Chapter

Resident Memory T Cells

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Abstract

Until recently, T cells were thought to remain in circulation until recruitment of the inflammation and only a small number of T cells remained in the peripheral tissues without inflammation. However, studies have found that a group of T cells settled in the tissues and remained there for a long time. Those cells are named as tissue-resident memory T cells (TRM). TRM cells are transcriptionally, phenotypically, and functionally distinct from other T cells, which recirculate between blood, secondary lymphoid organs, and non-lymphoid tissues. They undergo a distinct proliferation that discriminates them from circulating T cells and their main cell surface markers are CD69, CD103, and CD49a. Upon exposure to the same or similar diseases, TRM cells provide a first line of adaptive cellular defense against infection in peripheral non-lymphoid tissues, such as skin, lungs, digestive, and urogenital tracts. This approach forms the basis of a novel vaccination strategy called "prime and pull", which ensures long-term local immunity. On the other hand, abnormal activated and malignant TRM may contribute to numerous human inflammatory diseases such as psoriasis and vitiligo. Here in this chapter, we aimed to emphasize TRM cell location, migration, phenotypic structure, maintenance, and diseases associated with TRM cells.

Keywords: resident memory T cell, CD8+ TRM, CD69, CD103, CD49a, prime and pull, autoreactive human disease

1. Introduction

Tissue-resident memory T cells were discovered about a decade ago. Before the discovery of TRM cells and acceptance as a new subset of T cell, memory T cells have been subdivided into two populations: effector memory and central memory T cell [1, 2]. Traditionally, it was thought that T cells taken into the tissues during infection and leave the tissue after the pathogen clearance or undergo apoptosis [3]. However, at the beginning of this millennium, it was observed that some CD8+ T cells remain long-term in the tissues after infection.

The discovery of antigen-specific CD8+ T cells located in the lung after influenza virus infection was the first example of phenomenon [4]. Later, this finding was also observed in other non-lymphoid tissues after infections with Listeria and vesicular stomatitis virus [5, 6]. Eventually, TRM cells have been described in almost all organs and can be either CD4+ or CD8+ but tissue residency has been predominantly described for memory CD8+ T cells [7]. The term "TRM cells" were used to refer to CD8+ cells, unless otherwise specified in this chapter.

The retention of TRM cells is based on two mechanisms. First, TRM cells do not express lymph node homing molecules, which are required for tissue exit such as CD62L, CCR7, and S1PR1. Second TRM cells express adhesion molecules to their

host tissue such as CD103 and CD49a [8–12]. Not all of these markers are essential for TRM identification and function of many of them are still not fully understood.

The major function of TRM cells is to establish frontline defense against previously encountered pathogens in barrier tissues where they first encounter [13, 14]. Due to their robust systemic responses, TRM cells provide superior protection compared with circulating memory T cells in peripheral tissues [15–17]. However, dysregulation of TRM can contribute to human autoimmune and inflammatory diseases such as psoriasis, vitiligo, and multiple sclerosis [18–20].

In this chapter, we aimed to emphasize TRM cell location, migration, phenotypic structure, maintenance, and diseases associated with TRM cells. We discuss the TRM cells in a basic and perceptible form as a whole, where there is no unity due to a large number of tissue variations use. We have reviewed the subject not only on the molecular level, but also on the perspective of disease formation and therapeutic usage.

2. Location

T cells can be distinguished based to their microenvironment or their location in the host tissues and thereby it is possible to classify them as TRM cells or other T cell subsets [21–23]. TRM cells are easily identified in the tissues that have direct exposure to the pathogens such as the gut, skin, lungs, and reproductive system, where they receive signals that are required for their unique development program from these microenvironments [20, 24–27].

TRM cells have different phenotypes that show heterogeneity depending on the host tissue microenvironment. Requirement for TRM generation, proliferation, migration, and maintenance vary in different kind of tissues [9, 25, 26]. In particular, the majority of TRM cells are CD8+ memory T cells, and the TRM cell population in the skin is known as CD103+ and Cd69+. However, CD4+ TRM cell populations have been identified in the skin, lungs, reproductive tract, and salivary glands. Similar to CD8 TRM cells, they express the surface molecules CD69 but expression of CD103 is low or negative [28–31]. These requirements will be detailed below according to tissue types.

The locations of the TRM cell can be classified according to host tissues as shown in **Figure 1**.

