Efficacy of IP-10 as a biomarker for the diagnosis of tuberculosis

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Efficacy of IP-10 as a biomarker for the diagnosis of tuberculosis

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ABSTRACT

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Background: The aim of this study was to evaluate inducible protein 10 (IP-10) as an additional biomarker for specific tuberculosis (TB) infection in an area of intermediate TB burden and to evaluate the ability of IP-10 to distinguish between active TB and latent TB infection (LTBI).

Method: Eighty individuals were prospectively enrolled: 25 with active pulmonary TB, 25 household contacts, and 30 healthy controls. We measured IP-10 in serum and in supernatants from whole blood stimulated with *Mycobacterium tuberculosis*-specific antigen. Enrolled individuals were also tested using a QuantiFERON-TB Gold In-Tube assay (QFT-GIT) and a tuberculin skin test.

Results: TB antigen-dependent IP-10 secretion (IP-10 TB-Nil) was significantly increased in the active TB and LTBI groups compared with controls, but did not differ significantly between the active TB and the LTBI groups. Serum IP-10 levels were higher in the active TB group (174.9 pg/ml) than in the LTBI group (102.7 pg/ml, *P*=0.002). When the IP-10 response to TB antigen was scored based on receiver operating characteristic analysis, active TB was predicted with 88% sensitivity and 90.5% specificity. The QFT-GIT assay showed 96%

sensitivity and 81% specificity for active TB. The combination of the TB antigen-dependent IP-10 response and serum IP-10 level resulted in 81.6% correct classification of active TB or LTBI.

Conclusion: The IP-10 response to TB antigen stimulation may represent a specific biomarker for TB infection, but does not by itself distinguish between active TB and LTBI. Serum IP-10 may help to distinguish active TB from LTBI when used in combination with another marker.

Key words: IP-10, IGRA, latent TB infection

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I. INTRODUCTION

Despite the global effort to reduce the tuberculosis (TB) burden, TB is the highest infectious cause of mortality and morbidity worldwide, with 1.7 million deaths and 9.4 million incident cases in 2009 alone [1]. Efforts to reduce the TB burden are linked to the development of rapid diagnostic tests for infection with *Mycobacterium tuberculosis* .The interferon-γ (IFN-γ) release assay (IGRA), a recently developed immunodiagnostic test for tuberculosis, is commercially available as the QuantiFERON-TB Gold In-Tube assay (QFT-GIT; Cellestis, Australia) and the T-SPOT.*TB* test (Oxford Immunotec, UK). Compared with the tuberculin skin test (TST), the IGRA is less influenced by the BCG vaccine and environmental mycobacterial exposure [2]. However, its sensitivity is suboptimal in immunocompromised patients, and it is unable to discriminate between active TB and latent TB infection (LTBI)[3,4]. The sensitivity of the IGRA can be enhanced by using alternative or additional biomarkers. In this context, IFN-γ-inducible protein 10 (IP-10) has been extensively studied in both adults and children [5-9].

IP-10 is produced primarily by monocytes/macrophages and has a role in trafficking of Th1 lymphocytes to inflamed foci through an interaction with a CXC chemokine receptor[10]. High levels of IP-10 were found in the pleural effusion and lung tuberculosis granuloma of TB patients [11]. Previous studies

have reported that IP-10 expression following stimulation with *M.tuberculosis* is a promising biomarker with high sensitivity for the immunodiagnosis of tuberculosis infection [5,6].In contrast to IFN-γ, IP-10 expression in response to TB-specific antigen was not influenced by the ability to respond to mitogens or by the CD4 cell number in HIV-infected patients [12,13]. However, there were discordant results as to whether IP-10 can distinguish between active TB and LTBI. Plasma levels of IP-10 were higher in active TB than in LTBI and showed a reduction at the end of *M.tuberculosis* treatment[14]. In addition, baseline plasma IP-10 and CFP-10-stimulated IP-10 levels were significantly higher in active TB than in LTBI in patients with rheumatoid arthritis[15]. Conversely, TB-specific antigen-stimulated IP-10 could not distinguish between active TB and LTBI in children diagnosed by IGRA[7,16].

