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Abbreviations
APC, antigen presenting cell; BM, bone marrow; CCR7, C-C chemokine receptor 7; DC, dendritic cell; FOXO1, Forkhead O 1; FRC, fibroblastic reticular cell; KLF2, Krüppel-like factor 2; KO, knockout; LCMV, lymphocytic choriomeningitis virus; LN, lymph node; miRNA, microRNA; MP, memory precursor;

The Roles of CCR7 for the Homing of Memory CD8+ T Cells into Their Survival Niches

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ABSTRACT

Memory CD8+ T cells in the immune system are responsible for the removal of external Ags for a long period of time to protect against re-infection. Naïve to memory CD8+ T cell differentiation and memory CD8+ T cell maintenance require many different factors including local environmental factors. Thus, it has been suggested that the migration of memory CD8+ T cells into specific microenvironments alters their longevity and functions. In this review, we have summarized the subsets of memory CD8+ T cells based on their migratory capacities and described the niche hypothesis for their survival. In addition, the basic roles of CCR7 in conjunction with the migration of memory CD8+ T cells and recent understandings of their survival niches have been introduced. Finally, the applications of altering CCR7 signaling have been discussed.

Keywords: CD8-positive T-lymphocytes; Immunologic memory; Receptors, CCR7; Cell movement; Chemotaxis; Immunotherapy

INTRODUCTION

The defense against pathogens is composed of innate and adaptive immunities. While innate response mounts in a few hours by the recognition of molecular patterns, adaptive immune system takes a few days to initiate Ag-dependent specific response. The adaptive immune system employs B cells, which produce antibodies, and T cells to mediate cellular immunity. One cardinal feature of the adaptive immune system is "memory" response to the same Ag. Once the adaptive immune system has been stimulated with vaccines or pathogens, challenges with the same Ag induce a faster and stronger response than the primary response. These memory responses are mainly mediated by Ab-producing plasma cells and memory T (T_M) cells. Through these memory responses, vaccines can protect our body against fatal or serious infectious agents. Although vaccination is the most efficient way to prevent infectious disease, few vaccines have been developed to induce functional T_M cells for certain infectious diseases, which is probably because of the lack of knowledge about T_M cell development and homeostasis.

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Migratory capacity is another important feature of the adaptive immunity, which enables adaptive immune cells to circulate constantly among tissues. Depending on their activation status, these cells generally circulate throughout the body to search for their cognate Ags. For example, naïve T cells are activated with Ags in the secondary lymphoid organs (SLOs) where adaptive immune responses initiate. When T cells are properly activated, they develop into effector T (T_E) cells and migrate into infected sites. While effector CD4+ T cells provide "help" to other immune cells, effector CD8+ T cells, also called CTLs, kill infected or damaged cells. Hence, T cell homing is crucial to fight against invading pathogens so that their migration is tightly regulated. It has been well documented that stimulation of chemokine receptors and adhesion molecules on T cell surface allows for an orderly access to a specific microenvironment. Therefore, it is known that various chemokine receptors are sequentially expressed in the course of immune response to pathogens. Recently, the migratory capacities of T_M cells have been highlighted because their recall response and survival are affected by their localization.

In this review, we discussed memory CD8+ T cells and their migratory capacities, particularly the C-C chemokine receptor 7 (CCR7)-dependent pathway, for their survival and longevity. We also highlighted recent studies describing the expression of CCR7 and its ligands, CCL19 and CCL21.

