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THE EMERGING ROLE OF RESIDENT MEMORY T CELLS IN PROTECTIVE IMMUNITY AND INFLAMMATORY DISEASE

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Abstract

Over the past decade, it has become clear that there is an important subset of memory T cells that resides in tissues — tissue resident memory T cells (T_{RM}). There is an emerging understanding that T_{RM} have a role in human tissue specific immune and inflammatory diseases. Furthermore, the nature of the molecular signals that maintain T_{RM} in tissues is the subject of much investigation. In addition while it is logical for T_{RM} to be located in barrier tissues at interfaces with the environment in human and mouse, T_{RM} have also been found in brain, kidney, joint, and other non-barrier tissues in both species. Their biology and behavior make it likely that they play a role in chronic relapsing and remitting diseases of both barrier and non-barrier tissues. This review will discuss recent understandings of the biology of T_{RM} with a particular focus on their role in disease.

Introduction

Memory T cells provide rapid and highly effective protective immunity to previously encountered antigens derived from pathogen, tumor, or environmental proteins. It was previously thought that T cells consisted of two major subsets: central memory T cells (T_{CM}) and effector memory T cells (T_{EM})[1]. T_{CM} express the chemokine receptor CCR7 and the vascular addressin L selectin (CD62L), permitting them to access and enter lymph nodes from blood. T_{EM} express low levels of CCR7 and CD62L but have receptors that allow them to access peripheral tissues (e.g., the E selectin ligand Cutaneous Lymphocyte Antigen, or CLA) which grants them access to the skin, and $\alpha 4\beta 7$ which is an integrin that allows them access to the gut[2,3].

Over the past decade, it has become clear that there is another important subset of memory T cells—tissue resident memory T cells, or T_{RM}. T_{RM} reside in epithelial barrier tissues at the interface between the host and the environment, such as the gastrointestinal tract, respiratory tract, reproductive tract, and skin. T_{RM} can respond rapidly to pathogen challenge at these sites without recruitment of T cells from the blood[4,5]. They thus mediate the rapid protective immunity that is the hallmark of adaptive immune memory[4]. T_{RM} in a tissue are enriched for T cells specific for pathogens and other antigens that have been encountered previously through that barrier epithelium. Thus, the TCR repertoire of skin T_{RM} is different from lung T_{RM}, and both are different from gut T_{RM}[5]. However, T_{RM} are not simply memory T cells in an unexpected location; rather, they have a transcriptional program that distinguishes them from peripheral blood T_{EM} and T_{CM} [6].

The cell signaling interactions that maintain T_{RM} in their resident tissues is the subject of much investigation. The role of T_{RM} in human tissue specific immune and inflammatory diseases is just beginning to be appreciated[5]. In addition while there is good logic for T_{RM} to be stationed at our interfaces with the environment, T_{RM} have also been found in brain, kidney, joint, and other non-barrier tissues. T_{RM} that appear in non-barrier tissues have similar transcriptional programs[7], and their biology and behavior make it likely that they play a role in chronic relapsing and remitting diseases of non-barrier tissues.

We will discuss how T_{RM} are generated after an immune response, and review both common features of T_{RM} as well as unique features of T_{RM} in various barrier tissues, including skin, lung, and GI tract. We will further discuss how T_{RM} may be formed in sterile non-barrier tissues like brain and kidney, and will speculate as to the role of T_{RM} in immune and inflammatory diseases involving tissues. Finally, the role of T_{RM} in cancer, and the goal of generating T_{RM} during vaccination for both infectious diseases and cancer will be reviewed. The field is developing at a rapid rate, and new observations are being made on an ongoing basis.

T_{RM} generation during an immune response

Naive T cells circulate between blood and lymph nodes, where they remain for 12–24 hours before exiting into blood and sampling another lymph node microenvironment[8]. Naive T cells are abundant but highly diverse with regard to T cell repertoire, and hence pathogens to which they are targeted, such that naive T cells specific for any given antigen are rare[9]. Dendritic cells are the first to encounter infectious challenge in peripheral tissues, and they ferry pathogen fragments to draining lymph nodes where they present processed peptides (antigens) to naive T cells. Those T cells that recognize the antigen become activated and clonally expand, such that one naive T cell gives rise to tens of thousands of progeny[9,10]. Although all these T cells have the same T cell receptor, the dividing T cells become heterogeneous with regard to homing molecules that they express[11]. Some gain the ability to access peripheral tissues, and others will retain the capacity to enter lymph nodes from blood (T_{CM}). Effector T cells also acquire new functions that are specific to the pathogen encountered; for example, Th1 cells secrete IFNγ production (a cytokine that induces a broad range of antiviral factors) in response to viral pathogens and Th17 cell produce IL-17, a potent inducer of neutrophil activation and recruitment, in response to bacterial and fungal pathogens[12].

The anatomic location of the draining lymph node determines expression of tissue homing molecules on formerly naive T cells first activated in that microenvironment[11,13]. Naive T cells that are activated in skin draining lymph nodes are induced to express Cutaneous Lymphocyte Antigen (CLA, a glycosylated variant of P selectin glycoprotein ligand 1)[2,14–16], a ligand for E selectin, as well as a subset of chemokine receptors that facilitate skin homing (e.g., CCR4, CCR6, CCR8, CCR10)[17–19]. Alternatively, activation of naïve T cells in gut draining lymph nodes induces expression of α4β7 integrin[20,21], the receptor of mucosal addressin cell adhesion molecule (MAdCAM), expressed on post capillary venules in intestinal lamina propria[22], in addition to distinct chemokine receptors including CCR9[23] which binds to CCL25 produced by intestinal epithelium.

The clonally expanding T cell population includes cells that differentiate into tissue homing effector cells, but also cells that retain CD62L and CCR7 and remain more like T_{CM}. These latter cells leave the draining lymph node and travel to other lymph nodes, where a subset can differentiate to express different tissue homing molecules[11]. After effector T cells exit the lymph node, those with skin homing markers are preferentially trapped by inflamed vessels in skin and extravasate into dermis[24]. These T cells migrate along chemotactic gradients to the site of pathogen invasion, where they become activated by antigen, and produce cytokines and other effector molecules (e.g., granzymes) that lead to pathogen elimination[25–27]. It is now clear that some of these newly arrived T cells remain in place as T_{RM}. This sequence of events can play out again and again, in multiple barrier tissues, over the lifetime of an individual, and the result is the accumulation of diverse and largely (but not completely) non-overlapping populations of T_{RM} in each barrier tissue[4,5]. Thus, lung contains influenza specific T_{RM} [28–30], gut contains rotavirus specific T_{RM} [31], and skin contains candida specific T_{RM} [32,33], and reproductive mucosa contains HSV specific T_{RM} [34–37]. It was recently shown that the unique naive T cells that give rise to these T_{RM} have also given rise to T_{CM}, thus the T_{RM} population in tissue is “duplicated in function” by a population of T_{CM} with an identical T cell repertoire[38].