The skin is one of the primary barrier tissues against infectious agents. Epidermis, dermis, and subcutaneous fatty region form a 3-layer structure of the skin and

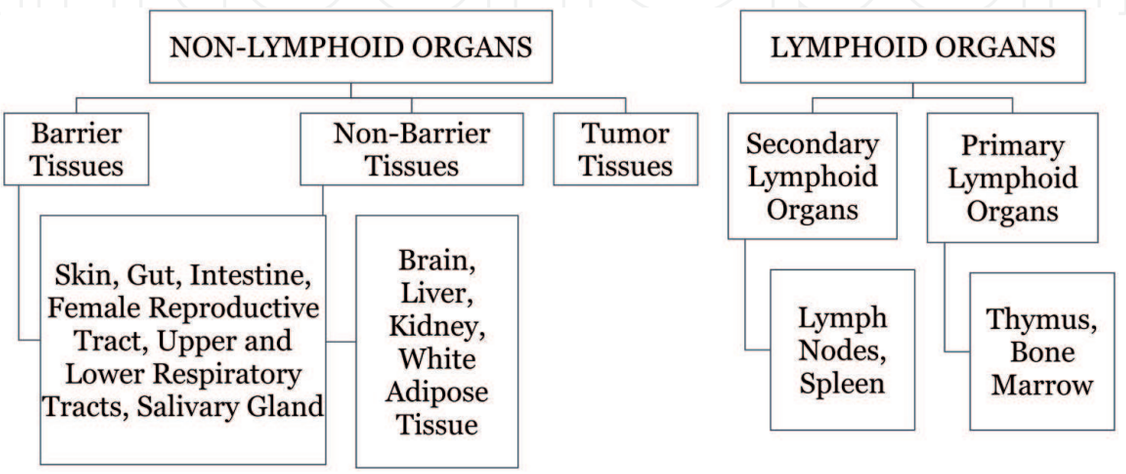

Figure 1.
Classification of TRM cell locations according to their host tissue.

TRM formation has been shown in all layers [32–34]. The skin has very complex cell populations and hosts both natural and adaptive immune system cells. These immune system cells provide a biological barrier to invasive pathogens. CD8+ TRM constitutes the majority of the memory T cell population in the epidermis. CD8+ TRM cells are commonly resident in the skin and their numbers increase rapidly when they are exposed with the infectious agents. Skin TRM cells may easily characterized due to their surface markers such as marker CD69, CD103, and CD49a [9, 27, 35]. These markers and others will be described in detail in terms of their function.

The intestinal mucosa consists of a layer of single epithelial cells and provides a barrier tissue against infectious agents. This layer is also considered as an immunological site for the maintenance of TRM cells. Following intestinal infections, a significant number of pathogen-specific TRM cells have been shown to form in the intraepithelial compartment [36, 37].

The female reproductive tract (FRT) is another organ that is directly exposed to external pathogens. FGT can be divided into two parts. Upper female reproductive tract consists of endometrium and endocervix and lower FRT consists of vagina and ectocervix. FRT is a variable tissue that undergoes significant cyclic changes in women. Under the control of estrogen and progesterone hormones, growth, differentiation, and degeneration occurs periodically [38, 39]. Although this suggests that anatomical sites are limited for the localization of TRM cells, it has been showed that numerous immune system cells, including memory T cells are present throughout FRT. Generation of FRT TRM cells is a promising vaccination strategy against HSV-2, and potentially against other sexually transmitted infections such as HIV and HPV [16, 39, 40].

Respiratory tract (RT) is also a structure which is directly exposed to external pathogens. RT can also be divided into two parts as upper (URT) and lower (LRT). Most common airborne pathogens in humans primarily infect URT [41, 42]. URT contains lymph nodes known as tonsils, which contain B cell follicles and T cell subsets. URT is considered a mucosal inductive region for humoral and cellular immune responses. Although the effector CD4+ T cells predominate the tonsils, the presence and the localization of TRM cells is also shown in the lungs [15, 43].

Salivary glands are exocrine epithelial tissues, which are the targets of viral infections. The presence of TRM cells in these tissues has also been shown in various studies [28, 44].

The liver is an organ, which is the member of the immune system. Through the portal vein, antigen-rich blood enters the liver and encounters the immune system cells that are resident in the tissue [22, 45, 46]. Studies have shown that CD8+ TRM cells are established in the liver especially after systemic infection or vaccination [47, 48].

Due to the presence of a blood-brain barrier, immune cells are not thought to be resident in the central nervous system [49]. However, after clearing a viral infection in the central nervous system, some of the antigen-specific CD8+ T cells maintained in the brain as TRM cells [50].

The kidney has a very high amount of blood vessels and has a very high circulating volume. This helps to eliminate toxins from the body. Therefore, healthy kidneys are not suitable tissues for the localization of immune system cells. Even so, it has been shown that a small number of resident TRM cells may be present in the kidney. White adipose tissue is another tissue in which TRM cells have been shown to be resident and they act as a reservoir of TRM cells [51–53].

CD8+ TRM cells have been reported in solid tumors [54]. Studies have shown that infiltrating T lymphocytes (TIL) are phenotypically similar to TRM cells that TRM cells from neighboring peripheral tissues could infiltrate into solid tumors [55, 56]. It was found that presence of CD8+ TRM cells is associated with good prognosis in various cancers [57].

Secondary lymphoid organs and lymph nodes are the tissues where TCM and TEM cells are more common and pass through. However, recent studies have shown that a small number of non-circulating memory T cells are present in these tissues. TRM cells in SLO show phenotypic characterization similar to those in non-lymphoid tissues [1, 58].

