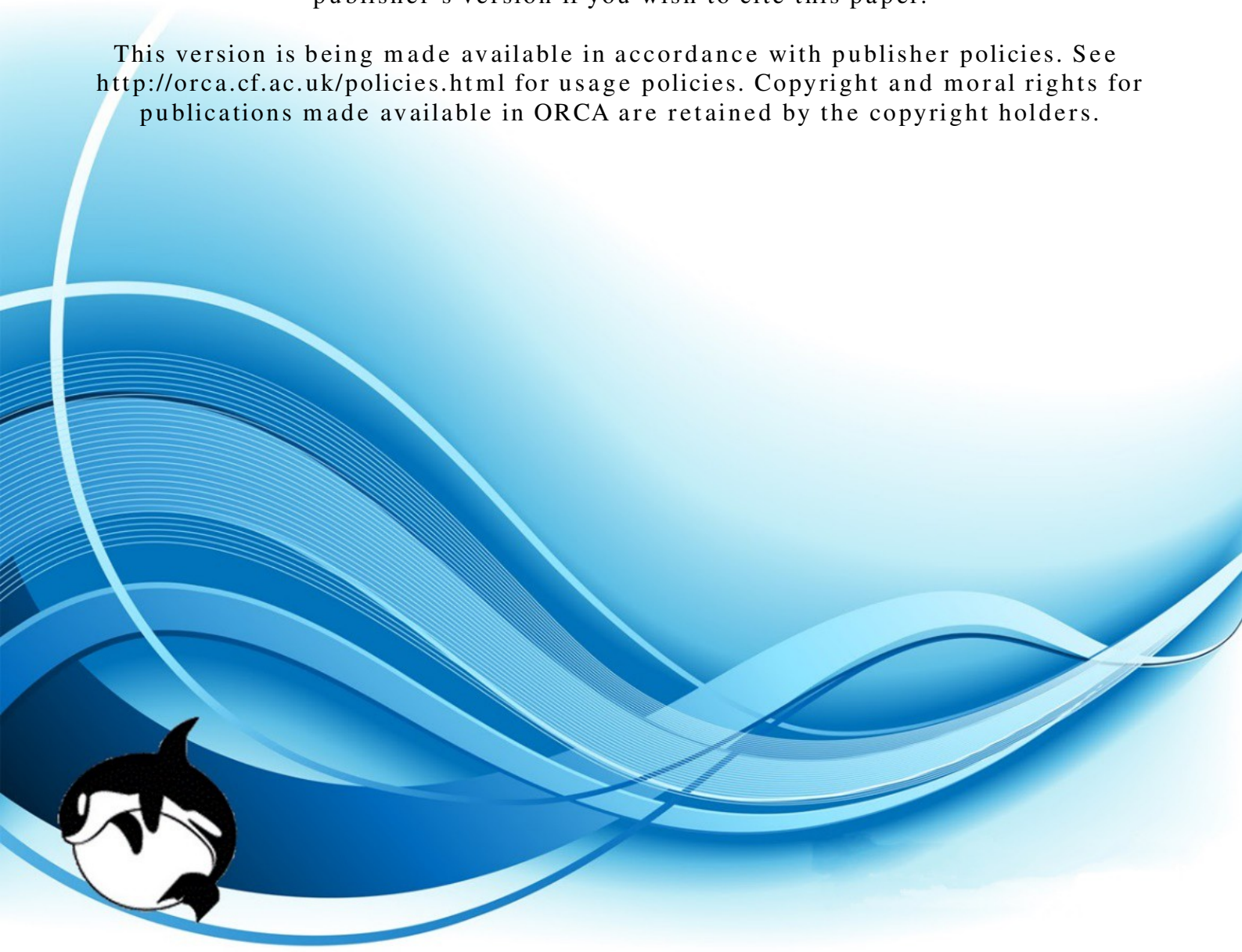

Peripheral tissue chemokines: homeostatic control of immune surveillance T cells

Michelle L. McCully[1], Ariadni Kouzeli[1] and Bernhard Moser[1,*]

[1]Department of Infection, Immunology & Biochemistry, School of Medicine, Cardiff University, Heath Park, Cardiff CF14 4XN, United Kingdom

[*] *Corresponding author*: Bernhard Moser (moserb@cardiff.ac.uk)

Cellular immunity is governed by a complex network of migratory cues that enable appropriate immune cell responses in a timely and spatially controlled fashion. This review focuses on the chemokines and their receptors regulating the steady state localization of immune cells within healthy peripheral tissues. Steady-state immune cell traffic is not well understood but is thought to involve constitutive (homeostatic) chemokines. The recent discovery of tissue-resident memory T (TRM) cells illustrates our need for understanding how chemokines control immune cell mobilization and/or retention. These studies will be critical to unravel novel pathways for preserving tissue function (aging) and preventing tissue disease (vaccination).