The process of T_{RM} formation involves some additional nuances not mentioned above. For example, when mouse skin is infected with Vaccinia virus by scarification, effector T cells accumulate not only at the vaccinated site, but throughout the skin[4], and this was recently shown to be true for skin immunization with proteins and haptens [38] Non-inflamed skin contains post capillary venules that express low levels of E selectin, chemokines, and ICAM-1, all of the requisite molecules for extravasation of skin homing T cells[24], allowing them to home to uninfected skin sites. In the same fashion, endothelial molecules specific for gut homing T cell are expressed on resting lamina propria endothelium[22], allowing gut homing T cells to home to normal gut. Additionally multiple sequential encounters with a pathogen at distinct sites on skin leads to a further accumulation of pathogen specific T_{RM} throughout skin; thus more T_{RM} are present for pathogens encountered more frequently[4]. Furthermore, while each naive T cell (and its progeny) has a unique T cell receptor, the expanded clone is otherwise heterogeneous. T_{CM} have limited effector function or protective capacity themselves[4], but have the potential to replenish the T_{RM} compartment upon activation[38]. The relationship of T_{RM} and T_{CM} is unclear, but both express low levels of KLRG-1[6], a molecule strongly expressed by effector and T_{EM} cells. These data, in addition to a recent report demonstrating T_{RM} and T_{CM} clones sharing the same variable sequence (CDR3) of the T cell receptor[38] suggest that there is a common precursor of T_{RM} and T_{CM}. With regard to the balance of T_{RM} and T_{CM}, a recent report suggested that the mTOR pathway may regulate this balance, since mTOR inhibitors like rapamycin favor T_{CM} generation in mouse models[39]. Another recent study suggested that high expression of the transcription factor T box specific protein 21, or T-bet, favored T_{EM} over T_{RM} differentiation, while lower expression of this protein was found in T_{RM} [40].

While T_{RM} are most likely to have evolved to protect us against infection from dangerous environmental pathogens, normal flora of tissue microbiomes, as well as innocuous environmental proteins, can all give rise to T_{RM}. A recent report in mice found that allergic contact dermatitis was mediated by T_{RM} that had been generated in response to a topically

applied allergens as well as a protein plus adjuvant[38]. T_{RM} were described as early as 2001[41], and this same group demonstrated that T_{RM} in gut did not recirculate between parabiotic mice, in contrast to T cells in lymph node and spleen[42].

Common features of T_{rm} in barrier tissues

Homing of T_{RM}

T_{RM} are characterized by their inability to re-circulate between tissue, lymph node, and blood[4,43–47], although understanding the factors that help them achieve this is an active area of research. The glycoprotein CD69 is a marker of T_{RM}, and is expressed on T_{RM} in skin, lung, GI tract, and everywhere T_{RM} have been identified[4–6,28,48–50]. CD69 was originally thought to be a marker of recent T cell activation in the lymph node;[51] however most T_{RM} in tissues are at rest. CD69 appears to be involved in peripheral tissue retention of T_{RM} which appears to involve the downregulation of the G protein coupled receptor for sphingosine 1 phosphate (S1P1)[52]. There is a gradient of levels of sphingosine 1 phosphate in the body in humans and mouse, with the lowest levels in peripheral tissue, intermediate levels in lymph node, and the highest levels in blood[50,53,54]. These S1P gradients normally function to guide T cells out of tissues to lymph node, and out of lymph nodes into blood. Expression of CD69 by T_{RM} interferes with cell surface expression and function of S1P1, thus blocking the capacity of these T cells to sense S1P gradients and supporting their stationary nature[50]. The transcription factor Kruppel-like Factor 2, which normally enhances S1P1 expression, is downregulated in T_{RM}, thus indirectly enhancing CD69 expression [53]. The mechanism by which CD69 and S1P1 compete with each other for cell surface expression is not completely understood[54].

The chemokine receptor CCR7 is another G protein coupled receptor that senses molecular gradients of its ligands CCL19 and CCL21, and directs T cells and dendritic cells from skin to lymph node via afferent lymphatics[55]. Expression of CCR7 allows T cells to migrate in response to gradients of its chemokine ligands, which are normally not abundant in tissue but are at their highest levels in lymph node and afferent lymphatics. It was recently shown in a mouse model that $CD4^+$ T cells in skin require CCR7 to migrate to afferent lymphatics, and that blocking CCR7 expression prevented T cells from leaving skin[56]. In human skin, expression of CCR7 was seen on a population of T cells that migrated out of skin (so called T migratory memory or T_{MM} cells), while $CCR7^-$ T cells remained in skin as T_{RM}[57]. The relative contributions of S1P1 and CCR7 expression on T cells to migration out of tissues have not been determined.

The integrin CD103 (also known as αE, and which pairs with β7) is another marker of T_{RM}; however, its expression is more predominant on CD8 than CD4 T_{RM}. It is a known ligand of E-cadherin, a homotypic adhesion molecule expressed by epithelial cells in barrier tissues[58]. In mouse models, CD8 T cells specific for HSV-1 enter the skin lacking CD103 expression, and then in response to epidermal TGFβ upregulate CD103[6]. CD103 is also found expressed by T_{RM} in the lung and GI tract, and even in T_{RM} in the brain upon CNS viral infection[7,40,48,59]. It is tempting to assume that αEβ7 on these cells is binding to epithelial cells via interactions with E cadherin. However, binding to E cadherin is not required for tissue residence, as $CD103^+$ CD4 and CD8 T_{RM} can be found in the dermis, and $CD103^+$

dendritic cells are plentiful in the dermis without ever entering the epidermis[60]. While E cadherin is expressed during brain development, it is absent in adult CNS tissue[61], despite abundant CD103 on brain CD8 T_{RM}. Thus while its role is incompletely understood, it does appear that CD103 expression is a marker of differentiation of T_{RM}[6] rather than a functional requirement for tissue residence. It is notable that CD103 T_{RM} have less proliferative potential and more significant effector cytokine production capacity than $CD103^{-}$ T cells in several human and mouse models[7,40,41,48,59,62,63]. CD103 expression is also not a strict requirement for human skin cells being T_{RM} [57]. A recent report suggested that CD103− T_{RM} may play a different role in gut in a mouse model, being generated in inflammatory microenvironments in the lamina propria and playing a unique role in controlling infection[64].