MEMORY CD8+ T CELLS

Development of memory CD8+ T cells

Naïve CD8+ T cells constantly circulate throughout the body through SLOs including the lymph nodes (LNs), spleen, and Peyer's patches (PPs) (1-4). The activation of T cells was first reported in 1970s using a mouse model of lymphocytic choriomeningitis virus (LCMV) infection (5,6). During viral infections, antigen presenting cells (APCs) such as dendritic cells (DCs) obtain viruses and migrate into the SLOs where naïve T cells search for their cognate Ags. Activated CD8+ T cells by these APCs undergo several pathways to proliferate and gain effector functions important to fight against infectious agents. In addition, CD8+ T_E cells modulate the expression of their homing receptors to egress from the SLOs and move into the infected area to induce protective immunity (7,8). After the pathogens are cleared, majority (up to 90%) of the activated CD8+ T cells dies, while only a fraction (up to 10%) survives and are maintained as T_M (9) cells. These T_M cells survive for an extended period of time and provide rapid and robust secondary response to the same Ag. In addition, they undergo self-renewal without Ag exposure and subsets of T_M cells undergo a series of steps to re-circulate the whole body searching for re-infections. These prominent characteristics enable T_M cells to fight against secondary infections with the same pathogens efficiently (10).

The subsets of memory CD8+ T cells

CD8+ T_M cells with these cardinal characteristics can be categorized into diverse subsets including effector memory T (T_{EM}) (11), central memory T (T_{CM}), and tissue-resident memory T (T_{RM}) cells (**Fig. 1**) (12). These subsets were initially identified based on their differential localizations by the expressions of homing receptors, but they also differ from each other in terms of their cytokine production and proliferation capacities. These abilities are regulated by a series of expression of their receptors, signaling molecules, transcription factors, and other important factors. Of note, different subsets of T_M cells form depending on the tropism and characteristics of infectious agents and these subsets cooperate to eradicate infections.
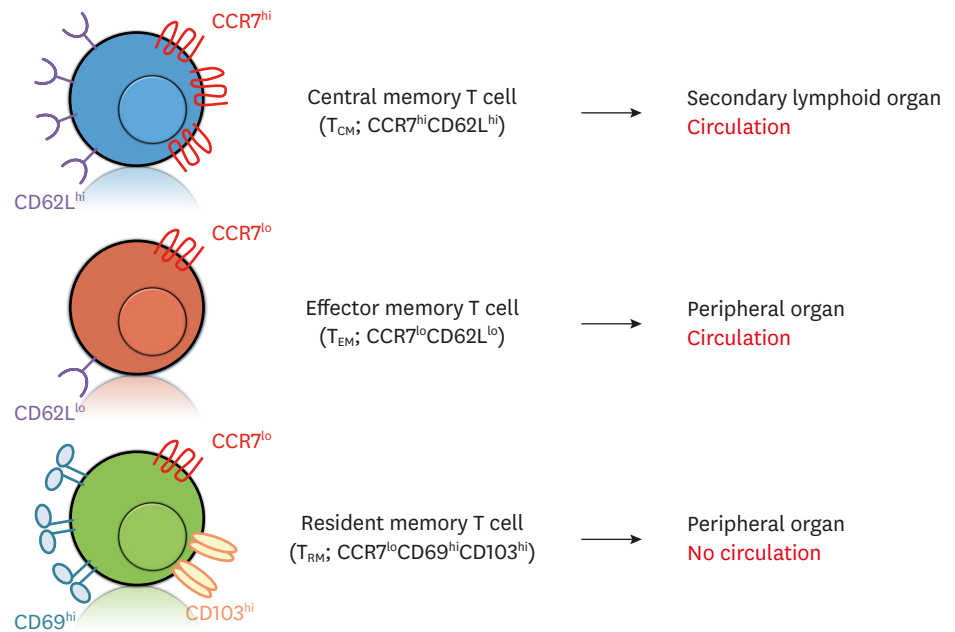
Figure 1. Subsets of T$_M$ cells. There are 3 major subsets of T$_M$ cells: T$_{CM}$, T$_{EM}$ and T$_{RM}$. These subsets are identified on the basis of differential expressions in several chemokine receptors and adhesion molecules. While T$_{CM}$ cells express high levels of CCR7 and CD62L (L-selectin) (CCR7^{hi}CD62L^{hi}), T$_{EM}$ cells express low levels of CCR7 and CD62L (CCR7^{lo}CD62L^{lo}). These phenotypes indicate that T$_{CM}$ cells circulate to SLOs, whereas T$_{EM}$ cells circulate to peripheral organs. T$_{RM}$ cells express low levels of CCR7 and high levels of CD69 and CD103 (CCR7^{lo}CD69^{hi}CD103^{hi}) to remain in peripheral organs.