The aim of this study was to evaluate IP-10 as an additional biomarker for specific TB infection in an area with intermediate TB burden and to evaluate the ability of IP-10 to distinguish between active TB and LTBI. We measured IP-10 levels in unstimulated serum and after whole blood stimulation with *M.tuberculosis* antigen.

II. MATERIALS AND METHODS

1. Study population

Participants were recruited from November 2010 to July 2011, after the protocol was approved by the Severance Hospital Ethics review committee. Eligible subjects consenting to the study were recruited into three groups. Patients older than 20 years of age with suspected active TB based on clinical symptoms and radiographic examinations were included in the active TB group. Individuals with HIV infection, end stage renal disease, or leukaemia/lymphoma and those who had received anti-TB therapy for more than 2 weeks or immunosuppressive therapy, including anti-cancer chemotherapy for malignant disease, within 3 months of enrolment were

excluded from the study. For the household contact group, household members who had close contact and lived with a microbiologically confirmed active pulmonary TB patient for longer than 1 month were recruited. None of the household contacts showed clinical symptoms or chest X-ray signs suggestive of active TB. Community controls consisted of healthy adults who were free of TB symptoms and did not have close contact with active pulmonary TB patients. All control subjects had normal chest X-rays, negative AFB smears, and negative cultures. All study subjects gave informed consent to the use of obtained samples.

A. Definitions of active TB, latent TB infection (LTBI), and non-TB control groups

For the active TB group, the presence of active TB was confirmed by culture of *M. tuberculosis* from respiratory specimens; abnormalities suggestive of tuberculosis on chest X-rays were classified as consolidation, nodules, or cavities. As no gold standard exists for the diagnosis of LTBI, household contacts with a positive TST were defined as the LTBI group. Community controls with negative TST results were defined as the non-TB control group.

2. Tuberculin skin test and IFN-γ determination by QuantiFERON-TB Gold In- Tube

A. Tuberculin skin test

A TST was performed by intradermal injection of 2 Tuberculin units of purified protein derivative (PPD, RT23; Statens Serum Institute, Copenhagen, Denmark) using the Mantoux method. The induration was measured 48-72h later, using a cut-off of 10mm for positivity inimmunocompetent subjects.

B. IFN-γ determination by QuantiFERON-TB Gold In-Tube (QFT-GIT) assay

IFN-γ release assays were performed using a QFT-GIT assay. Briefly, 1ml of whole blood was collected in each of three tubes pre-coated with saline (control), *M.tuberculosis*-specific antigen (ESAT-6, CFP-10, and TB7.7), or mitogen and incubated for 20 h at 37°C. The plasma supernatant was collected after centrifugation and stored frozen at −20°C until assayed. The concentration of IFN-γ was determined using a QFT ELISA. Results were calculated using QFT-IT software provided by the manufacturer. To facilitate comparisons with IP-10 levels, IFN–γ results are presented in pg/ml. One international unit (IU) of IFN-γ corresponds to 50 pg/ml, according to the National Institute for Biological Standards and Control (Potter's Bar, UK) (5, 8).

3. **IP-10 determination**

The IP-10 level was measured in duplicate in supernatants collected from the plasma of QTF-GIT tubes and in sera from all participants, using a commercial ELISA according to the manufacturer's instructions (R&D Systems, Minneapolis, MN, USA). The upper limit of IP-10 for the assay was set at 20,000 pg/ml.