Primary lymphoid organs (PLO) are bone marrow and thymus. Antigen-specific TRM cells have also been found in these tissues and have been shown to facilitate long-term maintenance in the PLO. TRM cells in the PLO express CD69 and CD103 as a characteristic of TRM phenotype [59–61].

3. Migration

Circulation of T cell in the blood, secondary lymphoid organs, and non-lymphoid tissues is a complex system. Numerous receptors, ligands, chemokines, cytokines, and transcription factors has a role on this [31, 32]. T cells can be classified according to the organs or tissues in which they recirculate. Schematic illustration for migration of T cell subsets is shown in **Figure 2**.

- Naive T cells: recirculate in the blood, secondary lymphoid organs, and non-lymphoid tissues [62, 63].

- Effector memory T cells: recirculate in the blood, secondary lymphoid organs, and non-lymphoid tissues, same as naive T cells.

- Central memory T cells: recirculate between nonlymphoid tissues, lymph, and lymph nodes [64, 65].

- Tissue-resident memory T cells: do not recirculate between blood, secondary lymphoid organs, nonlymphoid tissues, but may migrate within the tissue it settled [8, 11, 66, 67].

CC-chemokine receptor 7 (CCR7), CD69, CD49, S1PR1, KLF2, and integrins are the main factors responsible for the migration of T cell subsets. The role of these factors may differ depending on the location of the host tissue [68, 69]. These will be further explained in more detail in phenotype and localization parts.

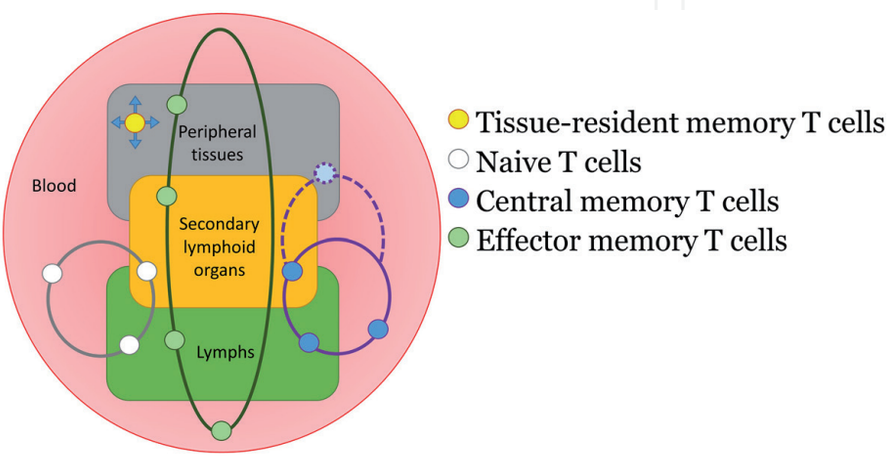

Figure 2.
Schematic illustration of circulation and migration of T cell subsets.

4. TRM markers

In order to distinguish TRM cells from other T cell subsets, in most of the studies in both mice and humans, identification markers such as CD103, CD69, Cd49a, and CD44 have been widely investigated.

4.1 CD103

αEβ7 integrin (CD103) was first discovered in the late 1980s. After that several new monoclonal antibodies were produced as a specific marker for intestinal intraepithelial T cells in humans, mice, and rats, presumably contributing to their tissue-specific localization [70]. Integrins are transmembrane αβ heterodimers that bind to extracellular matrix components and to cellular counter receptors. They have important roles on cell localization, migration, and signaling and are important for T lymphocyte adhesion and stimulation [71].

Following the discovery of the ligand called E-cadherin, interest in CD103 has been increased considerably. E-cadherin is a transmembrane protein with an extracellular region containing extracellular cadherin domain repeats, which mediates cell-cell adhesion by homodimerizing in trans with E-cadherin domains of neighboring cells [72].

CD103 is important in adhesion as well as T cell activation and TGF-B induced defense in tumor microenvironment. In TGF-B environment, CD103 TRM cells have been shown to release more efficient granzyme. Although CD103 is an important marker, CD103 alone is not sufficient to detect TRM cells. CD103 negative TRM cells were found in several tissues. Furthermore, there are different types of CD103 T cells such as CD4 CD103 T cells and CD8 CD103 Treg cells.

4.2 CD69

CD8+ TRM cells can be characterized by their expression of the surface molecules CD69 and CD103. These markers are usually not expressed on circulation T cells [73]. CD69 is a type II C-lectin membrane receptor with a scarce expression in resting lymphocytes that is rapidly induced upon cell activation [74]. Because of these features, CD69 was considered as early activation antigen of immune cells. However, recent studies have shown that this molecule is an important indicator of TRM differentiation as well as activation of the immune response.