Tissue immune surveillance, the last frontier in immunology

For many reasons that include restricted access to healthy human tissue and sample sizes, there exists a formidable gap in our knowledge about how immune surveillance cells are recruited and retained in healthy tissues. This situation is remarkable for two reasons: 1) the significant complexity of immune surveillance cells present in healthy tissues/organ, notably those constantly exposed to environmental microbes and toxins and, 2) the extended duration this system needs to operate, which can exceed 80 years in humans. Peripheral tissue immune surveillance compartments are composed of both cells of the innate and adaptive immune systems and the diversity in their composition reflects the special need for immune surveillance tailored to distinct body locations.

As, thankfully, most individuals are healthy most of the time, the maintenance of tissue immune surveillance is a long-lasting process whose duration vastly exceeds that of rare episodes of infection and inflammation. Obviously, chemokines and their receptors expressed on target cells in collaboration with adhesion receptors and their ligands are intimately involved in both processes. The reader interested in general aspects of the chemokine system and its involvement in host defence is referred to excellent reviews published in recent years [1-3]. The vast majority of the literature deals with the inflammatory side of the chemokine network. Homeostatic immune cell processes are also controlled by chemokines whose expression is constitutive and tissue-specific. Again, our current understanding of the control of immune cell traffic by chemokines in primary (bone marrow, thymus) and secondary lymphoid tissues (LNs, spleen, Peyers Patches) is well advanced [3]. In clear contrast, our understanding of immune cells localization in peripheral tissues and healthy organs is still very limited. Exciting new findings revealed the importance of the tissue environment on shaping local immune cells, as best examined for tissue macrophages [4-6], and some types of tissue-resident memory T (TRM) cells [7-10]. In this article, we will discuss recent advances in our understanding of how chemokines and their receptors help orchestrate T cell compartments in healthy peripheral tissues with the view that this knowledge may help us understand the steady-state immune processes underpinning tissue health.

Migration control of circulating T cells

Antigen-experienced T cells in peripheral blood include lymph node-homing central memory T (T_{CM}) cells and memory precursor T (T_{MP}) cells as well as effector memory T (T_{EM}) cells that are largely excluded from secondary lymphoid tissues [11-13]. Naïve, T_{CM} and T_{MP} cells, express CCR7 as well as CD62L (E-selectin) for binding to GlyCAM-1 on high endothelial cells (HEV), which enables their sequential entrance into tissue-draining lymph nodes in response to CCL19 and CCL21 under steady-state conditions (reviewed in [14]). T_{EM} cells lack CCR7 but express combinations of receptors for inflammatory chemokines guiding them to peripheral sites during episodes of inflammation. As such, T_{EM} cell recruitment is transient and ceases to occur with resolution of inflammation.

In line with the underlying paradigm linking immune function with cell migration properties, the chemokine system defines distinct subsets among circulating memory T cell subsets. This is best exemplified by T helper cell subsets whose functional properties (cytokine secretion profile) correlate with the combinatorial cell surface expression of chemokine receptors, as expertly discussed in recent review articles [2, 15]. Under steady-state conditions, circulating T_{CM} and T_{EM} cells are largely excluded from healthy peripheral tissues and organs and, as such, do not appear to contribute to the peripheral immune surveillance system.

During immune responses, pathogen-specific T cells are activated in relevant tissue-draining LNs where they expand and differentiate into effector T cells before being released into the blood stream. The type of chemokine receptors present on effector T cells matches their functional demand at the site of infection/inflammation. Interestingly, early work in mice has demonstrated that effector T cells also gain access, in reduced numbers, to healthy peripheral tissues throughout the body [16, 17]. This process may help to prevent the spreading of infections to secondary sites and, in addition, may contribute to long-lived peripheral memory T cell compartments in unaffected (healthy) tissues. Further, the gene expression signature of T_{MP} cells, the survivors of effector T cell contraction phases, includes the lymphoid tissue chemokine receptors CXCR4, CCR7 as well as the inflammatory chemokine receptors CXCR3 and CXCR6 that may potentially guide these cells to inflammatory sites [18, 19]. Collectively, memory T cells in peripheral blood do not gain access

under steady-state conditions to healthy tissues, indicating that their study does not reveal the characteristics typically associated with memory T cells present in healthy peripheral tissues.

Control of T cell positioning by homeostatic chemokines

It is becoming increasingly clear that T cells present in healthy (steady-state) peripheral tissues are not simply a mirror image of circulating T cells. This fundamental understanding raises many exciting questions regarding the mechanisms governing their generation as well as their tissue-specific localization and retention. Recent findings emphasise the importance of target tissues themselves in this process [15, 20]. A point in case is tissue macrophages, many of which are derived from “primitive” myeloid progenitor cells generated in the yolk sac or foetal liver (reviewed in [4, 6, 21, 22]). Following recruitment into diverse tissues, these progenitors develop into specialized macrophages, such as microglia, Kupffer cells, peritoneal macrophages or Langerhans cells.