4. **Data analysis**

Data are expressed as number (percentage) or median and interquartile range (IQR). The majority of the data did not follow a normal distribution. Categorical variables were analysed using Pearson's Chi-square test or Fisher's exact test. Continuous variables were analysed using a Kruskal-Wallis test with Bonferroni correction for multiple comparisons. The most appropriate cut-off values for serum IP-10 and antigen-stimulated IP-10 for the detection of active TB disease were established by ROC curve

analysis. TB antigen-dependent cytokine secretion was determined as the difference in cytokine levels between the control tube and the TB antigen-coated tube. The stimulation ratio was defined as the cytokine concentration in the plasma of antigen-stimulated whole blood divided by the cytokine concentration in unstimulated whole blood [7]. A P value ≤ 0.05 was taken to indicate a significant difference. All data were analysed using GraphPad Prism software (GraphPad, Inc., San Diego, CA, USA) and SPSS software (version 18.0, SPSS, Inc., Chicago, IL, USA).

III. RESULTS

1. Characteristics of the participants

A total of 25 active pulmonary TB patients and 55 subjects without TB were studied. Among those without active TB, 30 participants were community controls and 25 were household contacts. Table 1 presents the age, gender, BCG vaccination, and TST results for each group.

All patients in the active TB group were diagnosed by a positive culture from a respiratory specimen. TST results were available for five patients in the active TB group, and all five were positive. All household contacts and control subjects received a TST, and 22 household contacts (88%) and nine community control subjects (30%) had a positive TST result.

Table 1. Demographic and clinical characteristics of the subjects

Characteristic	Active TB patients (n=25)	Household contacts (n=25)	Community controls (n=30)
Age, years	31.0(29,52)	39(30,48)	30(28,33)
Gender, Male/Female	13/12	5/20	11/19
Body Mass Index	21.1(19.3,23.6)	21.6(20.4,24.0)	21.5(20.7,23.3)
Presence of BCG scar	18(72)	23(92)	26(87)
Prior TB treatment	4(16)	2(8)	0(0)
Co-morbidity			
Hypertension	2(8)	0(0)	1(3)
Diabetes mellitus	3(12)	0(0)	1(3)
Others*	4(16)	2(8)	0(0)
Pulmonary TB diagnosis			
AFB smear, positive	5 (20)		
AFB culture, positive	25 (100)		
Extent of lesion in pulmonary TB			
One-third of lung field	11(44)		
One-half of lung field	10(40)		
More than half of lung field	4(16)		
TST induration, mm	18(17,19.5)	16(13,20.5)	2.5(0,12)
TST negative	0(0)	3(12)	21(70)
TST positive	5(100)[#]	22(88)	9(30)
IFN-γ concentration, IU/ml	5.70(1.7,9.8)	2.51(0.91,6.63)	0.02(−0.03,0.11)
QFT-GIT negative	1(4)	3 (12)	26(87)
QFT-GIT positive	24(96)	22(88)	4(13)

Data are presented as the number (percentage) for categorical variables. Continuous variables are presented as median (interquartile range).* Active TB group: Langerhans cell histocytosis, thyroid cancer, non-small cell lung cancer, colon cancer. Household contact group: breast cancer, endometrial cancer. [#]available for five patients

IQR: interquartile range, BCG: BacilleCalmette-Guerin, AFB: acid-fast bacillus, TST: tuberculin skin test, IFN-γ: interferon-γ, QFT-GIT: QuantiFERON-TB Gold In-Tube assay