Less is known about CD4 T_{RM} than CD8 T_{RM} in part because these cells are less efficiently generated by viral infection in mouse models in which T_{RM} have been most completely characterized. Studies of HSV infection of the female mouse reproductive tract suggest that local chemokine gradients from tissue mononuclear cells maintain CD4 T_{RM} in place[37]. In skin, evidence suggests that CD4 T_{RM} do not preferentially localize to the epidermis, and express lower levels of CD103 than CD8 T cells[4,63]. HSV specific CD4 T cells in mouse skin may be more mobile than CD8 T_{RM}, and limited to the dermis[65]. CD4 T cells in skin may express CCR7 and/or CD69 [5,56]. In a recent study the authors treated highly immunocompromised NOD/Scid/IL-2Rγ-deficient (NSG) mice bearing human skin xenografts with alemtuzumab (an antibody that binds human CD52, a molecule present on all T cells**).** This humanized antibody has been shown to deplete human T cells in blood but not tissue[57,66]. Two populations of CD4 T cells could be isolated from skin of these mice: those that expressed both CCR7 and L selectin (markers of T_{CM}), and those that expressed CCR7 but not CD69 (dubbed T migratory memory, or T_{MM} by this group). The two populations of CD4 T cells that remained within the skin both expressed CD69 and lacked CCR7 (and were thus unresponsive to S1P and CCL19/21 gradients), and contained CD103+ and CD103− populations. Thus, four distinct populations of CD4 T cells could be identified in human skin, two of which were short term residents and could exit skin into blood, and two that were true T_{RM}[57].

Maintaining TRM in tissues

The molecular factors that maintain T_{RM} in their resident tissue are less well understood, but IL-15 TGFβ, TNFα, and IL-33 have all been implicated in maintenance of T_{RM} [6,53]. TGFβ, TNFα, and IL-33 have all been shown to have a role in induction of CD103 expression and acquisition of a T_{RM} phenotype. Factors that upregulate CD69 include TNFα and type I interferons[50,67]. The aryl hydrocarbon receptor is important for maintenance of γδ T cells in mouse skin[68], and a recent report suggests that it is important for the generation of αβ TCR CD8 T_{RM} [69]. A recently described additional common activity of CD8 T_{RM} was highlighted by several recent papers. One of the first cytokines made by CD8 T_{RM} upon antigen reactivation is IFNγ. In both skin and reproductive mucosa, the IFNγ released by reactivated T_{RM} created a generalized anti-viral microenvironment in tissue, by upregulating a series of antiviral and antimicrobial genes from keratinocytes, enhancing vascular adhesion molecule expression endothelium, and activating other resident cells including NK cells and dendritic

cells[70,71]. In this fashion, T_{RM} can amplify and activate the innate immune system, creating an environment inhospitable for even completely unrelated viruses and other pathogens.

Properties of T_{rm} in distinct barrier tissues

Skin T_{RM}

In 2006, it was discovered that normal resting human skin contained twice as many T cells as blood[5,72,73], and it is now appreciated that the majority of these cells are T_{RM}[57]. Thus, memory T cells previously generated in response to pathogens in the cutaneous environment are present in abundance in the skin, allowing for immediate response to pathogenic invasion[5]. These cells have a diverse T cell receptor repertoire and can be activated by pathogens at a much lower threshold than circulating T cells via the T cell receptor[72]. Moreover, they are heterogeneous; they include $CD4^+$ and $CD8^+$ T cells that produce IL-17, IFNγ, TNFα, IL-9, IL-13, and other cytokines, alone or in combination[5,32,72–76].

Human peripheral blood T cells enriched in skin (CLA), gut (α4β7), or lung (CLA/α4β7-) tropic memory T cells are specific to previously encountered pathogens of those tissues[32]. Mouse models have been instrumental in our understanding of skin T_{RM}. Early studies showed that mice transfused with transgenic T cells specific for HSV peptides, and then infected with HSV, showed that HSV specific CD8 T cells could be transferred from one mouse to another by a previously infected skin graft, and that these cells maintained their ability to clear virus upon challenge[63]. In another study it was shown that skin scarification by vaccinia virus (VACV) was far superior to other routes of immunization in generating skin resident CD8 T cells[77]. These investigators also showed that skin T_{RM}, in the absence of T_{CM} and antibody, could clear virus on re-challenge. Furthermore, skin scarification generates lung T_{RM} that, in the complete absence of circulating antibodies and T_{CM} can partially protect naive mice from an otherwise lethal pulmonary challenge with VACV[77]. Thus, skin immunization can lead to widespread T_{RM} throughout skin and also in distant barrier tissues. Another study showed that after HSV challenge in mice**,** CD8+ T_{RM} migrate to the epidermis and acquire a sessile phenotype, while CD4+ T_{RM} localize to the dermis and show greater mobility[65]. This is not only at the site of infection, but also at distant sites, and more CD8 TRM accumulate throughout the skin after multiple infections at distinct sites [4]. However, CD8 T_{RM} do not re-circulate, and mice that contain T_{CM} but lack T_{RM} are cannot effectively clear VACV from skin, in contrast to mice that have immune skin T_{RM} [4].

Interestingly, T_{RM} from skin, lung, and gut have transcriptomes that have common core features in mouse[6]. This same study showed that localization of $CD8^+$ T_{RM} in the epidermis and CD103 expression of T_{RM} was induced in the epidermis by TGFβ, these $CD8^+$ T_{RM} cells homed to epidermis by an uncharacterized chemokine mediated process[6]. Mouse CD8 T_{RM} were also shown to occupy epidermal niches formerly filled by a population of T cells that seed the epidermis prior to birth--γδ Dendritic Epidermal T Cells--, and when viewed by intravital microscopy moved laterally between keratinocytes, unlike sessile γδ DETC. These CD8 T_{RM} interacted transiently with Langerhans cells, suggesting that they were scanning the environment for antigen [69]. In humans, there are two isoforms of the dimeric CD8 molecule on T cells, composed of αβ or αα chains, respectively. After cutaneous HSV

infection, CD8αα T_{RM} localize at the dermal epidermal junction. These cells, but not CD8αβ T cells, protected against reactivation of HSV and lesion formation[78].