Obviously, (but with the notable exception of murine dendritic epidermal T cells [DETCs], see below), peripheral tissue memory T cells are not derived from embryonic precursors but instead reflect past immune activation events involving effector T cells and, potentially, TMP cells [16, 17]. Tissue-homing properties are imprinted in part by soluble tissue-derived migration cues that effector T cells are exposed to in draining LNs. Again, and in contrast to inflammatory diseases marked by an array of inducible (inflammatory) chemokines, the functions of constitutively produced chemokines within distinct healthy peripheral tissues are not well understood. In this section, we will describe chemokine receptors and ligands that have been associated with controlling the location of peripheral tissue memory T cells (Table 1). For clarity, we will refer to the entire population of T cells present in healthy non-lymphoid tissues at any given time as peripheral immune surveillance T (TPS) cells. TPS cells include TRM cells as well as migratory memory T cells, NKT cells and $\gamma\delta$ T cells [23]. Please note that numerous chemokines have dual functions, i.e. are present in healthy tissues yet become upregulated in response to inflammatory stimuli.

CXCR4/ACKR3 – CXCR4 is the most widely expressed chemokine receptor and binds the single chemokine CXCL12 that is constitutively produced in lymphoid organs and peripheral tissues (reviewed in [24]). It also binds gp120 envelope protein of HIV-1 and acts as HIV-1 co-receptor, together with CD4, for CXCR4-tropic (X4) HIV-1 particles (reviewed in [25]). Besides controlling the positioning of bone marrow and thymic progenitor cells during steady-state immune cell development (reviewed in [3, 26]), this chemokine receptor system participates in embryonic tissue development and wound healing (reviewed in [26, 27]). Recent work has revealed that ACKR3, an atypical chemokine receptor, fulfils an essential role in controlling homeostatic immune (and tissue) cell traffic through its ability to internalize and degrade extracellular CXCL12 (reviewed in [28]). Thus, homeostatic immune/tissue cell traffic is finely tuned by two opposing receptors; cell recruitment and/or retention of $CXCR4^+$ cells by CXCL12 and inhibition of these $CXCR4^+$ cell migration processes by ACKR3-mediated CXCL12 degradation. A role for CXCR4/ACKR3 in controlling TPS cell traffic has not been reported.

CXCR6 – CXCR6 is found on activated and memory lymphocytes, including $\alpha\beta$ T cells, $\gamma\delta$ T cells, NK T cells, NK cells and B cells and is also present on TPS cells. Similar to $CD8^+$ TRM cells, $CXCR6^+$ memory T cells in human and mouse liver express CD69 and the transcription factor Hobit, that causes tissue retention by preventing the expression of the tissue-emigrant receptors CCR7 and S1P1R [29, 30]. TRM-like $CXCR6^+$ NK cells have also been detected in human liver [31, 32]. The relative contribution of soluble *versus* membrane-bound CXCL16 to the tissue residency of liver T cells and NK/NK T cells is not known although it is tempting to speculate that hepatocyte/cholangiocyte-associated CXCL16 plays a particular role in this process. Recently, CXCR6 was shown to support retention of memory T cells in mouse skin, supporting the notion that membrane-bound CXCL16 on local tissue cells may facilitate adhesive interactions with local $CXCR6^+$ T cells [33]. Still, the CXCL16-CXCR6 axis in skin may be more relevant to inflammatory diseases since CXCL16 levels are low in healthy skin but become strongly upregulated during inflammation [34, 35].

CCR6 – CCR6 is broadly expressed on memory T cells, including Th17 cells, Treg cells, $\gamma\delta$ T cells, and NK T cells, NK cells, B cells, DCs/LCs and neutrophils (reviewed in [24]). CCL20, the only selective ligand for CCR6, was reported to be present in

normal skin and mucosal epithelia as well as perivascular cells, suggesting a role in homeostatic immune cell traffic [36, 37]. However, it needs to be pointed out that CCL20 is prominently upregulated in inflammatory diseases of the skin and intestine, in agreement with the selective expression of CCR6 on distinct T helper cell subsets, especially Th17 cells [15]. IL-17-producing γδ T cells (γδT17) also express CCR6 (together with CCR2) and are widely distributed in mouse mucosa/cutaneous tissues where they contribute to IL-17-driven inflammatory diseases [38]. CCR6 governs the retention of long-term memory γδ T cells in healthy tissues as well as LNs [39-41], linking this chemokine receptor expression with tissue immune surveillance by a special subset (Vγ4$^+$ γδT17) of γδ T cells. It is not clear whether CCR6 controls the same process in human mucosa/cutaneous tissues where γδ T cells are far less numerous than in mice.

CCR9 – CCR9 is selective for only one chemokine, CCL25, whose expression is prominent in intestinal epithelia already in the steady-state but is further enhanced under inflammatory conditions (reviewed in [42]). CCR9 is abundant on small intestinal T cells, including intraepithelial and lamina propria αβ and γδ T cells, as wells IgA$^+$ plasmablasts, plasmacytoid DCs and intestinal/hepatic macrophages, which is in clear contrast to peripheral blood where CCR9$^+$ leukocytes are rare. The CCL25-CCR9 axis contributes to the recruitment of α4β7$^+$ αβ and γδ T cells to the small intestine, although T cell recruitment to this region does not solely depend on this chemokine system (reviewed in [43]). Despite the importance of the vast T cell compartment exceeding 10^{11} cells in the human intestinal mucosa, it is currently not clear how (if at all) CCR9 contributes to the immune surveillance traffic at this particular location.