2. IFN-γ-inducible protein (IP-10) and IFN-γ release after antigen stimulation

Table 2 shows IP-10 and IFN-γ following antigen stimulation in the active TB, LTBI, and non-TB control groups. The level of IP-10 in the control tube differed significantly among the three groups, particularly between the LTBI and non-TB control groups (P=0.019). The median IFN-γ and IP-10 responses to TB antigen were significantly greater in the active TB and LTBI groups than in the non-TB group. Neither the IP-10 nor IFN-γ response to TB antigen differed significantly between the active TB and LTBI groups (IP-10: P=2.29; IFN-γ: P=0.60). Figure 1 shows the TB antigen-dependent secretion and stimulation ratio of IP-10 and IFN-γ in the three groups. TB-specific antigen-dependent IP-10 was significantly higher in the active TB group (median, 20,000 pg/ml; IQR, 9339-20000; $P<0.001$) and LTBI group (median, 15,798 pg/ml; IQR, 605820000; $P<0.001$) compared with the non-TB group (median, 270pg/ml; IQR, −42-1412). However, the TB-specific antigen-dependent IP-10 and IFN-γ responses showed no differences between the active TB and LTBI groups (P=0.356 and P=0.329, respectively). The stimulation ratio of IP-10 was increased in the active group (median, 14.06; IQR, 5.93-24.74; $P<0.001$) and LTBI group (median, 5.59; IQR, 1.72-21.90; P=0.016) compared with the non-TB group (median, 1.61; IQR, 0.94-3.02), but did not differ significantly between the active TB and LTBI groups (P=0.247). Similarly, the stimulation ratio of IFN-γ failed to differentiate between active TB and LTBI (P=0.182).

Table 2. Interferon (IFN)-γ, IFN-γ inducible protein (IP-10) release after antigen stimulation, and serum IP-10 levels in active TB, latent TB, and healthy control groups

Test	Active TB group N=25	LTBI group N=22	Non-TB group N=21	*P*-value
IFN-γ				
Nil	6.5(2.8,12.5)	12.3(4.1,36.1)	5(2.3,8.5)	0.079
TB antigen	291.5(122.3,500)	148.8(96.9,500)	8(2.5,16.8)	<0.001[#]
Mitogen	500 (430.5,500)	500(500,500)	500(500,500)	0.144
IP-10				
Nil	1151 (723,3233)	2248(750.2,12010)	508.9 (272.3,1635)	0.012[†]
TB antigen	20000 (11126,20000)	20000 (17076,20000)	965.9(550.5,3232)	<0.001[‡]
Mitogen	15739(6520,20000)	20000(11577,20000)	12308(9273,20000)	0.134
Serum IP-10	174.9(123.8,368.4)	102.7(72.9,144.5)	71.14 (60.1,111.8)	<0.001[§]

Data are presented as median concentration in pg/ml (interquartile range).

[#] *P*=0.60 for active TB vs. LTBI, *P*<0.001 for active TB vs. non-TB, *P*<0.001 for LTBI vs. non-TB.

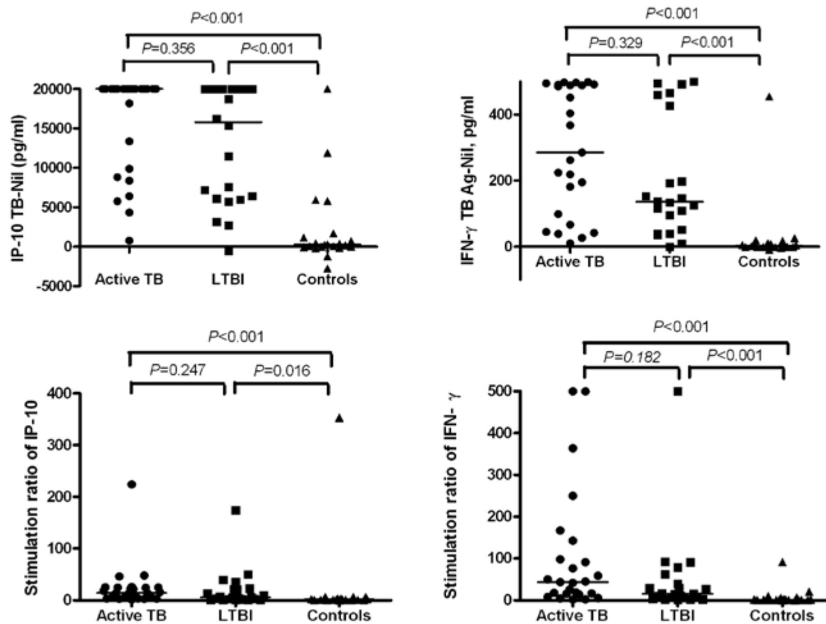
[†] *P*=0.591 for active TB vs. LTBI, *P*=0.109 for active TB vs. non-TB, *P*=0.019 for LTBI vs. non-TB.