Somewhat less is known about CD4 skin T_{RM} in mice than about CD8 skin T_{RM}. It has been shown, however that CD4 Treg are a major population of T cells emigrating from skin to lymph node after an immune response to contact hypersensitivity, as well as in the absence of stimulus[79]. Another group characterized CD4 T cells in mouse skin, and demonstrated at least two populations, one that did not leave skin (lacking expression of CCR7), and another that left skin by a CCR7-dependentmechanism and expressed low levels of CD62L, high levels of E selectin ligand, and was negative for CD69[56]. This is consistent with a very recently published study from human skin[57].

T_{RM} in the GI tract

T_{RM} in gut are defined here as T cells that reside in the epithelium or in lamina propria[80]. It has been shown that a subset of CD103+ dendritic cells in gut draining lymph node can skew naive T cells toward differentiation into α4β7 gut homing memory T cells, primarily under the influence of TGFβ secreted by these DCs[81]. Gut infiltrating T cells have been most exhaustively studied in mice during disease states, such as experimentally induced colitis, in which mice lacking CD103 had attenuated inflammation suggesting a role for T_{RM} in inflammation. Less attention has been paid to T_{RM} that emerge after pathogen infection, until very recently[48,70]. Several infections, including lymphocytic chorionomeningitis virus, listeria, and others have been shown to generate long lived intraepithelial T cells with potent effector activities in mice [42]. While many of these infections were delivered intravenously, in a recent study mice were infected orally with Listeria to study gut T_{RM}[48]. This study found that long lived gut T_{RM} express KLRG-1 at low levels (consistent with skin T_{RM}), while cells that highly expressed KLRG-1 (as in T_{EM}) and entered gut underwent apoptosis. This oral immunization induced abundant long lived gut T_{RM}, unlike nasal immunization which induced entry T cells highly expressing KLRG-1 into gut that did not persist long term. Gut CD8 T_{RM} expressed CD69 and CD103**,** as do mouse skin T_{RM}, and their maintenance in the gut was enhanced by TGFβ[80]. When transcriptional profiles of skin T_{RM} generated by HSV infection were compared to gut T_{RM} induced by an LCMV infection[6], of 127 genes up or down regulated in T_{RM} in comparison to T_{CM}, 68 showed a pattern common to skin and gut, and the remainder were unique to gut (or possibly to the difference between LCMV and HSV infection) [6]. Thus, the T_{RM} that form in gut epithelium and lamina propria bear many features common to T_{RM} in other barrier tissues, although they express gut-specific homing molecules.

As regards what is known about gut T_{RM} in humans, a recent study that surveyed resident T cell populations in various human tissues demonstrated the presence of T_{RM} in both colon and small intestine[82]. We have further analyzed human GI tissue by deep sequencing of TCRBV1 and identified a highly diverse T cell repertoire in normal tissue (data not shown). Liver T_{RM} have been demonstrated after malaria infection[83], and the T cells that infiltrate the liver during viral hepatitis likely become tissue resident as well, causing significant tissue injury in the absence of effective therapy[84].

T_{RM} in Lung/respiratory tissue

The possibility that T_{RM} cells might exist in lung stemmed from the identification of CD69+ CD8+ T_{RM} cells that remained in lung after influenza infection[28]. The previous explanation of the expression of CD69 was that they were in an activated state, perhaps as a result of retained antigen; however, we now know that CD69 expression is a generic characteristic of resting T_{RM}.[29] There is good evidence that $CD8^+$ resident memory T cells can be protective against subsequent infection with influenza. Intranasal, but not intraperitoneal infection with influenza in mice results in the presence of lung T_{RM}, though both routes of infection efficiently produced influenza-specific T_{EM}[30]. Furthermore, the nasal influenza immunized mice, but not the intraperitoneally immunized mice, are protected against a lethal intranasal challenge with influenza. This echoes the work in skin showing that resident, but not circulating, memory T cells are most effective at limiting viral replication at the site of viral entry[4]. However, in this lung infection study the T_{RM} had essentially vanished from lung 90 days after a single influenza infection. Whether they could be made more abundant at this late stage after boosting strategies such as additional antigen challenge was unexplored.

The anatomic location within the lung where T_{RM} need to reside to be most protective against a flu challenge is also controversial -it is clear that lung T_{RM} express CD103, and its epithelial ligand, E-cadherin, is most strongly expressed on large and intermediate bronchial epithelial cells and less so on small or alveolar epithelia[85]. However, as discussed above, $CD103^+$ cells can persist at a distance from E cadherin expressing cells. As regards the levels of $CD4^+$ vs. $CD8^+$ T cells TGFβ promotes the development of lung $CD103^+$ $CD8^+$ T_{RM} cells, but in a fashion not dependent on Smad4[86]. CD4+ T cells in lung help to develop $CD103^+$ $CD8^+$ T_{RM} cells after influenza virus infection[40], but the relative roles of CD4 and CD8 T cells, and whether (as in skin) these two populations have different migratory capacity, have not been explored.

There is a growing body of evidence that points to the existence of T_{RM} in normal human lung, though this tissue is difficult to obtain. While T cells have been observed in bronchialveolar lavage samples, these are typically done in the setting of diseased lung, and thus it is not known whether they are authentic T_{RM}. Pneumonectomies from human lung derived from tissue very distal tumors is regarded as normal [87] and T cells isolated from such normal lung samples produce TNFα and IFNγ[87]. They also express CD69, their TCR repertoire is diverse, and from these data it is estimated that the number of T_{RM} in lung approximated the number of T cells in blood**,** on the order of 10 billion cells. Moreover, these populations of T cells are enriched in the cells that proliferate in response to inactivated influenza[87]. Lung T_{RM} express abundant α1β1, though this is expressed in other tissues and is thus not lung-specific[87]. CD8+CD103+ T cells in human lung were specific for influenza, rather than CD8+ CD103− T cells which are also found[59]. T_{RM} in human lung were also demonstrated in a large survey study that looked at multiple human tissues[82].