CCR10 – CCR10 plays a dual role in the control of mucosa/cutaneous lymphocyte traffic where it is found on subsets of αβ and γδ T cells, Treg cells, innate lymphoid cells (ILCs) and IgA$^+$ plasmablasts [44, 45]. The tissue selectivity is provided by the two chemokines, CCL27 and CCL28 that specifically bind to CCR10. CCL27 is produced in the skin by basal keratinocytes and perivascular cells in the dermis, is highly elevated in inflammatory skin diseases but is absent in intestinal tissues [46-48]. In clear contrast, CCL28 is produced by mucosal epithelial cells in the colon and secretory organs (salivary and mammary glands) where it orchestrated IgA$^+$

plasmablasts traffic [45, 49-52]. In addition, CCL28 was also demonstrated to control memory T cells traffic in the nasal mucosa where it is constitutively expressed by vascular endothelial cells [53]. Intriguingly, in this study CCL28 was proposed to act *via* CCR3, the second receptor for CCL28.

The CCL27-CCR10 axis plays a redundant role in the recruitment of effector T cells to the inflamed skin [54]. Still, constitutive expression of CCL27 in human and mouse skin also suggests an involvement in the traffic control of TPS cells under steady-state conditions. In addition, resident CCR10$^+$ CD8$^+$ T cells in murine skin were shown to enhance the survival of local Treg cells and, *vice versa*, local CCR10$^+$ Treg cells affected the number of local conventional $\alpha\beta$ T cells in the absence of skin inflammation [55, 56]. A similar role has been attributed to ILCs, a major cellular constituent of murine TPS cells in body-lining tissues, whose localization to healthy skin was also CCR10 dependent [57]. However, despite CCL27 expression, CCR10$^+$ cells are absent in healthy human skin, denoting a species difference regarding the role played by the CCL27-CCR10 axis in controlling the local TPS cell compartment.

CX3CR1 –Similar to CXCL16 (see above), CX3CL1, the ligand for CX3CR1, is a chemoattractant in its soluble form whereas membrane-bound CX3CL1 mediates adhesion of CX3CR1$^+$ cells (reviewed in [24]). Besides distinct tissue macrophages, such as microglia, CX3CR1 is present on NK cells and T cells as well as monocytes, where its variation of expression distinguishes two major monocyte subsets. A function in tissue homeostasis is inferred from CX3CR1$^+$ DCs during microbial surveillance in intestinal tissue and from the effect of CX3CR1$^+$ microglia on neuronal plasticity and synaptic pruning [58, 59]. Of note, the CX3CL1-CX3CR1 axis has recently been implicated in tissue immune homeostasis. Similar to blood monocytes, the level of CX3CR1 expression in murine CD8$^+$ T cells defines three subsets, TCM and TEM cells that either lack or express high level of CX3CR1, and a memory T cell subset with intermediate CX3CR1 expression [60]. CX3CR1^{int} T cells are long-lived, recirculate through peripheral tissues (thus differing from TRM cells, which are sessile) and give rise to effector and TEM cells upon reinfection. Conversely, another group reported that LNs contain a sessile memory T cell subset characterized by CX3CR1 (and CD62L) expression with proposed pathogen surveillance function [61]. It is not clear at present whether the CX3CL1-CX3CR1 axis plays any role in the generation and/or maintenance of these novel memory T cells subsets.

Emerging chemokine systems with a role in tissue homeostasis – GPR15, a G-protein coupled receptor induced on skin and colon immune cells by local TGF-β1 [62], was recently shown to facilitate the localization of fetal Vγ3$^+$ (alternatively called Vγ5$^+$) γδ T cells in the embryonic epidermis of mice [63]. Fetal Vγ3$^+$ γδ T cells are the precursors of dendritic epidermal T cells (DETCs) whose stress surveillance function in mouse skin is well described (reviewed in [64]. The γδ T cells equivalent to mouse DETCs do not exist in humans. GPR15 is also involved in the intestinal immune homeostasis in mice (but not humans) *via* its regulation of the local Treg cell compartment [65, 66]. The two identified ligands, a thrombomodulin-derived protein fragment [67] and *C10ORF99*-encoded protein GPR15L [68], do not mediate chemotaxis of GPR15$^+$ cells, suggesting that a migration-unrelated mechanism underlies the GPR15 controlled processes in tissue immune homeostasis.

CXCL14 and CXCL17 are highly expressed at the steady-state in a broad range of epithelial tissues and organs, suggesting important contributions to tissue immune homeostasis. CXCL14 is broadly expressed in body-lining tissues and internal organs (reviewed in [69]). A large body of literature describes the pro- or anti-tumour effect of CXCL14, which was linked to its function in angiogenesis and tumour immune surveillance. Similar to CXCL12, CXCL14 is involved in tissue development and glucose metabolism that may explain, in part, the striking survival defects observed in CXCL14-KO mice [70-72]. It is a chemoattractant for myeloid cells, notably blood monocytes, and also synergizes with CXCL12 in CXCR4-mediated chemokine responses [73]. Slow progress in CXCL14 research is largely due to the fact that its receptor has remained elusive.