CD69 has been found to suppress the activity of sphingosine-1 phosphate receptor 1 (S1P1), helping the TRM cells that remain in peripheral tissues [75]. The S1P1 receptor/gene, originally known as endothelial differentiation gene 1, acts by binding with a bioactive signaling molecule S1P1 [76]. It was suggested that CD69 expression might help retaining TRM cells in peripheral tissues by suppressing the activity of S1P1. Decreased expression of transcription factor of KLF2 is another factor affecting S1P1 expression to remain down-regulated in TRM cells [77, 78].

Moreover, CD69 expression is not limited to TRM cells and is not essential for TRM formation. CD69 has also been shown to be expressed in cells such as natural killer cells, dendritic cells, and in the absence of CD69, TRM formation decreased but is not completely eliminated [32, 79]. Therefore, CD69 is a good TRM marker, but it is not sufficient to be the sole determinant.

4.3 CD49a

CD49a or integrin α1 paired with CD29 (integrin-β1) to form very late antigen (VLA-1). VLA-1 is a collagen-binding integrin and receptor for collagen and laminin such as ColIV and ColI [9, 80, 81].

Collagen IV enriched in the basement membrane separating epidermis and dermis. CD49a is therefore a good marker for skin TRM cells. In human skin epithelia, CD8+ CD49a+ TRM cells produced interferon-γ, whereas CD8+ CD49a TRM cells produced interleukin-17 (IL-17). It has been reported that CD8+ T cells with a TRM phenotypes (CD103+ and CD49a+) are present in solid tumors as well as lung interstitium [9, 35, 82].

VLA1 is a receptor not only involved in adhesion but also to migration and survival. In the formation and proliferation of TRM cells, CD49a together with CD103 and CD69 are the most determinative markers of TRM presence.

4.4 CD44

The CD44 antigen is a cell-surface glycoprotein involved in cell-cell interactions, cell adhesion, and migration [83]. The most well-studied function of CD44 is as a receptor for hyaluronic acid, a component of the extracellular matrix. In regard to accessing peripheral tissues during an immune challenge, CD44 can bind hyaluronic acid expressed on vascular endothelial cells and facilitate transmigration. CD44 is a classical marker of previous activation, expressed on newly generated effector cells as well as resting memory cells [23, 84, 85].

It is important to specify that TRM cells express different markers depending on the host tissues. It should not be ignored that there may be some differences between TRM subsets in various tissue types. The results obtained by using in vivo techniques such as parabiosis, organ transplantation, using transgenic mice, and bone marrow chimera techniques were more effective in the identification TRM cell proliferation. The main factors that enable scientists to identify TRM cells as a subset of T cells have been obtained by these methods.

4.4.1 Parabiosis

Parabiosis is a surgical process that allows the sharing of blood circulation in two organisms. Bringing the skin of the two animals, in particular mice, together stimulate the capillary blood vessel formation in this region. Blood and immune cells circulate between parabiotic partners [86]. Therefore, migration or residence can be examined by investigating whether the immune system cell in one organism is in equilibrium with the other.

4.4.2 Bone marrow chimera (BMC)

BMC is another widely used technique to study donor organism, which has congenitally distinctive or labeled bone marrow, and a recipient organism, which have been irradiated, thus losing its all bone marrow-derived cells (lymphocytes) are two component of this method. Then, bone marrow cells of donor organism are transferred to the recipient organism [87, 88].

4.4.3 Organ transplantation

Transplantation is a similar approach to BMC in TRM cell studies. In this method, organ or skin graft of the donor organism is transplanted into the recipient. The equilibrium between the established T cell populations of donor and recipient organisms are examined to investigate the TRM cells. Moreover, TRM cells have important roles in organ transplantation and tissue rejection [89, 90].

4.4.4 Transgenic organism

Transgenic organisms are widely used in TRM studies. Numerous studies have been performed using knockout mice where proteins involved in tissue localization or tissue exit cannot be expressed [32, 57, 91, 92].

5. Phenotype

There is not a single phenotypic character to be used to identify TRM cells. Many researchers have examined the TRM cell phenotype in different tissues including lungs, liver, lymphoid sites, skin, and intestines both in mice and humans.

Characteristically, TRM cells express CD103 and CD69. CD49a, which binds to the extracellular collagen and laminin, can be added to these two for the skin tissue [21, 23, 93]. TRM cells do not express or express very low levels of lymph node homing molecules which are required for tissue exit such as CD62L, CCR7, and S1PR1 and it is critical for TRM cell tissue residency [1, 15, 53, 67, 69]. S1P1 is mediated by the downregulation of the transcription factor KLF2 [93].

TRM cells also express cluster of chemokines and chemokine receptors including CXCR3 and CCR6, and was able to produce chemokine ligands such as CCL19 andCCL21 [2, 93, 94].

Tissue microenvironment also promotes TRM differentiation. TRM precursors that are KLRG1 negative, are more likely to differentiate into TRM cells [53, 55].

Broad range of transcription factors is associated with TRM formation. Most common transcription factors are AHR (aryl hydrocarbon receptor), Notch, Blimb1, Hobit, Eomes, and T-bet [30, 95]. These phenotypic structures are illustrated in **Figure 3** and each is described in detail in **Table 1**.