[‡] *P*=2.29 for active TB vs. LTBI, *P*<0.001 for active TB vs. non-TB, *P*<0.001 for LTBI vs. non-TB.

[§] *P*=0.002 for active TB vs. LTBI, *P*<0.001 for active TB vs. non-TB, *P*=0.047 for LTBI vs. non-TB.

TB: tuberculosis; LTBI: latent TB infection.

Figure 1. Distribution of IP-10 and IFN-γ responses to *Mycobacterium tuberculosis*-specific antigen in QFT-GIT assays, in active TB, LTBI, and non-TB groups (a, b). Stimulation ratio of IFN-γ and IP-10 in active TB, LTBI, and non-TB groups (c, d).



Horizontal lines indicate median values.●, Active TB; ■, Contacts; ▲, Controls. TB Ag -Nil: MTB antigen-dependent response measured as the difference in cytokine levels between the nil tube and TB antigen-coated tube. Stimulation ratio: cytokine concentration in the plasma of antigen-stimulated whole blood divided cytokine concentration in unstimulated whole blood. IP-10: IFN-inducible protein 10,TB: tuberculosis, LTBI: latent TB infection, IFN-γ, interferon gamma, QFT-GIT: QuantiFERON®-TB Gold In-Tube assay.

3. Serum IP-10 level

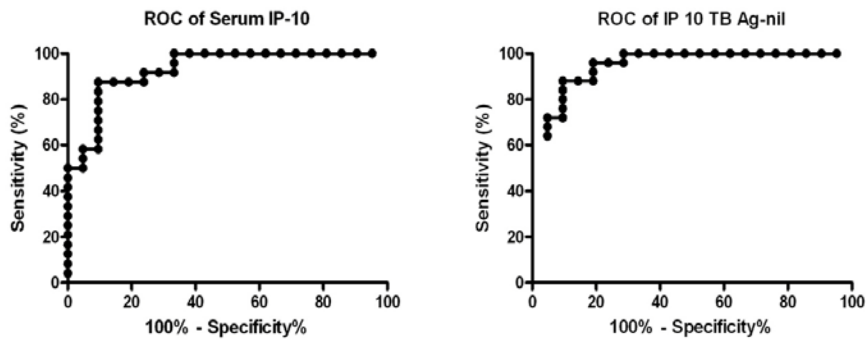
The level of serum IP-10 was significantly different among the three groups. Serum IP-10 was significantly higher in active TB patients (median, 174.9pg/ml; IQR, 123.8–368.4) than in LTBI subjects (median, 102.7pg/ml; IQR, 72.9–144.5; $P<0.05$) or non-TB subjects (median, 71.14pg/ml; IQR, 60.1–111.8; $P<0.001$).

4. Diagnostic performance of serum IP-10 and antigen-dependent IP-10 (IP-10 TB-Nil)

To evaluate the diagnostic performance of IP-10 for detecting TB-specific infection, we performed a receiver operating characteristic (ROC) analysis of serum IP-10 and the antigen-dependent IP-10 response, comparing the active TB and non-TB groups. We selected cut-off points to maximize the sum of the sensitivity and specificity. The cut-off points for best performance were 119.5 pg/ml for serum IP-10 (sensitivity 87.5%, 95% CI 67.6–97.3; specificity 90.5%, 95% CI 69.6–98.8; area under the curve 0.931, 95% CI 0.86–1.00; $P<0.001$) (Fig. 2a) and 6168 pg/ml for TB antigen-dependent IP-10 (sensitivity 88%, 95% CI 68.8–97.5; specificity 90.5%, 95% CI 69.62–98.8; area under the curve0.939, 95% CI 0.86–1.01; $P<0.001$) (Fig. 2b).