Genitourinary tract

The mucosa of the female reproductive tract is an important barrier tissue. In mouse HSV infection, CD4 T cells must first enter the tissue and provide a recruiting cytokine and chemokine signal to facilitate entry of CD8 T cells into infected vaginal mucosa[34]. This is

different from skin, in which CD4 help is not required to recruit antigen specific CD8 T cells after VACV infection[4]. Protective immunity against HSV can also be generated by direct topical infection of the vaginal mucosa followed by accumulation of T_{RM} [35], suggesting the generation of T_{RM} should be a goal of vaccination[88]. Analogous work was performed independently, comparing skin and mucosa with HSV infection[36]. Approaches like these are likely to be attempted to generate a protective vaccine against HSV-2. Very recently, it was shown that a local chemokine gradient maintained HSV specific CD4 cells in situ, a novel mechanism for maintenance of T_{RM} residence[89]. Furthermore, it was recently shown that the HPV vaccine delivered to mice intravaginally generated CD8+ T_{RM} in vaginal mucosa[90,91]. This work is very promising, since not only HSV and HPV, but also HIV can infect through this route, and the possibility of rapidly killing virally infected cells with T_{RM}, however generated, is appealing (box 1)[88]. More recently, work on cervical tissue—normal, dysplastic, and malignant—has demonstrated that vaccination against oncogenic papilloma virus generates T_{RM} in these tissues which are highly protective against reinfection [92].

Box 1

Cancers of Skin Resident T Cells

TRM's and cancer. Certain skin lyphomas appear to be malignacies of skin TRM. Tumor infiltrating lymphocytes have features of TRM. Infiltration of tumors by T cells appears to be associated with a positive response to immune checkpoint blockade drugs, such as antibodies to PD-1, PD-L1, and CTLA4.

Cutaneous T Cell Lymphomas (CTCL) are a heterogeneous group of rare malignancies of T cells[118]. Recent reports have supported the idea that one form of this disease, mycosis fungoides (MF), is a malignancy of CD4+ T_{RM} from skin[66,98]. MF forms patches and plaques on the skin with well demarcated borders, and tends to recur in precisely the same locations after remission. It is responsive to skin directed therapy in its early stages[118]. The malignant T cell does not express CD62L, is CLA^+ and CCR4+, and often expresses CD69[66]. In advanced stages, T cells can travel to distant skin sites or to lymph node. It is not known whether this represents acquisition of markers such as CCR7 (which facilitate exit from skin) or a malignant de-differentiation program that reduces skin tropism[119]. The other most common type of CTCL is leukemic CTCL, often called Sezary Syndrome[98]. In these patients, skin lesions are typically characterized by confluent erythema, also known as erythroderma, and lesions do not have well defined borders. Malignant T cells are found in skin as well as blood, and sometimes lymph node. The malignant cells bear not only skin homing markers (CLA, CCR4) but also T_{CM} markers (CD62L, CCR7). The humanized antibody alemtuzumab depletes CD52+ cells, including the malignant T cell clone, in blood, a process largely mediated by neutrophil and NK ADCC[66]. However, even though alemtuzumab binds to T cells in skin, it does not deplete them. Interestingly, alemtuzumab has absolutely no efficacy in MF, supporting the idea that MF T cells are T_{RM} and do not traffic into blood from skin[66]. It has very high efficacy in L-CTCL, a malignancy of recently described skin homing T_{CM}[57,119].

T_{RM} in solid tumors. We have proposed that T cells that enter tissue acquire the T_{RM} phenotype, characterized by a unique transcriptional profile including expression of CD69 and CD103 (particularly on CD8 T cells), and downregulation of KLF-2 and S1P1. The infiltration of tumors, or peritumoral tissue, with T cells (so called tumor infiltrating lymphocytes or TILs) is associated with a better long term response[120]. One recent study suggested that such infiltration predicted response to immunotherapy with antibodies to PD-1[121]. CD103 expression on T_{RM} in ovarian cancer predicts a more favorable prognosis[122], and analogous results were recently seen in lung cancer[123]. Thinking of T cells entering tumors or peritumoral tissue as having a T_{RM} phenotype may be a useful way of conceptualizing these cells. Expression of inhibitory molecules like PD-L1 on tumor stroma, or production of other immuosuppressive factors will blunt the activity of these tumor specific T_{RM}. However, antibodies to PD-1 and PD-L1 suggest that activating these T cells may be a very useful way of activating immune mediated tumor destruction[112,121].

The role of T_{RM} in human disease

Pathologic T_{RM} in non-barrier tissues

The best characterized role for T_{RM} in disease is in mediating skin diseases, with fixed drug eruption being the first and best described[93]. More recently, established psoriasis has been shown to be mediated largely by T_{RM}. Transcriptomic analysis of resolved lesional psoriatic skin in humans reveals the presence of T cells and cytokines thought to be important in the pathogenesis, suggesting the residence of these T_{RM} cells [94,95]. Even more recently, analysis of cells extracted from resolved psoriatic lesions revealed CD8+ T cells that produce IL-17 and CD4+ T cells that produce IL-22, providing additional proof for the role of T_{RM} in psoriasis[96]. A recent report demonstrated that allergic contact dermatitis (ACD) in both human and murine settings is also T_{RM} mediated[38]. In psoriasis, the antigen is considered to be autoantigen, while in ACD it is often an innocuous environmental molecule[97] and in fixed drug eruption a chemical. Lesions in psoriasis that are treated, resolve, and then recur in the same place suggest that while the activity of disease-causing T_{RM} was suppressed by therapy, their localization was unaffected. Vitiligo, as well as some forms of atopic and eczematous dermatitis may also be T_{RM} mediated[5]; here the antigen is a melanocyte specific antigen. Interestingly, a variant of Cutaneous T Cell Lymphoma was found to be a malignancy of T_{RM}[98] while another variant (Leukemic CTCL/Sezary syndrome) is a malignancy of skin homing T_{CM} [66,98](see box 2).

Box 2

T_{RM} and vaccination

TRM and Vaccines. It is known that TRM are highly protective against pathogens that have been encountered previously. Increasingly, vaccine approaches that target the generation of TRM in the tissue likely to be infected by the pathogen are being considered.