CXCL17 is prominently expressed in the tongue, airways (trachea, lung) and stomach as well as in psoriatic (but not healthy) skin and was shown to chemoattract myeloid cells (macrophages, monocyte-derived suppressor cells) [74, 75]. CXCL17 was recently reported to be a selective chemokine ligand for GPR35 (subsequently called CXCR8), although others could not confirm this finding [76, 77]. GPR35 has long been known for its selectivity for the tryptophan derivative kynurenic acid (and related compounds), linking endogenous and/or microbial amino acid metabolism with intestinal disease (reviewed in [78]). The correlation between homeostatic CXCL17 production and GPR35-linked intestinal disease requires further investigations.

CCR8 designates tissue-resident memory T cell in healthy human skin

A brief history of CCR8-related chemokine research is summarized in Box 1. The following discussion is restricted to human αβ T cells, although similar mechanisms may underlie the generation/maintenance of other numerically minor CCR8$^+$ lymphocyte subsets (γδ T cells, NKT cells, NK cells). CCR8 is found on approximately half of all human skin CD4$^+$ and CD8$^+$ T cells [79]. Considering the enormous number of T cells present in human skin [80], we estimate that >10^{10} cells express CCR8, which is equivalent to all (naïve and memory) T cells present in peripheral blood. In clear contrast, CCR8 expression is rare (approx. 5%) among peripheral blood T cells and is absent on any other type of blood leukocytes, such as γδ T cells, B cells, NK cells, monocytes and neutrophils. All peripheral blood CCR8$^+$ T cells are memory cells belonging to either T_{CM} or T_{EM} subsets and also co-express cutaneous lymphocyte-associated antigen (CLA), indicating that they may be on their way to the skin.

The presence of two memory T cells subsets of equal size in healthy human skin that are distinguished by CCR8 expression raises the question as of how they relate to each other. The hallmark of T_{RM} cells are receptors associated with their tissue residency (CD69$^+$, CD103$^{+/-}$) and transcription factors (Hobit^{hi}, Blimp^{hi}, Eomes^{low}, T-bet^{low}, KLF2^{low}) controlling their tissue location and residency as well as their long term survival [7-10, 29]. Of interest, Runx3 was recently reported to be a master regulator of the transcription factor landscape underpinning the generation of T_{RM} cells [81]. Human skin CCR8$^+$ T cells bear many of the hallmarks ascribed to mouse T_{RM} cells [7-10], including CD69/CD103 expression, proliferation responses to steady-state growth factors IL-7 and IL-15 and lower expression of Eomes and T-bet. In contrast, skin T cells lacking CCR8 were more variable in phenotypic and functional markers, expressed inhibitory receptors, including PD-1, showed poor proliferative responses *ex vivo* and had substantially higher levels of transcripts for effector molecules (perforin, granzymes, CXCR3, etc.). Underscoring these striking differences, the two major skin populations distinguished by CCR8 also recognized different antigens as demonstrated by TCR Vβ clonotype analyses [79].

How human skin CCR8$^+$ T cells relate to their CCR8$^+$ counterparts in blood is not known. Similar to the recently described “migratory” memory T cells in human and mouse skin [82, 83] and “circulating” memory T cells in peripheral blood of mice [60], it is possible that the human blood CCR8$^+$ compartment contains a subset of recirculating memory cells with homing preferences for healthy skin. Peripheral Treg cells seed mouse skin very early in life [84]. Although a recent report indicated human skin Treg cells were non-migratory [85], studies in mice have demonstrated their continuous emigration from the skin in the steady state [86]. Human skin Treg cells uniformly express CCR8 and, likewise, human peripheral blood contains CCR8$^+$ Treg cells that co-express the skin-homing marker CLA and account for between one third and one half of all circulating FoxP3$^+$ Treg cells [79, 87]. Interestingly, human CCR8$^+$ Treg cells have also been found in skin-unrelated tumours, such as breast, lung and colorectal tumours, and their presence has been associated with a poorer prognosis [88, 89]. One group reported that triggering of CCR8 signalling enhanced the suppressive function of Treg cells [90]; however, a similar pro-Treg cell effect was not found by another group [88]. Since alternatively activated M2 macrophages frequently found in tumour tissue and Treg cells themselves produce CCL1, it is possible that the CCR8/CCL1 axis has been co-opted by the tumour to promote local immune suppression [91, 92]. How tumour and skin Treg cells relate to each other is not known but CCR8 expression may indicate shared localisation properties.

Collectively, we propose that CCR8 may serve one or several roles in the localisation of CCR8$^+$ TRM cells in human skin as discussed in Figure 1. Our understanding of CCR8 expression on mouse lymphocytes is rudimentary. In support of our model, CCR8 mRNA was detected late during anti-viral immune responses in mouse skin CD8$^+$ TRM cells [93]. Also, lack of CCR8 did not prevent T cell recruitment to skin infection, suggesting that in mice CCR8 may be more important in steady-state immune surveillance processes [33]. A role for CCR8 in effector T cell traffic was also recently reported in a mouse model of atopic dermatitis [94].