The rate of positive responders was compared among the active TB, LTBI, and non-TB control groups using the selected cut-offs for IP-10 and IFN-γ (Table 3). Based on serum IP-10, the rates of positive responders were 87.5%, 45.5%, and 9.5% in the active TB, LTBI, and non-TB control groups, respectively. Based on TB antigen-stimulated IP-10, the positive response rates were 88%, 72.7%, and 9.5% in the respective groups.

Figure 2. ROC curve analysis of (a) serum IP-10 and (b) IP-10 release after *Mycobacterium tuberculosis*-specific antigen stimulation.



ROC curve analysis was performed using active TB patients and controls as a comparison.
(a) AUC, 0.930 (95% CI, 0.86–1.0, P<0.001) for serum IP-10. (b) AUC, 0.939(95% CI 0.86–1.01, P<0.001) for *Mycobacterium tuberculosis* antigen-dependent IP-10 release.

Table 3. Diagnostic performance of interferon (IFN)-γ, IFN-γ inducible protein (IP-10) release after antigen stimulation, and serum IP-10

Test	Active TB group N=25	LTBI group N=22	Non-TB group N=21	*P* value
QTF-GIT				
Positive	24(96)	20 (90.9)	4(19.0)	<0.001
Negative	1(4)	2 (9.1)	17 (81.0)	
Serum IP-10 (119.5pg/ml‡)				
Positive	21(87.5)	10 (45.5)	2 (9.5)	<0.001
Negative	3(12.5)	12 (54.5)	19 (90.5)	
IP-10 release after TB antigen stimulation (6168 pg/ml)				
Positive	22(88)	16 (72.7)	2(9.5)	<0.001
Negative	3(12)	6 (27.3)	19 (90.5)	

Data are presented as number (percentage).

QFT-GIT: QuantiFERON®-TB Gold In-Tube assay.

‡Serum IP-10 was measured in 24 active TB patients.

5. Classification of active TB and LTBI combining the diagnostic results

To classify subjects as active TB or LTBI, the QFT-GIT assay results, TB antigen-dependent IP-10 levels, and serum IP-10 levels were considered together (Table 4). Using ROC analysis, two serum IP-10 cut-off values were obtained to differentiate active TB and LTBI: 106.1pg/ml (sensitivity 95.8%, 95% CI 78.9–99.9; specificity 54.6%, 95% CI 32.2–75.6) and 139.4 pg/ml(sensitivity 70.8%, 95% CI 48.9–87.4; specificity 77.3%, 95% CI 54.6-92.2). When a positive QFT-GIT result and serum IP-10 level of 106.1pg/ml were used together to differentiate active TB and LTBI, 79.1% (34 of 43) were correctly classified. Using the TB antigen-dependent IP-10 value and serum IP-10 level of 106.1 pg/ml, 81.6% (31 of 38) were correctly classified as active TB or LTBI.

Table 4. Stepwise approach for differentiation between active TB and LTBI

Positive criteria	Active TB	LTBI	Sensitivity, % (95% CI)	Specificity,% (95% CI)	Classified correctly
QFT-GIT with serum IP-10_106.1	23/23 (100)	9/20 (45)	100 (72.2–100.0)	55.0 (39.7–55.0)	79.10%
QFT-GIT with serum IP-10_139.4	17/23 (73.9)	5/20 (25)	73.9 (58.0–85.0)	75.0 (56.1–88.2)	74.40%
TB antigen-stimulated IP-10 with serum IP-10_106.1	22/22 (100)	7/16 (43.75)	100 (86.8–100)	56.3 (38.1–56.3)	81.60%
TB-Ag stimulated IP-10 with serum IP-10_139.4	16/22 (72.7)	3/16 (18.75)	72.7 (57.1–82.3)	81.3 (59.8–94.4)	76.30%

Data are presented as number (percentage), unless otherwise indicated.