The observation that pathogenic virus can be rapidly eliminated by T_{RM} in animal models, even in the absence of antibody, has led to a burgeoning interest in the induction of T_{RM} as a goal of vaccination[4,77]. Viruses show tissue tropism, with influenza specific for lung, rotavirus specific for gut, and HSV specific for skin and other stratified squamous epithelia. T_{RM} based vaccination would direct pathogen specific T_{RM} to the relevant epithelial tissue[88]. Currently, the titer of neutralizing antibodies generated by a vaccine is considered a proxy for its efficacy. But for viruses invading barrier tissues, infection of a resident cell and subsequent hijacking of the cells program to make more virus is largely insensitive to extracellular antibody. In contrast, such infected cells express viral peptides on cell surface class I molecules, making CD8 T_{RM}'s. Vaccination at epithelial surfaces, rather than intramuscularly, is thus an effective way to generate robust T_{RM}'s[30,48,77,91]. Promising approaches in lung for influenza and in other mucosal tissues have been recently reported[39,40].

Proof of principle in animal models for Vaccinia vaccinations of skin and lung, influenza vaccinations of lung, and Listeria immunization through oral administration have all shown generation of highly effective tissue resident T_{RM}'s. A recent HIV vaccine engineered to generate effector memory T cells showed great promise, and while the investigators focused on blood they did find memory T cells in mucosal tissue[124]. The wisdom of generating lung T_{RM} specific for conserved portions of the influenza virus, or anogenital mucosal T_{RM} specific for conserved portions of HIV, is clear. Virally infected cells could be targeted by T_{RM} for elimination shortly after exposure. The challenge with this approach to vaccination is at the level of practicality—how to immunize through an accessible tissue (like skin) and generate T_{RM} in tissues that are specific to the infectious virus. One of several promising approaches involves using Vaccinia vectors delivered by skin scarification—this has been shown to generate lung T_{RM} in one model. Also, because skin immunization in general generates both skin T_{RM} and a TCR identical population of T_{CM} in lymph node[38], sequential skin and peripheral tissue immunization (to convert the T_{CM} into tissue relevant T_{RM}) is a possible approach. While most work on T_{RM}'s has been done in the setting of viral infection, this approach should be applicable to other tissue selective pathogens. Mycobacterium tuberculosis, Listeria, Cholera, and M. Leprae are all candidate pathogens. What remains to be understood is what collection of factors in regional lymph nodes govern the acquisition of tissue homing markers on effector T cells, and how to ensure that these T cells that enter tissue remain as long lived T_{RM}, poised to respond to pathogens through the appropriate environmental interface[88].

The GI tract is another site where certain diseases exhibit the behavior of T_{RM} mediated diseases. The discrete waxing and waning skip lesions –areas of disease separated by areas of normal mucosa--in Crohn's disease suggest a role for T_{RM}, while ulcerative colitis involves a more contiguous circumferential area of the large intestine[99]. It is unknown, however, whether immune mediated diseases of the lung (i.e., asthma) involve T_{RM}. There is no data that addresses this possibility, though the presence of T_{RM} in normal lung makes the hypothesis a reasonable one. Certainly, the excessive inflammation in lung in the setting of fatal influenza infection may well involve hyperactive T_{RM}. Additionally, that T cell mediated diseases of the skin are mediated by T_{RM}, and that these diseases can often be

treated with skin-directed rather than systemic therapy, suggests that this approach of local rather than systemic treatment may apply to other tissues as well.

Pathologic T_{rm} in non-barrier tissues

It has been shown experimentally that accumulation of T_{RM} can also occur in tissues generally considered to be sterile, such as the brain[7]. T_{RM} were identified in the brain after intranasal infection with vesicular stomatitis virus, and CD103+ T_{RM} had a potent effector function after in vitro stimulation. The transcriptional profile of these brain CD8 T_{RM} resembled that of T_{RM} in skin, gut and lung[6,7]. Whether such T_{RM} can form in human brain after viral infection is unknown, and a putative role for these cells in diseases of the CNS requires additional evidence, though recent reports have linked putative pathogenic brain T_{RM} to multiple sclerosis and even schizophrenia.[100,101] While T cell responses in non-barrier tissues may be necessary episodically to deal with a potentially lethal infection, the unintended consequence of such an event may be the generation of long lived T_{RM} and predisposition to potential autoreactive and autoimmune diseases. One hypothesis is that the program to generate T_{RM} exists in all activated T cells, and that a subset those that gain entry into tissue (whether a barrier tissue or a normally sterile tissue) show activation of this program.

Spondyloarthropathies such as human ankylosing spondylitis involve inflammation of enthesial tissues (attachment of tendon to bone) and one recent study demonstrated enthesial resident Th17 T_{RM} to be essential for disease progression[102]. In human rheumatoid arthritis, the clinical recurrence of disease in individual joints bears the hallmarks of a T_{RM} driven process, and a preliminary report describes the presence of T_{RM} in human joint synovium in rheumatoid arthritis [103]. Sterile chronic inflammation of peripheral tissues in human disease is thus probably often mediated by these cells. For example, T cells from blood and kidney were examined in lupus nephritis, and a relatively limited set of T cell clones appeared to be responsible for progressive disease in individual patients, even over periods separated by months to years[104]. While this study did not examine CD103 or CD69, it provides indirect proof for pathological renal T_{RM}. In murine models of insulin dependent diabetes mellitus and pancreatic islet β cell rejection, infiltrating CD8 T cells acquire CD103 and remain in place during the immune response[105]. In the pancreas, it is conceivable that in human type 1 diabetes mellitus, T cells that infiltrate pancreas and attack β cells may take on the phenotype of T_{RM}, thus favoring their long term persistence *in situ*. In solid organ allograft rejection, infiltrating allogeneic T cells are able to acquire T_{RM} properties like CD103 expression[106], and urinary CD103 is associated with acute graft rejection[107]. If these human diseases involve pathological T_{RM}, immunosuppressive regimens may suppress their activation, but will not affect their location and persistence, thus setting the stage for recurrence and persistence of disease.