T$_{CM}$ cells monitor infection in the body by circulating in the SLOs. In contrast, T$_{EM}$ and T$_{RM}$ cells do not survey SLOs and are located in peripheral tissues (**Fig. 1**). However, T$_{EM}$ cells can return to the SLOs if the Ags exist in the SLOs even after Ag is cleared in the infected target area (13-16). In 2009, Gebhardt et al. (17) reported that T$_{RM}$ cells stay in the non-lymphoid tissues (NLTs) without returning to the SLOs. They prepare to fight against local infections and are found in many different organs including the brain, lung, gut, skin, and other peripheral organs (18-20).

The generation of specific subsets of CD8+ T$_M$ cells has been attempted using different animal models. It is generally assumed that systemic infections or vaccinations can induce T$_{CM}$ and T$_{RM}$ cell formation, while local infections induce T$_{RM}$ cell development (21). Thus, Ag tropism or location determines the fate of T$_M$ cells. In addition, the generation of certain subsets may be crucial to protect against specific pathogens (22). For example, the presence of T$_{RM}$ cells in the liver substantially enhances protection against *Plasmodium* (23). Altogether, the modulation of T$_M$ cell mobility would benefit our body to fight properly against pathogens by placing T$_M$ cells in proper positions.

The survival and homeostasis of T$_M$ cells

A remarkable aspect of T$_M$ cells is their longevity and homeostasis without further antigenic stimulation. The underlying mechanisms of their homeostasis are based on the exposure to the homeostatic cytokines such as IL-7 and -15 (24-31). IL-7 has been well documented as a survival cytokine of naïve, memory precursor (MP) and T$_M$ cells. This cytokine is provided by stromal cells including fibroblastic reticular cells (FRCs) in the spleen and LNs (32-34). In conjunction with IL-7, IL-15 can induce homeostatic proliferation of T$_M$ cells. IL-15 also helps for the survival of KLRG1^{hi} terminally differentiated T$_E$ and T$_M$ cells. Therefore, it is crucial for T$_M$ cells to "see" these cytokines in order to develop and maintain homeostasis.

T_M cells develop and maintain in multiple organs including the spleen, LNs, liver, lung, and bone marrow (BM) (35). After systemic infection, T_M cells can survive and proliferate in these organs, particularly in the BM (36). However, different T_M cell subsets are differentially localized within different organs, suggesting that these cells may be exposed to different survival factors depending on their location (37,38). Since leukocyte recruitment is tightly regulated, it is interesting to understand the homing of each subset.

CCR7—CHEMOKINE RECEPTOR FOR MEMORY CD8+ T CELLS

CCR7 is a homing receptor

CCR7 is a lymphocyte-specific G-protein-coupled receptor with 7 transmembrane spanning alpha helices for CCL19 and CCL21 as ligands. It was first named Epstein-Barr virus (EBV)-indicted gene 1, a gene induced by EBV and Burkitt's lymphoma cells in B-lymphocytes. In the same study, it was shown that it plays an important role in response to virus infection and is detected only in B- and T-lymphocytes (39,40).

In the late 1990s, a study using CCR7-deficient mice showed that CCR7 plays an important role in controlling T cell movement to SLOs, particularly LNs and PPs. In addition, the formation of T cell zone was abolished due to abnormal T cell migration. After immunization, the migration of mature skin DCs into the LNs resulted in delayed immune response to injected Ags (41,42). Based on this observation, CCR7 has been established as one of the crucial receivers responsible for lymphocyte homing (41).

CD8+ T cells and CCR7

Among the CD8+ T cells, naïve and T_{CM} cells generally express high levels of CCR7 (3,12,43,44), hence they can migrate to the T cell zone of the LNs and spleen. These T cells can be activated in the T cell zone by the APCs and developed into T_E cells. During this process, T_E cells can move from the T cell zone to the red pulp and the infected area by the downregulation of CCR7 expression (45). Through this regulation of CCR7 expression, CD8+ T cells can find their cognate Ag in the SLOs to be activated and migrated into infected locus. After infections are cleared, T_M cells form and circulate to different parts of the body based on the levels of CCR7 expression (45-47).