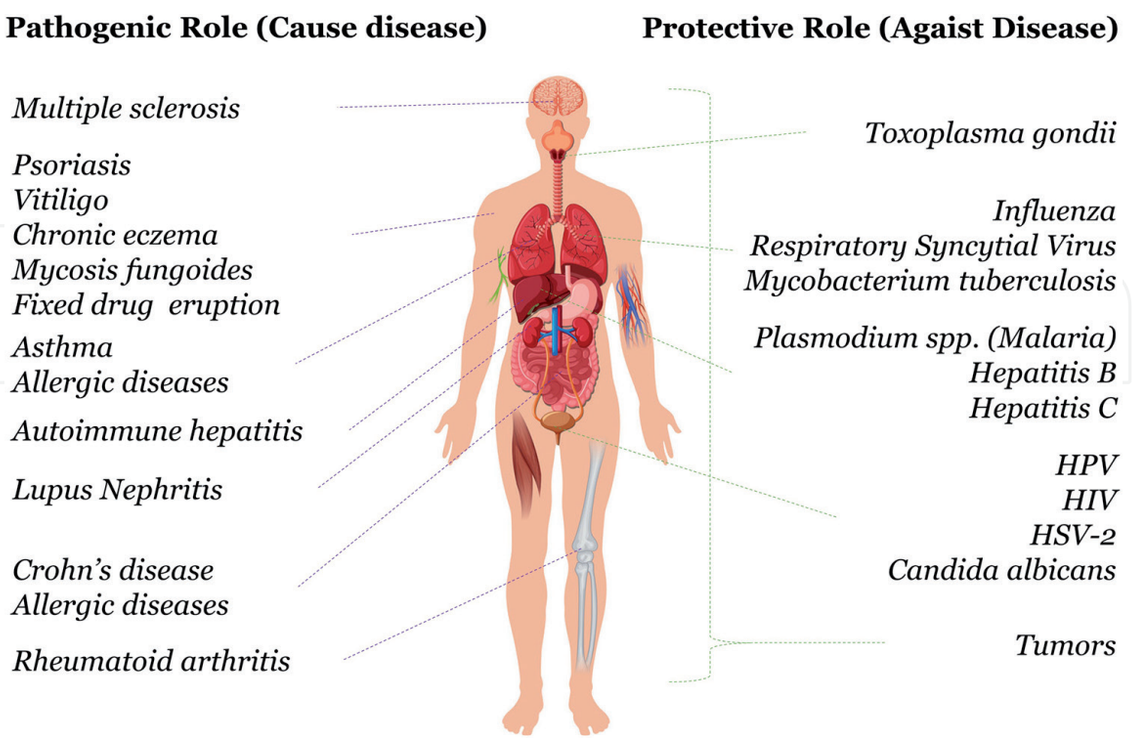

Figure 3.
Schematic illustration of some of the most common, receptors, transcription factors, ligands, and molecules involved in differentiation and maintenance of TRM cells and their regulation for TRM formation.

Marker	Function	Regulation
CD103 (integrin αEβ7)	CD103 is as a receptor for E-cadherin, an adherent junctional protein interlocking epithelial cells [96]	↑
CD49a (integrin α1β1)	CD49a pairs with CD29 (integrin β1) to form the heterodimer called VLA-1 which is a collagen-binding integrin [35]	↑
CD69	Human transmembrane C-Type lectin protein. CD69 is a lymphoid activation antigen whose rapid expression makes it amenable for the early detection of T-cell activation and for subset activation analyses [97]	↑
Krüppel-like Factor 2 (KLF2)	Klf2 also plays a role in T-cell differentiation and regulate the migration of mature thymocytes from the thymus and to control the circulation of peripheral T cells. In the absence of Klf2, mature T cells exist in an activated state and are more prone to apoptosis [98]	↓
Ki67	Function of the Ki67 protein is still unclear. Ki67 protein has been widely used as a proliferation marker that is expressed by cells mitotic phases [99–101]	↓
Killer cell lectin-like receptor subfamily G member 1 (KLRG1)	KLRG1 is expressed by NK and T-cell subsets and recognizes members of the classical cadherin family. KLRG1 is widely used as a lymphocyte differentiation marker in both humans and mice [102]	↑
C-C chemokine receptor type 7 (CCR7)	CCR7 is a chemokine receptor which regulates T cell trafficking and compartmentalization within secondary lymphoid organs [103]	↓
Sphingosine-1-phosphate receptor 1 (S1PR1)	S1PR1 was implicated in lymphocyte trafficking and it has an important role in regulating endothelial cell cytoskeletal structure, migration, and T cell maturation [104]	↓
Chemokine receptor 3 (CXCR3)	CXCR3 plays a role to regulate leukocyte trafficking. Ligand that binds to CXCR3 induces cellular responses, such as integrin activation, cytoskeletal changes and chemotactic migration [94]	↑
CD62L (L-selectin)	L-selectin is an adhesion molecule that regulates both the migration of leukocytes at sites of inflammation and the recirculation of lymphocytes between blood and lymphoid tissues [105]	↓
Chemokine ligand 21 (CCL21)	CCL21 is a high affinity functional ligand for chemokine receptor 7 [106]	↓
Eomesodermin (Eomes) and T-bet	Downregulation of T-bet and Eomes enables increased TGF-β responsiveness, thereby creating a feedback loop that promotes TRM differentiation [30]	↓
Blimp-1 and Hobit	Loss incompatible with development of tissue-resident cell types; in combination enforces tissue retention by depression of KLF2, S1PR1, and CCR7 [69]	↑
Aryl hydrocarbon receptor (Ahr)	is required for long-term persistence of T_{RM} as a survival pathway for T cells residing in the epidermis [33]	↑
Notch	Required for maintenance of CD8 T_{RM}; proposed to control metabolic functions in T_{RM} and CD103 expression [23]	↑