LTBI: Latent TB infection, QFT-GIT: QuantiFERON®-TB Gold In-Tube assay, CI: Confidence interval

IV. DISCUSSION

This study demonstrates that IP-10 is a useful immunodiagnostic marker of *M. tuberculosis* infection in an area with an intermediate TB burden. We confirmed previous findings that IP-10 was secreted at high levels following *M.tuberculosis*-specific antigen stimulation after TB infection, in a manner similar to IFN-γ[7,15]. In addition, the serum IP-10 level differed among the active TB, LTBI, and non-TB control groups.

IP-10, a member of the CC-chemokines, is increased in monocytes and polymorphonuclear granulocytes following *M.tuberculosis* infection [17]. Increased IP-10 levels have also been identified in autoimmune disorders, including systemic lupus erythematosus[18], autoimmune hepatitis, primary biliary cirrhosis [19], bronchial asthma [20], and atopic dermatitis [21].

Distinct from the assumption that IP-10 may reflect only inflammation and may be too non-specific to be used alone in diagnosing tuberculosis, Ruhwald et al. reported that the IP-10 response to *M.tuberculosis*-specific antigen could be used to diagnose tuberculosis infection [5]. Similarly, the present study demonstrated that the area under the ROC curve for TB antigen-stimulated IP-10 (0.939, 95% CI 0.86–1.01; P<0.001) was as high as that for IFN-γ (0.962, 95% CI0.90–1.012;P<0.001). The sensitivity was similar between IFN-γ and TB antigen-stimulated IP-10 in active TB patients (Table 3), but TB antigen-stimulated IP-10 was not able to discriminate between active and latent TB infection. Our results agree with previous studies demonstrating that the IP-10 response to RD1 selected antigen did not differ significantly between active and latent TB infection [22].

The stimulation ratio, i.e., the positive response to *M.tuberculosis* antigen divided by the generalized activation of cytokine-producing cells, also failed to discriminate between active and latent TB infection. The stimulation ratio of IFN-γ was higher than that of IP-10 in active TB (IFN-γ, 43.48; IP-10,

14.06) and latent TB (IFN-γ, 15.16; IP-10, 5.59) owing to a lower background level in unstimulated samples. Although the stimulation ratio did not discriminate between active and latent TB, it may provide a diagnostic marker of TB infection, being significantly higher in active TB and LTBI compared with non-TB controls, in a fashion similar to the cytokine levels of TB antigen.

Our results showed higher background IP-10 levels in whole blood from LTBI subjects compared with active TB and non-TB subjects. Whittaker and Lighter reported similar findings in children[7,8]. This could be explained by the presence of a chronic inflammation state, evoking the recruitment of neutrophils, monocytes, and Th1 lymphocytes to control TB infection, in LTBI subjects. Chen showed that the levels of unstimulated IP-10 in the control tubes paralleled the occurrence of active TB and the clinical remission of TB after anti-tuberculosis treatment in rheumatoid arthritis patients[15]. Whether high levels of unstimulated IP-10 in whole blood during latent TB infection can serve as an additional marker to predict the disease status of tuberculosis requires further evaluation.

It is worthwhile to note the differences in serum IP-10 levels and in *M.tuberculosis*-antigen stimulated IP-10 levels among the three different TB groups. The serum values are the circulating cytokine levels at a given time point, and the *M.tuberculosis*-stimulated levels reflect the potential for *M.tuberculosis* reactivity by circulating mononuclear cells. Thus, the higher level of serum IP-10 in the active TB group compared with the LTBI group represents the progressing inflammatory state of active TB patients. However, serum IP-10 can be elevated in a number of inflammatory diseases [18-21], and thus because of its low specificity, the serum IP-10 level alone is insufficient for diagnosing active TB. When the TB antigen-stimulated IP-10 level and a serum IP-10 level higher than 106.1pg/ml were used as criteria to differentiate active TB and LTBI, more than 80% of the subjects were correctly classified,

with a sensitivity of 100%. Therefore, the serum IP-10 level may be useful as part of a panel of diagnostic markers.