During T_E–T_M cell transition, CCR7 expression influences the fate of these cells. It was reported that the mRNA levels of CCR7 were more pronounced in memory precursor T cells (MPECs) than in short-lived effector cells (SLECs) (48). In addition, the T_{CM} and T_{EM} cells were found in different locations of the SLOs depending on CCR7 concentration.

CCR7 expression was inhibited in T_{RM} cells, the recently identified T_M cell subset, making it possible for T_{RM} cells to act as the first line of defense within peripheral tissues (49). Altogether, the regulation of CCR7 expression controls the recruitment and release of CD8+ T cells from SLOs, determining the CD8+ T cell response outcome.

Transcriptional regulation of CCR7 and microRNAs (miRNAs)

The expression of CCR7 on CD8+ T cells is regulated by several transcription factors. In the CCR7 promoter region, there are 3 binding sites specific for protein 1 (Sp1) and one Ets-1-binding site (50), which suggests that the increased expression of CCR7 is mediated at least
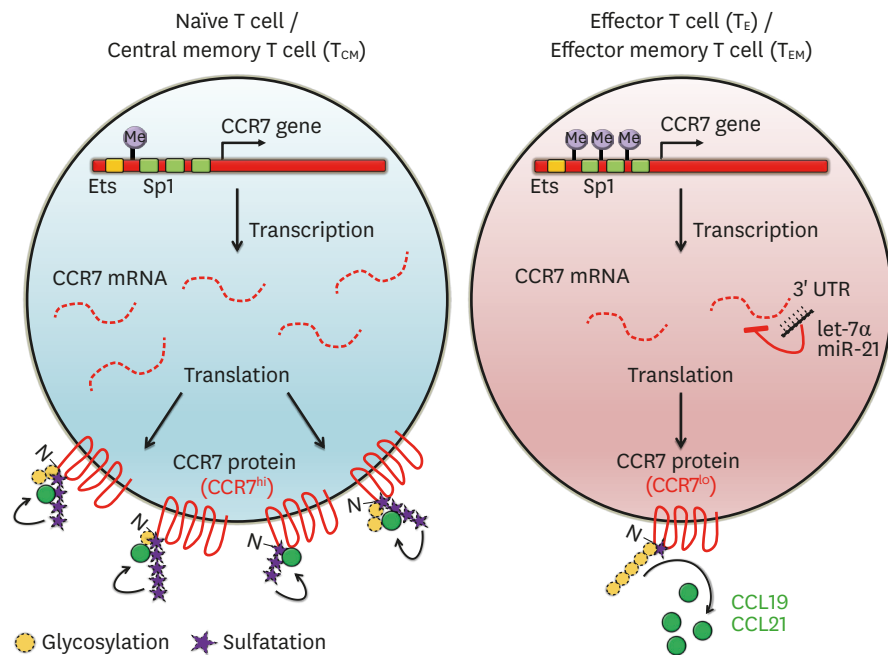
Figure 2. The regulation of CCR7 expression in T cells. The distinguishing features of naïve, T_E, and T_M cells reflect different programs of gene expression regulated by various factors. First, the gene encoding CCR7 protein is modulated by epigenetic mechanisms, such as methylation. The CCR7 chromatin can silenced by methylation of the promoter regions, in which transcription factor binding sites such as Sp1 and Ets-1 in effector and T_{EM} cells are located. In contrast, this locus is demethylated, allowing the gene to be expressed in naïve and T_{CM} cells. Additional inhibitory mechanisms of CCR7 gene expression include miRNA-dependent regulation. The indicated miRNAs such as let-7α and miR-21 bind to the 3′ UTR of CCR7 mRNA and decay the mRNA, thereby inhibiting translation efficiency. Following the translation, CCR7 protein can be post-translationally modified to modulate their affinity with their ligands, CCL19 and CCL21. The glycosylation of N-terminus of CCR7 protein suppresses CCR7 activity, while sulfation increases its affinity for the ligands.