The critical role of the tissue microenvironment in TPS generation

It is becoming increasingly clear that the tissue itself regulates the localization and residency of immune cells in peripheral tissues. For instance, homing to distinct

tissue sites, especially those with restricted access (i.e. skin, intestinal tract) requires specific migration cues to be imprinted in tissue draining lymph nodes and not elsewhere (reviewed in [95, 96]). Each tissue produces a characteristic set of soluble factors under steady-state conditions that are necessary to induce changes in gene expression. Human skin epidermis releases factors that induce CCR8 (together with CLA) in TCR-activated (but not resting) naïve αβ T cells during *ex vivo* culture [97]; and these factors were subsequently determined to be keratinocyte-derived PGE_2 and 1,25-dihydroxyvitamin D3, the active metabolite of vitamin D [98] (Figure 2). In addition, vitamin D also plays a role in the generation of $CCR10^+$ T cells for migration to epidermal layers, but instead of PGE_2 this requires the presence of IL-12 [99]. Likewise, in the gut, the local environment licenses resident $CD103^+$ dendritic cells with the ability to produce the vitamin A metabolite all-trans retinoic acid (atRA; reviewed in [100]). atRA in turn imprints a gut-tropism, defined by expression of CCR9 and integrin α4β7, in responding T cells [101], IgA-secreting B cells [102] as well as ILCs [103].

Interestingly, vitamin metabolites have also been shown to affect the transcriptional programme in tissue macrophages. In the peritoneum, locally produced atRA was shown to regulate the anatomical localization of peritoneal macrophages by inducing of GATA6 and downstream transcriptional changes [104, 105]. Whether vitamin A (in the gut) or vitamin D (in the skin) induce similar transcriptional programmes in TPS cells has not yet been explored. Still, it is worth noting that Treg cell generation is influenced by the presence of both vitamin A and D metabolites acting either directly [106] or *via* DCs [107, 108].

Vitamin A and D induce signal transduction by binding to specific nuclear receptors, RAR (retinoic acid receptor) and VDR (vitamin D receptor), respectively, which form heterodimers with the RXR (retinoic X receptor) nuclear receptor family members. In adipose tissue, the differentiation of Treg cells requires activation of PPARγ (peroxisome proliferator-activated receptor gamma), a nuclear receptor that also pairs with RXR to induce transcription. More importantly, PPARγ signalling was recently shown to increase survival of mouse and human skin $CD8^+$ TRM cells, linking nuclear receptor signalling with homeostasis of TPS cells [109]. Similar to vitamins A and D, the ligands for PPARγ are present in the tissues and, together with other local mediators like PGE_2, IL-15 or TGFβ, may significantly alter the phenotype and

function of T cells that enter the tissue [98, 110, 111]. The relative contribution of each nuclear receptor will likely depend on the site of T cell differentiation as availability of the functional vitamin metabolites (i.e. atRA in gut, 1,25-dihydroxyvitamin D3 in skin) varies across tissue sites. Together, *via* sensing of diverse tissue metabolites, these data suggest that RXR-containing heterodimeric nuclear receptors play an important role in the localization and functional specialisation of TPS cells and other types of tissue immune surveillance cells.

Concluding Remarks

Tissue health is the prevailing physiological state of our body whereas tissue disease is commonly short-lived (e.g. acute infections) and only rarely life-threatening and/or unremitting (chronic inflammation, cancer). Tissue health is governed by homeostatic chemokines with tissue-specific expression profiles that retain immune surveillance cells, including TRM cells and migratory TPS cells, which express the corresponding chemokine receptors and adhesion molecules. The peripheral tissue immune cell compartments are vast in terms of complexity and cellularity as best exemplified by the superficial skin or mucosal epithelia in humans. At these locations, homeostatic chemokines can function in different ways as discussed in Figure 1 for CCR8 in human skin TRM cells. In essence, tissue-specific homeostatic chemokines could act on effector T cells by retaining these cells within the tissue following resolution of the infection or they could specifically act on memory precursor T cells that have survived the retraction phase of an immune response. Alternatively, homeostatic chemokines could contribute to the longevity of TPS cells by controlling their sequestration to distinct niches within non-lymphoid tissues rich in survival factors, as reported for virus-specific TRM cells in the genital mucosa [112]. Finally, since memory T cells continuously survey the local tissue environment [113, 114], homeostatic chemokines could enable co-localization of TPS cells with local antigen-presenting cells (APCs) as a means of mounting immediate responses to pathogens that local TPS cells have been trained to recognize.

Many questions remain to be addressed (see Outstanding Questions) as we are only beginning to unravel which chemokine networks are at play in distinct tissues and how they affect the resulting local immune compartment under steady-state

conditions. For instance, we do know that TRM persist for many years/decades in tissues, but we don't know whether local tissue-specific homeostatic chemokines are important for their long-term localization and/or function. We also need to determine whether there is any redundancy in these roles. For example, CXCR6 is expressed by TRM in many tissues, excluding a role in tissue-specific immune cell localization, yet it may contribute to immune surveillance of micro-infections in response to unregulated CCL20. In fact, some peripheral tissue chemokines fulfill a dual function: homeostatic immune cell localization under steady-state conditions and control of immune cell traffic during brief episodes of local infections.