Table 1.
Detailed explanations of receptors, transcription factors, ligands, and molecules involved in formation and migration of TRM.

6. TRM and diseases

TRM cells may assume pathogenic roles if they become over-sensitized or autore-activated. However, TRM cells are the first line protector of the immune system against the pathogen at the same time. Therefore, they play or stimulate to play an important role in effective treatment or vaccination. **Figure 4** summarizes the diseases associated with TRM cells both in the perspectives of pathogenic and protective roles.

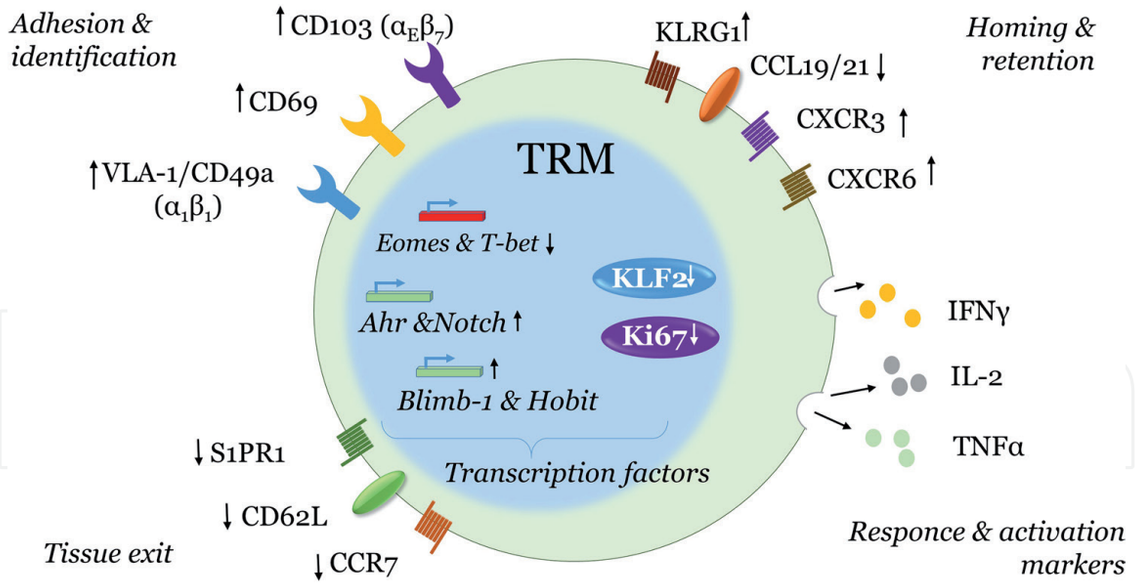

Figure 4.
Illustration of some of the TRM-associated diseases that has been reported.

6.1 Pathogenic roles

6.1.1 Psoriasis

Psoriasis is a common chronic inflammatory skin disease with a spectrum of clinical phenotypes and results from the interplay of genetic, environmental, and immunological factors [107]. Psoriasis can be divided into five types. The most common is plaque psoriasis, which causes itching and pain due to plaque formation. This type also maintains large areas of erythema or scaling of the skin, causing deformation of the skin [108]. Many studies showed that the chronic inflammation observed in psoriasis arises from an uncontrolled proliferation of T cells [66, 109]. Resident T cells play a role in the formation and recurrence of psoriatic lesions. Psoriasis lesion can be triggered and sustained by the local network of skin-resident immune cells in mouse models [110].

In recent studies, TRM cells were identified in healthy skin but were increased in psoriatic lesions. And these TRM cells have been found to produce perforin and IFN-gamma and to secrete IL-17 which is responsible for unwanted symptoms [111]. Demarcated, inflamed, and hyperproliferative plaques are maintained by interleukin-23 (IL-23) and IL-17 in psoriasis [41, 112].

For the treatment of psoriasis, an autoimmune disease, various immunosuppressive drugs, neutralizing antibodies, and cytokines have been tried for the treatment [42, 113–116]. These therapies have not been fully successful nowadays due to the systemic side-effects and the presence of autoreactive resident T cells in tissues without lesions.

