해 에스트로겐 수용체(ER)α, 안드로겐 수용체(AR), 당질코르티코이드 수용체(GR), 프로게스테론 수용체(PR), ERβ, CD3$^+$, CD4$^+$, CD8$^+$, FoxP3$^+$, PD-1 및 PD-L1에 대한 면역조직화학적 분석을 시행하였다. 나노스트링 분석으로 정상 상피조직 및 상피성 난소암 조직을 비교하였는데, 이 조직들은 상호 보완적인 생물정보학적 접근법을 이용하여 호르몬 수용체 발현 양식을 토대로 군집되었다. ERα, AR 및 GR의 발현은 상피성 난소암에서 증가한 반면, PR은 유의하게 감소하였고 ERβ 발현은 정상 상피와 비교하여 감소 추세를 보였다. 군집 분석

결과 AR$^+$/GR$^+$/PR$^+$하위 집단 (Triple dominant 집단)에서 무질병 생존율 (DFS)이 불량하게 나타났다. 반면, Cox 비례위험 모형은 이 Triple dominant 집단을 무질병 생존율에 대한 독립적 예후 인자로 조명하였다. 또한, 다른 집단과 비교하여 Triple dominant 집단에서 FoxP3$^+$ TILs, PD-1, 그리고 PD-L1의 유의한 상향조절이 관찰되었다. 더 나아가 나노스트링 분석은 Triple dominant 상피성 난소암 집단에서 *RELA, MAP3K5, TNFAIP3, BCL2L1, RIPK1, TRAF2, PARP1* 및 *AKT1*의 유의한 상향조절로 종양괴사인자(TNF)나 NF-κB 신호전달 경로가 활성화되었음을 제시하였다. Triple dominant 집단은 상피성 난소암의 불량한 예후와 관련이 있다. 뿐만 아니라, 종양괴사인자나 NF-κB 신호전달 경로는 면역 미세환경의 호르몬 매개 억제에 대해 책임이 있을 수도 있다.

핵심되는 말 : 상피성 난소암, 호르송 수용체, Triple dominant 집단, 종양침윤림프구, 조절 T 세포

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