partially by transcription factors such as Sp1 and Ets-1 (**Fig. 2**) (35,50). AP1 and NF-κB were also reported to upregulate CCR7 expression via binding to the CCR7 promoter locus in various cancer cell lines (51-53). In addition, Krüppel-like factor 2 (KLF2) and T cell factor 1 (TCF1) are significantly upregulated in naïve and T_{CM} cells and regulate the expression of several molecules including CCR7, CD62L (L-selectin; encoded by *Sell*), and sphingosine-1-phosphate receptor 1 in order to modulate the migration into the SLOs (54). In contrast, CD8+ T_{EM} and T_{RM} cells suppress KLF2 and TCF1, while simultaneously expressing Blimp-1 and suppressing the transcription of CCR7 independently (55-57).

It was also reported that Forkhead O 1 (FOXO1), another transcription factor, regulates CCR7 transcription during T_E–T_M cell transition, and not during naïve–CD8+ T_E cell transition. A study using FOXO1 knockout (KO) mice demonstrated that FOXO1 promoted enrichment of MP cells, thus wild-type T_E cells highly proliferated upon secondary infections in CD8+ T cells compared to FOXO1-deficient T_E cells (58). In a related study, it was observed that FOXO1 expression is significantly higher in MPECs than in SLECs, and it increase the levels of IL-7Rα and TCF7 expression to help create and maintain T_{CM} cells which were derived from MPECs (59).

CCR7 expression is also controlled by miRNAs. MiRNAs consisting of small RNA fragments under 23 nucleotides generally bind to 3' UTRs of complementary target sequences on target mRNAs to decay or stabilize the mRNA (60). Using big data analysis, several T-cell-associated genes including CCR7 were discovered to be targeted by miR-21, an anti-apoptotic factor

(61-63). MiR-21, a miRNA inhibiting post-transcription levels of CCR7, led to a significant reduction of CCR7 protein expression when naïve and CD4+ T_M cells are activated. Indeed, it is activated in inverse correlation to the amount of CCR7 protein (**Fig. 2**) (64). Further, it was reported that the expression of CCR7 was adjusted by miRNAs in several cancers, such as let-7α (in breast cancer cells and patients) (65), miR-320d (in oral squamous cell carcinoma) (66), miR-532-3p (in tongue squamous cell carcinoma) (67) and head and neck squamous cell carcinoma (68), and miR-199a (in human mantle cell lymphoma) (69).

Epigenetic and post-translational modification (PTM) of CCR7

Although there is little report of epigenetic regulators for CCR7, it has been documented based on CCR7 gene methylation using big data analysis. CCR7 methylation in human CD8+ T_M cells increased in the order of CD8+ T_M cell differentiation state: naïve<T_{SCM} (stem cell memory)<T_{CM}<T_{EM}, when this locus was analyzed using whole-genome bisulfite sequencing, a next-generation sequencing method (**Fig. 2**) (4). As the DNA methylation state is known as silent chromatin (called as heterochromatin), the expression of the gene was inhibited (70). Another report showed that monocyte-derived DCs in the mouse lung homing into SLOs are significantly lower in number than conventional DCs. In correlation with this observation, monocyte-derived DCs was highly methylated in H3K27 (H3K27me3), which forms heterochromatin, thus blocking their homing into the SLOs (71).

CCR7 can also be regulated by PTM (**Fig. 2**). Glycosylation in the N-terminus of CCR7 protein in T_E cells not only blocks, but also decreases receptor sensitivity, resulting in chemokine-induced downstream signaling modulation. It was also reported that de-glycosylation with enzymes produced by DCs changed the folding of CCR7 protein to increase the activity of this receptor (9). Conversely, the induction of sulfation in tyrosine residue of the CCR7 protein N-terminus can increase the affinity between CCR7 and its ligands (72).

Altogether the expression of CCR7 can be altered by many different factors in several steps, possibly indicating that the regulation of this receptor is critical for the immune response to pathogen. In addition, it has been suggested that this receptor can be modulated using multiple methods in order to enhance adaptive immunity.