6.1.2 Vitiligo

Another disease with several patchy appearance lesions in the skin like psoriasis is Vitiligo. These two diseases are often confused with each other. Vitiligo is an autoreactive T cell-mediated disease in which immune cells target and kill melanocytes, leading to depigmentation of the skin [73].

Vitiligo lesions recur in the same areas of the skin and this is a sign of the presence of resident autoimmune memory [117]. Recent studies have shown the presence of melanocyte-specific TRM cells in skin tissues with vitiligo. These TRM

cells are CD8+ cells secreting IFNg and TNFα and expressing common TRM markers such as CD69, CD103, and CXCR3 [19, 118]. In a mouse vitiligo model, it was showed that neutralization of the IL-15 receptor by anti-CD122 antibody decreases the IFNg production from TRM cells and leads to repigmentation of the lesion [91]. Currently, there is no FDA-approved vitiligo treatment and such studies targeting TRM cells are likely to have prosperous results in the future.

6.1.3 Multiple sclerosis

Multiple sclerosis (MS) is a chronic, immune-mediated, demyelinating disorder of the central nervous system [119]. The brain is not a frequently visited tissue for immune cells due to its barriers. In one of the few studies in this field, CD8+ TRM cells that persist within the brain after an acute systemic vesicular stomatitis virus infection were characterized [120]. These cells were not in equilibrium with circulating T cells as evidence for TRM establishment in the brain tissue [50]. However, the mechanism for the generation and maintenance of TRM cells in the brain remains unclear.

6.1.4 Asthma

Asthma, other allergic airway diseases are inflammatory lung diseases that are related to the TRM cells. Asthma is a heterogeneous disease and is characterized by chronic airway inflammation, increased susceptibility to respiratory viral infection, and altered airway microbiology [121, 122]. The lungs have been widely investigated for TRM cell formation due to their exposure to the external environment and recurrent infections. In one of those studies, house dust mite HDM-specific memory cells have been identified as central memory cells in the lymphoid organs and TRM cells in the lung [123].

The majority of T cells in the human lung are TRM cells. TRM cells provide important roles in the protection against asthma, multiple respiratory pathogens, and other allergic diseases and might be contributed for developing new therapies and vaccines [25, 26].

6.1.5 Rheumatoid arthritis

Rheumatoid arthritis is a chronic autoimmune disease which can cause cartilage and bone damage, progressive articular damage, as well as functional loss disability [124–126]. Rheumatoid arthritis, is known largely a disease of the joints, however many organs and systems are effected, including the pulmonary, cardiovascular, ocular, and cutaneous systems [127].

Recurrence of arthritis in the joints is the key for the treatment of human rheumatoid arthritis. The disease is propagated through resident cells in the synovium of the joint, resident synovial cells that interact with the infiltrating immune cells and transition from acute synovitis to chronic RA [128]. The link between recurrence and residency suggests the presence of TRM cells. Studies have shown that TRM formation was induced in the enthesis. The enthesis is the region at the junction between tendon and bone. This zone was shown to contain a unique population of resident T cells, when activated by the cytokine interleukin-23 and can cause pathogenesis [129, 130].

6.1.6 Crohn's disease

Crohn disease (CD) is an inflammatory condition of the gastrointestinal (GI) tract, characterized by unpredictable periods of symptomatic relapses and

remissions [131]. It has been suggested that CD has clinical similarities with TRM-mediated skin diseases. The skin lesion is similar "skip lesions" in the gut seen in CD [3, 67]. The use of immunosuppressive drugs for the treatment of CD can be considered as another similarity. However, the presence of a direct link between CD and TRM formation should be investigated.

Some of the other diseases that are related to the TRM formation are mycosis fungoides, contact dermatitis, chronic eczema, and fixed drug eruption and all needs to be further investigated.

6.2 Protective roles

Autoreactive TRM cells may contribute to the pathogenesis of autoimmune, atopic, and allergic diseases as described above. In contrast, they can provide rapid and efficient protection against wide range of pathogens and various types of tumors. Malaria, HSV, and cancer must be emphasized due to the role of TRM cell mediated treatment and vaccination strategies.

Malaria is a vector-borne parasitic tropical disease found in 91 countries worldwide [132]. *Plasmodium falciparum* (PF) is the dominant specie that produces high levels of parasites in critical organs and cause severe anemia, especially in African children, in whom. Malaria affected an estimated 216 million people causing 445,000 deaths in 2016 [133] around the World and the vast majority of malaria deaths occur in developing countries. Over the years, extensive research has been conducted on the prevention and treatment of malaria. However, increasing drug and insecticide resistance and threatens the successes. Moreover, the results obtained from current vaccine studies have not been sufficient to prevent malaria.