Finally, there is evidence that some tissues of immune privilege, like the eye, may have mechanisms to inactivate T_{RM} produced by inflammation[108], by expressing PD-LI and promoting T cell PD-1 expression[109]. Through mechanisms that are still unclear, cancers are also tissues of relative immune privilege. Binding of T cell PD-1 to its natural ligand PD-L1 induces a state of T cell unresponsiveness, and recently therapeutic antibodies to PD-1 have

been used in metastatic melanoma to interfere with this unresponsiveness and to augment the antitumor response. Tumor infiltrating lymphocytes by definition become “resident” to neoplastic tissue. It is notable that TIL with surface markers of T_{RM} were found to predict a more favorable prognosis in ovarian cancer[110]. The role of PD-1 PDL-1 interactions suppressing the activity of TIL’s is now well established[111,112]

Conclusions

Barrier tissues at interfaces with the environment **T_{RM}** are an important part of the adaptive immune system, providing the capacity to rapidly address and clear infections from previously encountered pathogens. When these cells pathologically accumulate in barrier tissues, in response to innocuous antigens, human disease can result. The molecular program that facilitates the T_{RM} phenotype in barrier tissues can be activated in other tissues as well, where persistent immune driven inflammation can cause chronic human disease. Regardless of the tissue involved, when T cells are seen in pathologic infiltrates, it was previously assumed that this represented chronic and dynamic T cell infiltration. It is more than a semantic difference to propose that these infiltrates in fact represent resident populations of T cells in which a T_{RM} molecular program has been activated. If this is the case, therapies that suppress T cell function will not necessarily change T cell localization, and reactivated T_{RM} will mediate recurrent disease. Whether in CNS, joint, pancreas, kidney, or heart, persistent and activated T_{RM} in tissues (where they were never intended to be) may drive human diseases. Therapies directed at selectively eliminating these T_{RM}, by depletion or by modifying their ability to persistently reside in tissue, represent novel approaches to the treatment of such diseases.

It is worth noting that skin T_{RM} have been unknowingly targeted for decades, far before the appreciation that these cells existed. Skin directed therapies, ranging from topical corticosteroids to UV-based phototherapy, to low dose radiation have all led to remission of what are now understood as T_{RM} mediated diseases. Would gut mucosal directed therapy via endoscope, or synovial directed therapy via arthroscope, suppress T_{RM} in those tissues? The advantage of skin targeted therapy is that repetitive therapy is straightforward and non-invasive, and the results to not require sophisticated imaging to assess. Other approaches might be directed at features that maintain T_{RM} in tissue, namely therapies that target CD69 and CD103. Blocking or interfering with the function of these molecules might flush pathogenic T_{RM} out of tissues, and of course a balance would have to be struck between depleting pathogenic T_{RM} and physiologically protective normal T_{RM}. Finally, it was noted that T_{RM} in immune privileged sites like the eye express PD-1, and presumably remain quiescent in this fashion. We speculate that tumor TIL’s are a form of T_{RM}, and the tumor may induce PD-1 on these T_{RM} to suppress their activity. If this suppressive pathway could be exploited in diseases where unrestrained T_{RM} activity causes tissue inflammation and injury, yet another approach to suppressing disease-causing T_{RM} would exist. None of these approaches (save those long employed in skin) are more than hypothetical at present. However, what is clear is that while simply suppressing the activation of T_{RM} in psoriasis, inflammatory bowel disease, or inflammatory arthritis may lead to transient remission, recurrence of disease is nearly inevitable if T_{RM} persist (as they are designed to do) in

tissue. The next decade of T_{RM} biology will be devoted to modifying their behavior and, perhaps, their location.

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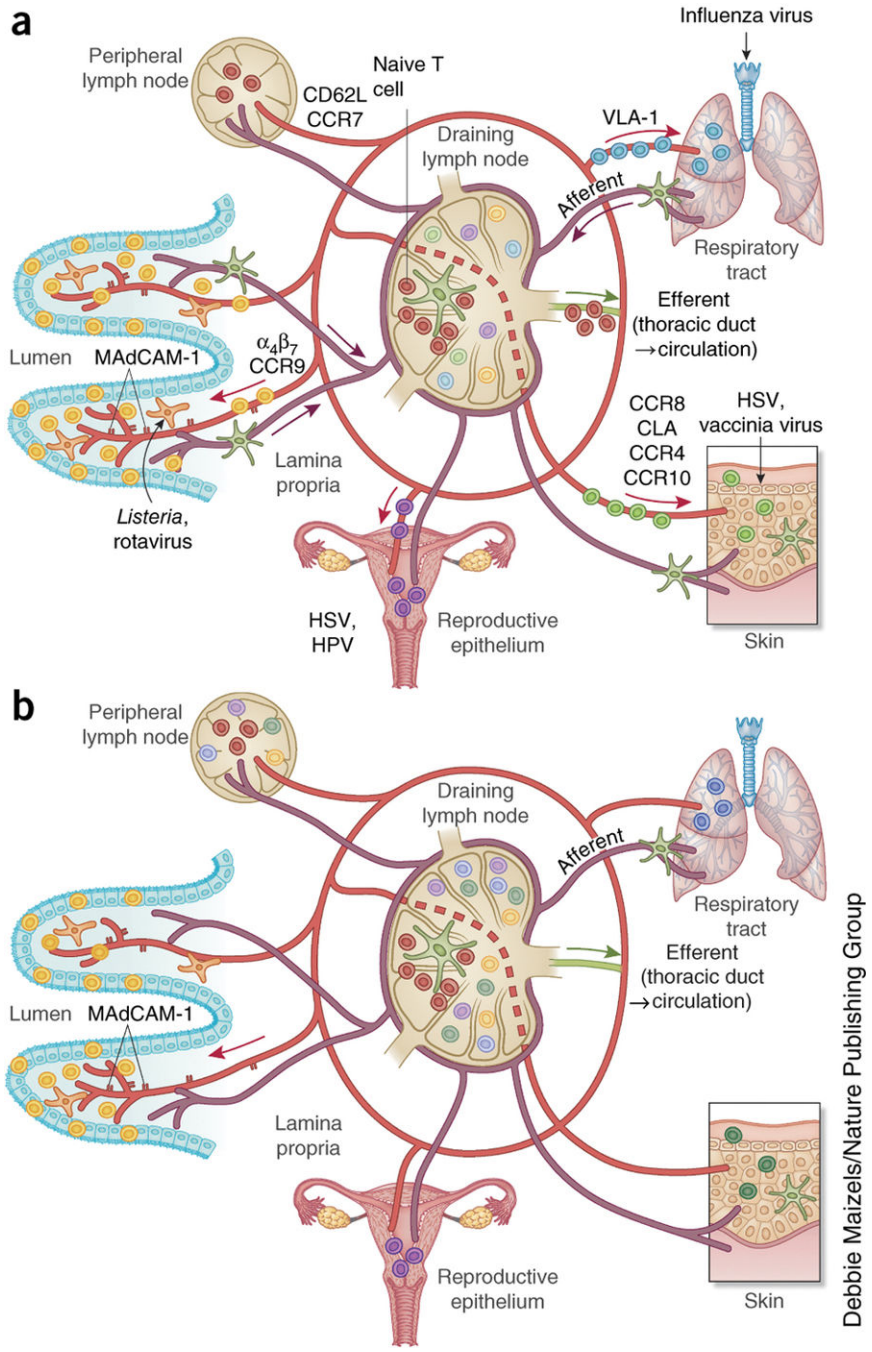

Figure 1.