CCL19 and CCL21, ligands of CCR7

$CCR7^{hi}$ CD8+ naïve and T_M cells have chemotaxis features toward CCL19 and CCL21 in a concentration-dependent manner (73-76). These chemokines were reported to be produced by high endothelial venules (63) in the T cell zone of SLOs (77,78). When naïve T cells enter the SLOs, they are located in the T and B cell zones. Particularly, naïve CD8+ T cells with CCR7 expression are enriched by FRCs in the T cell zones within the spleen and LNs, where CCL19 and CCL21 are highly enriched (33,79). Correlated with the role of these chemokines, the rate of movement of naïve T cells in the SLOs decreases in plt/plt mouse (paucity of LN; naturally weak CCL19 and CCL21 mutant mice) regardless of T cells lacking CCR7 (80,81). In the CCL21-deficient-special niche, CCR7-positive naïve and T_M cells circulate themselves within the interstitial lymphoid organs after being ejected from SLOs.

The quality and quantity of these microenvironmental niches were dynamically changed by several factors during the state of immune responses. Among these factors, IFN-γ, an antiviral-related cytokine, can transiently but substantially downregulate the expressions of CCL19 and CCL21 in the spleen and LNs. During viral infections, IFN-γ is released by effector immune cells including CD8+ T_E cells, which then reduces the concentration of CCL19 and

CCL21 in the T cell zone of the SLOs. In turn, T_E cells escape SLOs possibly due to the low levels of CCL19 and CCL21 (82).

CCL21 was also reported to participate in cancer metastasis. Certain types of cancer cells express CCR7, so that they have the ability to migrate towards the SLOs, particularly LNs (83). This migration facilitates cancer metastasis by pushing cancer cells into lymphatic vessels through LNs. Indeed, the patients with CCR7-positive tumors have significantly poorer prognosis than the patients with CCR7-negative tumors (84-86). These studies showed that the regulation of these chemokines is also important for the movement and localization of T and cancer cells.

CCR7 PROVIDES IMPORTANT HOMING SIGNALS FOR MEMORY CD8+ T CELLS

Niche for the survival of T_M cells

Survival cytokines are required for the longevity of T_M cells; however, it is incompletely defined how these cells "see" these cytokines. There are at least 2 possible explanations for these mechanisms. One hypothesis is systemic exposure, where one organ provides these cytokines and T_M cells recognize them anywhere in the body. Another possibility is that these cytokines are present only in specialized microenvironments called niches and T_M cells need to home these anatomical locations to receive the required signals. Although systemic exposure cannot be ruled out, evidence have been accumulated to explain the niche hypothesis. First, BM is the preferred site for the homeostatic proliferation, suggesting that survival cytokines are provided locally. Second, differential localization of T_E cell subsets within the organ may indicate that they receive different signals depending on their location (37,38). Third, IL-7 has been suggested to be bound to the extracellular matrix near the IL-7 producers (87). Finally, IL-15 has been shown to be trans-presented so that cell-to-cell contacts with IL-15 presenting cells are required for optimal simulation (88). Altogether, it is strongly suggested that T_M cells migrate to specialized microenvironments within the organ in order to survive.

Among the cytokines that are critical for T_M cells, it is known that CCL19 and CCL21 maintain a collaborative relationship with IL-7 and IL-15 (**Fig. 3**) (89). A rich CCL19 within the LNs works in conjunction with IL-7 to improve the survival of the T cells, but no exact mechanism has been identified (33). Whereas, the adjustment of CD8+ T_M cells by IL-15 was found within the NLTs, such as the BM and lung, where distinct from SLOs with large amount of CCL19 and CCL21 (36,90). This implies that the importance of the physical microenvironment is formed by CCL19 and CCL21, as well as sufficient CCR7 expression within the T cells.