Development of a broadly protective vaccine is required for the eradication of Malaria. For this purpose, TRM cell-mediated vaccination strategies can be very promising. Researchers identified that memory CD8+ T cells that expressed the gene signature of TRM cells and remained permanently within the liver [45, 48].

A recent study explored the mechanism of action of a newly developed malaria vaccine, *Plasmodium falciparum* sporozoites (PfSPZ), which has exhibited very promising efficacy in human clinical trials. The efficacy of this vaccine has been shown to be due to TRM formation within the liver was 100-fold higher [47]. Researcher also showed that this TRM cells within the liver can also be generated by a "prime and trap" or "prime and pull" vaccination strategy [16, 22].

This strategy has two stages. First is the conventional vaccination to obtain systemic T cell responses (prime), second is recruitment of activated T cells via topical chemokine application to the desired tissue (pull), where such TRM cells were established and mediate long-term protective immunity [16, 102, 134]. The robust protective immunity provided by memory T cells localized in peripheral tissues, together with localized memory T cells, provides hope that site-specific vaccination strategies can be developed [135].

Development of a T cells mediated vaccines are required for efficacious protection. Due to their robust systemic responses, TRM cells provide superior protection compared with circulating memory T cells in peripheral tissues [136]. Recent studies focused on TRM establishment of training to protect against infection agent where they first contact [40].

The female genital tract, which is a portal of entry for sexually transmitted infections such as HIV and HSV. In a recent study "prime and pull" strategy was used against HSV-2 infection in female genital tract. In this study, mice were infected by attenuated strain of HSV-2 subcutaneously and topical application of chemokines CXCL9 and CXCL10 have been used to recruit TRM cells in the vagina to prevent the development of clinical disease for further infections [16].

TRM-mediated vaccine development researches against infectious agents are not limited to PF HSV and HIV. Moreover, vaccine studies are being carried out in order to provide first step protection against many infectious agents such as influenza, varicella, Human papillomavirus (HPV), toxoplasma, etc. [8, 38, 43, 137, 138].

In the context of TRM cells, cancer should also be emphasized. Currently, developed cancer vaccines are generally aimed for the treatment and the number of prophylactic vaccines is relatively low. Therefore, vaccination studies for the formation of TRM against cancer are very promising.

Recent studies suggest that TRM cells also play a vital part in cancer surveillance [57, 139]. It was demonstrated in many studies that TRM cells generated by vaccines can protect against tumor challenge [10, 55, 140, 141]. Formation of CD8+ T cells is one of the main objectives in cancer vaccine development against solid tumors. The type of CD8+ T cells that can migrate and localize in tumor microenvironments are TRM cells. [55]. It was found that presence of CD8+ TRM cells is associated with good prognosis in various cancers [57]. TRM cells can act in three major ways against solid tumors [73].

- TRM cells can express cytokines: TRM cells can produce cytokines such as perforin and granzyme B, and other effector molecules such as IFNγ and TNFα and eliminate tumor cells [10, 73].

- TRM cells may promote tumor-immune equilibrium: CD8+ TRM cells can contribute tumor immunosurveillance and they prevent tumor outgrowth without completely eliminating cancerous cells [73, 142, 143].

- TRM cells express inhibitory checkpoint molecules: TRM cells also predominantly express checkpoint receptors such as programmed cell death protein-1 (PD-1), cytotoxic T-lymphocyte-associated protein-4 (CTLA-4), and T-cell immunoglobulin and mucin-domain containing-3 (Tim-3) [55, 80].

It is becoming increasingly clear that TRM cells play an integral role in tumor surveillance in both animal models and human cancers. However, the role of TRM cells in solid human cancers should be further investigated.

7. Conclusion

The knowledge about TRM cells is at an early stage. Moreover, it has been revealed only in recent decades that TRM cells are unique subsets. It was found that TRM cells become resident by their phenotypic characteristics by adopting the microenvironment of the host tissue. TRM cells are transcriptionally, phenotypically, and functionally distinct from other circulating T cell subsets.

TRM cells have different phenotypes show heterogeneity depending on the host tissue microenvironment. Requirement for TRM generation, proliferation, migration, and maintenance vary in different kind of tissues. In order to distinguish TRM cells from other T cell subsets, in most of the studies in both mice and humans, identification markers such as CD103, CD69, and Cd49a were the most common ones.

TRM cells may assume pathogenic roles if they become over-sensitized or autoreactivated. However, TRM cells are the first line protector of the immune system against the pathogen at the same time. Therefore, they play or stimulate to play an important role in effective treatment or vaccination. It was found that presence of CD8+ TRM cells is associated with good prognosis in various cancers.

Unlike other T cell subsets, TRM cells are not present in the blood. This is one of the major logistical barriers to the study of TRM cells. Therefore, TRM studies in humans have been limited due to the need for biopsy. In human NLT tissues, TRM isolation should be performed in a small biopsy volume, they should be phenotypically redefined and distinctive surface markers should be identified for humans. However, TRM cell-mediated vaccination and effective T cell treatments against solid tumors can be achieved by overcoming these problems in the following years.

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