A. Upon first encounter with pathogen in barrier tissues, dendritic cells carry antigen to draining lymph nodes and present to naive T cells. Depending on the anatomic location of the lymph node, trafficking molecules (indicated adjacent to the lymph) are expressed on the expanding activated T cell population, and effector T cells with specific tissue homing properties preferentially exit blood in peripheral tissues. Gut draining lymph nodes induce the expression of gut homing molecules on gut homing T cells, while skin draining lymph nodes induce the expression of skin homing molecules on skin homing T cells. Analogous

processes occur in lymph nodes draining lung and reproductive mucosa. B. Long after the pathogen has been eliminated from the barrier tissue and inflammation has resolved, populations of T_{RM} remain behind in each of these tissues. These T_{RM} retain the tissue homing molecules originally imprinted on them, and acquire a molecular program that contributes to maintaining these cells in peripheral tissue. In parallel, circulating memory T cells are generated, and these have the capacity to enter lymph node and recirculate into blood and tissue. Some evidence suggests that the same naive T cell may give rise to both the T_{RM} and the T_{CM} or circulating T cell.[38]

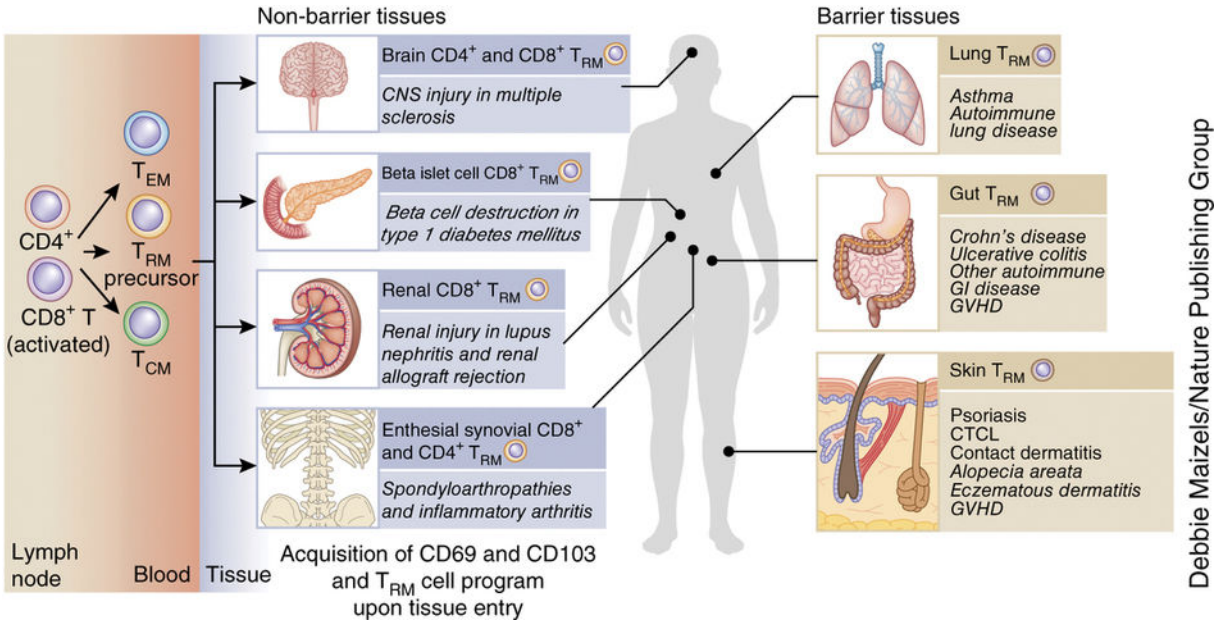

Figure 2.

The Role of T_{RM} in Tissue specific autoimmune and inflammatory disease. Left panels; diseases of skin, gut, and lung clearly or potentially mediated by inappropriately activated T_{RM}. Right panels; diseases of normally sterile non-barrier tissues mediated by infiltrating T cells that have acquired the properties of T_{RM}.

Table 1

Heterogeneity of T_{RM} cells in mouse and human skin

A comparison of the T cells that inhabit mouse and human skin. Some but not all of these T cells in this barrier tissue are authentic T_{RM} cells. NA, not available or not evaluated yet.

Location	Mouse cell	Cell type	Human cell	Cell type	Reference(s)
Epidermis	γδ DETC	$V\gamma3^+$	NA	NA	69,114
Epidermis	CD8-$\alpha\beta^+$ T	$CD103^+$	CD8-$\alpha\beta^+$ T	$CD103^+$ T_{RM}	4,6,63,73
Epidermis	NA	NA	CD4-$\alpha\beta^+$ T	$CD103^{+/-}$ T_{RM}	56,73
Dermis	γδ T	Non- $V\gamma3/IL^-17^+$	γδ T	Unknown	115,116,117
Dermis	CD8-$\alpha\beta^+$ T	$CD103^-$	CD8-$\alpha\beta^+$ T	$CD103^{+/-}$ T_{RM}	4,57,63,73
Dermis	CD4-$\alpha\beta^+$ T	$CCR7^+$	CD4-$\alpha\beta^+$ T	$CCR7^+$ T_{MM}	56,57,73
Dermis	CD4-$\alpha\beta^+$ T	$CCR7^-$	CD4-$\alpha\beta^+$ T	$CCR7^-$ T_{RM}	56,57,73
Dermis	NA	NA	CD4-$\alpha\beta^+$ T	$CCR7^+CD62L^+$ T_{CM}	57,66
Dermis	CD4- $\alpha\beta^+$ T_{reg}	$FoxP3^+$	CD4- $\alpha\beta^+$ T_{reg}	$FoxP3^+$ T_{MM}	57,73,79,118