CCR7 expression alters the fate decision of CD8+ T cells

To understand the roles of CCR7, Junt et al. (91) first reported normal T cell response to viral infection in plt/plt mice with spontaneous mutations in CCL19 and CCL21 locus. Thus, the viral clearance and secondary response to the same pathogen were comparable to those in littermate controls. However, they also observed that the formation of T_M cells were significantly reduced, when CCR7-deficient mice were infected with the same virus (92). It was also observed that viral clearance in CCR7 KO mice was slower than that in wild-type mice, if completely cleared. Probably due to the reduced number of T_M cells, CCR7-deficient mice contained reduced number of IFN-γ^+ CD8+ T cells in response to secondary infections. Since 2 different results were reported, it was suggested that plt/plt mice express CCL21b,
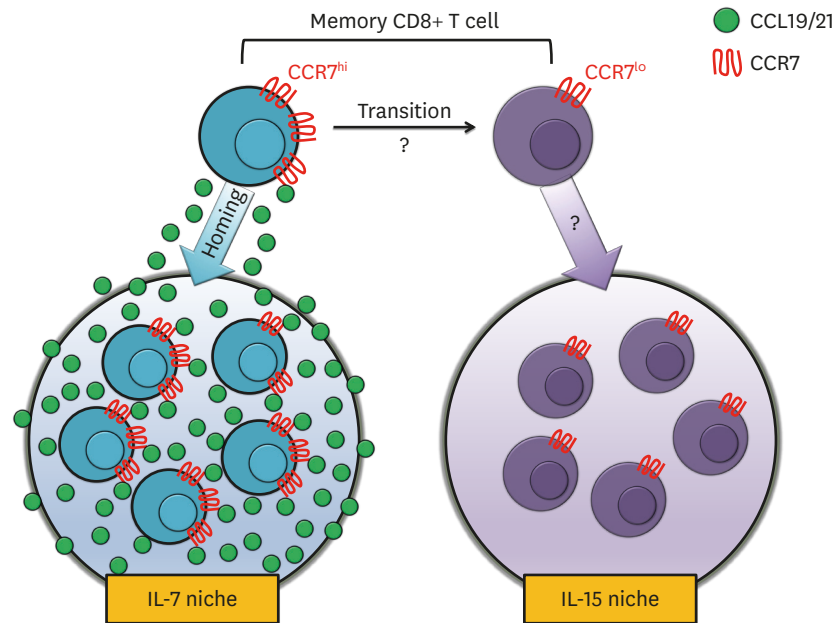
Figure 3. CCR7 introduces microenvironmental niche for memory CD8+ T cells. The schematic model indicates the trafficking patterns of CCR7^{hi} or CCR7^{lo} CD8+ T_M cells to find individual niches for their survival. CCR7^{hi} CD8+ T_M cells migrate toward high concentration of CCL19 or CCL21, where IL-7 is also expressed. In the contrary, CCR7^{lo} T_M cells migrate toward IL-15-rich microenvironment, even though the homing receptors for this migration have not been identified yet. Altogether, CCR7^{hi} and CCR7^{lo} CD8+ T_M cells do not share their survival cytokines, and CCR7 biases the survival of CD8+ T_M cells toward IL-7 niche.

a leucine isoform of CCL21, in lymphatic vessels. In addition, CCL21b was also found in peripheral tissue; thus, the recruitment of CCR7^{hi} cells into the peripheral tissues was compensated (78,93). In agreement with this report, mice with ubiquitous overexpression of CCL21 showed abnormal viral clearance (94). These altered immune responses are not restricted to viral infections, because CCR7 KO mice mounted reduced inflammation in response to *Toxoplasma gondii* infection, an intracellular protozoan parasite (95).