It is clear that distinct tissue factors, especially metabolites such as vitamins and lipid derivatives, act to imprint tissue residency. In human skin, αβ T cells are not the only lymphocyte subset expressing CCR8. In fact, minor fractions of TPS cells constituting skin-resident γδ T cells, NKT cells and ILCs, also express CCR8. This finding illustrates that factors governing tissue residence do not discriminate between different subsets of TPS cells within the same tissue.

Finally, as for inflammatory chemokines, homeostatic chemokine networks may be targeted for vaccine purposes to promote long-lived, tissue specific protection. Not only could the presence of receptors for peripheral tissue chemokines on TRM cells (such as CCR8 on cutaneous TRM cells) serve as a marker for successful vaccination regimens, it may be possible to promote T cell recruitment and survival by modulating their tissue expression. Clearly, future investigations of peripheral tissue chemokines will help us to identify novel pathways for interventions that control cellular processes underpinning tissue health and, in effect, long life.

Box 1. Summary of CCR8-related research

- *History of CCL1 and CCR8* – CCL1, the first identified CC chemokine, was discovered in the late 1980's in humans [115] and mice [116] and was originally reported to be a chemoattractant for blood monocytes [117]. CCR8, the receptor for CCL1, was discovered in 1997 and, in agreement with the original description of CCL1 activity [117], CCR8 transcripts were found in human blood monocytes [118]. The second group who cloned CCR8 was unable to detect CCR8 mRNA in human blood monocytes and did not find monocyte migration in response to CCL1 [119]. Identification of murine CCR8 was reported in 1998 [120].
- *Additional ligands for CCR8* – Murine (but not human) CCL8 controls inflammatory T cell recruitment in mouse model of atopic dermatitis [94]; human CCL18 was reported to be a lower potency ligand for human CCR8 with overproduction in inflammatory skin lesions [121].
- *CCR8-KO mice* – Early reports were inconclusive regarding the role of CCR8 in inflammation [122-124] but more recent data revealed that CCR8 modulates Treg cell and myeloid DC function in allergic airway disease [125] as well as Th2 cell recruitment in a mouse model of atopic dermatitis [94].
- *DC generation/localization* – Role of CCR8 in DC/LC function was inferred from studies showing a positive effect on DC differentiation during *in vitro* reverse transendothelial migration of human monocytes [126] yet showing a inhibitory (and possibly indirect) effect on skin DC emigration and LC repopulation in mouse models of skin inflammation and stress [127, 128].
- *T cell traffic* – Based on earlier work and studies with CCR8-KO mice, Th2 cells, notably IL-5 producing Th2 and Treg cells are targets for human CCL1 (and mouse CCL8) [87, 94, 129-137]. In addition, based on novel CCR8-specific antibodies, it is now known that human CCR8^{+} T cells include 50% of all TPS cells present in healthy human skin, including TRM cells, (Vδ2^{neg}) $\gamma\delta$ T cells, NKT cells and NK cells [79, 97, 138, 139]. In human blood, CCR8 is found on minor (5%) subsets of TCM and TEM cells and very few (Vδ2^{neg}) $\gamma\delta$ T cells [79,

139, 140]. In addition, CCR8 is present on all skin Treg cells and on all blood Treg cells that also co-express CLA.

- *Expression of CCL1* – At steady-state, CCL1 is produced by human skin LCs and dermal perivascular cells [134, 139]. Under stimulatory conditions, and in agreement with original findings [116], CCL1 is a product of activated T cells, including human TRM cells [139] and Treg cells [90, 91] in addition to activated mast cells [135, 141, 142], macrophages [92, 134, 143, 144] and vascular/lymphatic endothelial cells [126, 145].
- *Viral CCR8 ligands* – Molluscum contagiosum virus-encoded MC148 [146] and Herpes virus HHV8-encoded vMIP-II [147] are two CCR8 antagonists. Of note, molluscum contagiosum virus is a human skin-tropic poxvirus and its early secreted MC148 protein is a highly selective CCR8, conceptually linking viral infection with evasion of human skin CCR8$^+$ TRM and other skin-specific immune surveillance cells.

(Figure legends)