This study had some limitations. The sample size was too small to allow definitive conclusions and to establish cut-off points. Furthermore, the active TB group included only culture-proven pulmonary TB patients without HIV infection. Although the serum IP-10 cut-off in the present study (119.5 pg/ml) was similar to the value (132.8 pg/ml) in a previous study[23], the cut-off for TB antigen-stimulated IP-10 release (6,168 pg/ml) was higher than previously reported values of 300 pg/ml[24] and 673pg/ml[25]. The discordance among these levels may be attributable to the different disease activities of patients or the effects of additional factors such as geographic location and ethnicity. Further studies in diverse well-defined patient populations are required to elucidate the diagnostic efficacy of IP-10 and to improve the diagnosis of tuberculosis by combining IP-10 and IFN-γ assay results.

V. CONCLUSION

In conclusion, the present study showed that serum IP-10 and TB antigen-dependent IP-10 represent complementary markers to IFN-γ in the diagnosis of *M.tuberculosis* infection. Additionally, the serum IP-10 level, which is rapidly and easily detectable by ELISA, may provide an adjunct marker for differentiating between active TB and latent TB infection. Although the IP-10 level does not appear to be superior to the IFN-γ level as a tool for TB diagnosis, IP-10 has potential use as an adjunct biomarker to enhance diagnostic performance and evaluate disease activity in TB. Further studies in more diverse populations are required to validate the use of IP-10 as a diagnostic marker for TB.

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ABSTRACT (In Korean)

결핵 감염 진단을 위한 IP-10의 유용성 고찰

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배경: IP-10은 결핵 감염시 염증부위로 활성화된 T 세포와 단핵구를 모집하는 케모카인이다. IP-10은 IGRA(Interferon-gamma release assay)의 제한점을 보완하는 새로운 결핵 진단 지표로서 연구되어 왔으나, 양성 기준과 활동성결핵과 잠복결핵 감별 여부가 아직 불분명하다. 본 연구의 목적은 IP-10의 결핵감염 진단의 유용성을 IFN-γ 와 비교하여 평가하고 활동성 결핵과 잠복결핵을 구분할 수 있는지 알아보는 것이다.

방법: 2010년 11월부터 2011년 7월까지 세브란스병원에 내원한 활동성결핵 환자 25명과 결핵 가족접촉자 25명, 건강인 30명을 대상으로 결핵피부반응검사, IFN- γ, ELISA 를 이용한 결핵항원자극 IP-10과 혈청 IP-10을 측정하였다. 잠복결핵은 피부반응검사가 양성인 가족접촉자로, 비결핵군은 피부반응검사가 음성인 건강인으로 정의하였다.

결과: 결핵특이 항원 반응도는 활동성 결핵과 잠복결핵에서 비결핵군에 비해 유의하게 증가하였으나 활동성 결핵과 잠복 결핵 사이에는 유의한 차이를 보이지 않았다. 혈청 IP-10 수치는 활동성결핵(174.9pg/ml)이 잠복결핵보다(102.7pg/ml, *P*=0.002) 높았다. 결핵특이항원에 대한 IP-10 의 반응도를 ROC 곡선을

이용한 분리기준으로 구분했을 때 활동성 결핵에서 88% 의 민감도와 90.5% 특이도를 보였다. IFN- γ 은 활동성 결핵에 대해 96% 의 민감도와 81% 특이도를 보였다. 결핵특이 항원에 대한 IP-10 과 혈청 IP-10을 통합하였을 때, 활동성 결핵 및 잠복결핵 중 81.6%을 올바르게 분류할 수 있었다.

결론: 결핵 특이항원 자극 IP-10 수치는 결핵 감염 진단에 특이한 진단 지표이나 활동성 결핵과 잠복결핵 감염을 구분하지 못했다. 혈청 IP-10을 다른 지표와 조합했을 때 잠복결핵과 활동성 결핵 감별에 도움이 될 수 있을 것으로 사료된다.

핵심되는 말: 결핵, 인터페론감마유도단백