In order to exclude the possibility of delayed viral clearance and emphasize the role of CCR7 in the fate decision of CD8+ T_M cells, P14 transgenic mice, which recognize the D^bGP_{33-41} epitope of LCMV, were employed (90). By transferring small number of CCR7 wild-type or KO P14 CD8+ T cells into wild-type C57/Bl6 mice, these mice were able to clear the viral infection regardless of the genotypes of P14 cells. Using this model, increased number of CCR7 KO T_M cells was observed with normal recall abilities. Enhanced survival of CCR7 KO T_M cells by IL-15 signaling were found in the lung and BM, because the removal of IL-15, but not IL-7, maintained the comparable number of CCR7-deficient and -sufficient T_M cells. In addition, these CCR7-deficient T_M cells showed increased ratio of homeostatic turnover compared to CCR7-sufficient cells. These results suggest that CCR7 signaling directs the migration toward IL-7-niches, while CCR7^{lo} T_M cells migrate toward IL-15 niches for their survival. In addition, inhibition of CCR7 signaling may increase the number of T_M cells in the lung, where it has been suggested to be difficult for T_M cells to survive (**Fig. 3**).

When CCR7 was overexpressed in all T cells, the numbers of T_M cells in the spleen and LNs of CCR7-tg mice were increased compared to that in wild-type mice, while CCR7-tg T_M cell number reduced in the liver and lung. These mice showed difficulty in clearance of skin infection, suggesting that CCR7 forces the migration of T_M cells into the SLOs. It would be

interesting to see if increased survival of CCR7-tg T_M cells in the SLOs is IL-7-dependent. Taken together, the CCR7 expression of CD8+ T_M cells determines the fates of CCR7^{hi} and CCR7^{lo} CD8+ T cells by properly guiding them into survival niches.

CONCLUSION AND FUTURE PERSPECTIVES

The importance of T_M cell subsets has been well documented, and the roles of each subset shed light on individual infectious disease in the last decade. However, it is still not evident how each subset receives crucial signals for their longevity. Accumulating data suggest that specialized niches are present for the survival of T_M cells and the migration of MEPCs and T_M cells into these niches is crucial for their maintenance. CCR7 may determine the niche suitable for their survival, depending on the subtypes or functions of CD8+ T_M cells. Therefore, it can be inferred that CCR7 plays a crucial role in the activation of naïve T cells as well as the development and maintenance of CD8+ T_M cell subsets according to these studies.

Currently, the therapies using T cells, such as chimeric Ag receptor T cells, have shown remarkably effective progresses into clinical phases (96-98). Despite these successes, the cancer types where these therapies can be applied are limited till date. One of the reasons for this limitation is the type of T cells used in these therapies. Most therapies use naïve or *in vitro* activated T cells, which can quickly be inactivated in tumor microenvironments. Thus, T_M cells have been suggested to be utilized for these applications, particularly since they are seldom exhausted even in various types of immune diseases including cancer, allergic disease, autoimmune disease, and inflammatory bowel disease.

In addition to this suggestion, controlling the migration of T_M cells by CCR7 modulation may determine the destiny of CD8+ T_M cells by changing their location as discussed in this review. Depending on the diseases or cancers, the localization of T_M cells is crucial to promote optimal immune response. Taken together, T_M cells may be present and respond effectively at the target sites regardless of whether these sites are present in the SLOs or peripheral organs by inducing or inhibiting the CCR7 signaling in T_M cells.

In the past few decades, new respiratory diseases have been caused by virus infections such as influenza virus, severe acute respiratory syndrome coronavirus (SARS-CoV), middle east respiratory syndrome coronavirus, and severe acute respiratory syndrome coronavirus 2 repeatedly. All of these pathogenic viruses were derived from coronaviruses that commonly infect humans, but new mutations have made it difficult for our immune system to get rid of these viral infections. However, the survival of memory CD8+ T cell responding to SARS-CoV in peripheral blood of the patients possibly suggest the importance of T_M cells for the recovery from these diseases (99,100). Particularly, the Ab response to SARS-CoV was short-lived, indicating the biased immune responses toward T cell immunity. However, it is still not clear whether virus-specific T_M cells are also present in the lungs of these survived patients. Since the lungs were proposed to provide unfavorable microenvironments for T_M cell homeostasis, it would be particularly challenging to develop proper vaccines or therapies. However, Jung et al. (90) showed that CCR7-deficient T_M cells can heavily populate the lung, possibly indicating that the regulation of CCR7 signaling may give us a chance to prevent these diseases. These approaches may illuminate the future of our novel vaccines or therapies.

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