Figure 1. Hypothesis: CCR8$^+$ TRM cells contribute to tissue health by prevent excessive tissue inflammation. *Primary infection*: Microbes that have penetrated the skin are processed by local APCs, including epidermal LCs and dermal DCs. In case of first-time exposure, microbe-specific memory T cells are not present at the site of pathogen entry, thus enabling the initiation of a local inflammatory cascade through the interaction of microbial antigens with TLRs on macrophages and tissue cells. This in turn leads to rapid secretion of inflammatory chemokines as well as maturation of LN-homing of CCR7$^+$ DCs/LCs. CCR8 is expressed on T cells within the draining LNs as a consequence of TCR signalling induced during interaction with microbial antigen-presenting DCs/LCs in combination with skin-derived tissue factors (vitamin D, PGE_2). Besides CCR8, newly generated effector T cells express receptor for inflammatory chemokines (CXCR3, CCR2, CCR5, etc.) as well as skin-homing adhesion molecules (CLA, integrins) guiding the effector T cells selectively to the site of skin inflammation. CCR8 on effector T cells is probably not necessary in the recruitment phase of effector T cells. *Tissue recovery*: Following the resolution of infection and inflammation, surviving memory precursor T TMP) cells give rise to long-lived CCR8$^+$ TRM cells that co-localize with cells constitutively producing CCL1 in the epidermis or in perivascular niches of the dermis. Some TMP cells may acquire CCR7, which enables their tissue exit and potential survival as circulating TCM cells. Whether local tissue factors (vitamin D, PGE_2) are sufficient for maintaining CCR8 expression on skin TRM cells or whether TRM cells need to recirculate through draining LNs in order to maintain CCR8 expression is not clear. *Immune surveillance*: CCR8$^+$ TRM cells survey healthy skin by continuously interacting with local APCs (epidermal LCs, dermal DCs) in search of their cognate antigen. In case of re-infection, microbe-specific TRM cells become activated leading to two separate events. First, activated CCR8$^+$ TRM cells immediately release CCL1 enabling an amplification of the anti-microbial response by mobilizing additional CCR8$^+$ TRM cells. Second, activated CCR8$^+$ TRM cells turn into effector cells capable of neutralizing the infectious particles. This “memory” response quickly deals with micro-infections circumventing the need for an inflammatory response involving a new wave of circulating effector T cells. Such quick action of local TRM cells may indeed hold the key for maintaining tissue health and longevity. Finally, since all skin Treg cells

express CCR8, auto-reactive effector T cells may be inhibited by Treg cells following their mobilization in response to CCR8$^+$ T_{RM} cell-secreted CCL1.

Figure 2. Tissue environments control local memory T cell compartments.

Expression of the skin-homing markers CCR8 and cutaneous lymphocyte-associated antigen (CLA) on memory T cells is controlled by TCR stimulation in the presence of the CCR8-inducing factors 1,25$(OH)_2D_3$ (calcitriol) and prostaglandin E_2 (PGE_2). In addition to dietary supplementation, sunshine (UVB irradiation) in the epidermis of sun-exposed skin converts cholesterol into vitamin D_3, which is further processed by intracellular hydroxylases into bioactive 1,25$(OH)_2D_3$. PGE_2 is continuously formed in the upper layers of the epidermis where end-stage keratinocytes undergo apoptosis. 1,25$(OH)_2D_3$ and PGE_2 act on T cells during their engagement with DCs either in the skin or in skin-draining lymph nodes by means of engaging the nuclear receptor VDR-RXR and cell surface receptor EP4, respectively. The gut-homing markers CCR9 and integrin $\alpha4\beta7$ on intestinal memory T cells are controlled by food-derived vitamin A metabolites. The subset of CD103$^+$ DCs in the intestine is capable of converting the inactive metabolite retinol through intracellular reduction and oxidation reactions into bioactive all-trans retinoic acid (atRA) that acts on the nuclear receptor RAR-RXR. Induction of CCR9 and $\alpha4\beta7$ expression occurs during engagement of T cells with CD103$^+$ DCs in the mesenteric lymph nodes, and the development of T cell subsets such as T_H17 cells and Tregs is further controlled by additional cytokines (IL-6, TGF-β, etc.)

Glossary

Naive T cells (TN cells): Antigen-inexperienced circulating $CD4^+$ and $CD8^+$ $\alpha\beta$ T cells that are excluded from healthy and inflamed peripheral tissues. Expression of CCR7 and CD62L enables naïve T cells to continuously enter secondary lymphoid tissues (e.g LNs) *via* high-endothelial venules. In the T-zone of LNs naïve T cells make multiple contacts with DCs, screen the repertoire of presented antigenic peptide-MHC complexes and, in case of cognate interaction, proliferate and develop into effector T cells.

Effector T cells (TE cells): Effector T cells are produced in response to microbial challenges, are quickly recruited to sites of inflammation in response to locally produced inflammatory cytokines and provide immediate defensive functions during local re-challenge. Effector T cells are short lived ($KLRG1^+$, $CD127^-$) and disappear during the immune response contraction phase.

Helper T cells (TH cells): Circulating effector or memory $CD4^+$ $\alpha\beta$ T cells distinguished by the profile of cytokines they secrete upon re-stimulation. TH subsets include TH1, TH2, TH9, TH17, TH22, etc. and express characteristic combinations of chemokine receptors that enable their selective recruitment to inflammatory sites where the distinct cytokines are needed.

Follicular B helper T cells (TFH cells): Circulating memory $CD4^+$ $\alpha\beta$ T cells specialised in providing B cell help to T cell-dependent antigens during the germinal centre reaction in the B cell compartments of LNs. TFH cells express CXCR5, which guides them to the B cells at the follicular-medullary junctions where CXCL13 is being produced.

Regulatory T cells (Treg cells): $CD4^+$ $\alpha\beta$ T cells specialised in dampening T cell responses through engagement of inhibitory receptors (e.g. CTLA-4), secretion of anti-inflammatory stimuli (IL-10, IL-35, nucleotides) or depletion (CD25) of IL-2. Treg cells are distinguished by the transcription factor FoxP3 and high levels of CD25, which are generally absent in resting conventional T cells.

Central memory T cells (TCM cells): Circulating memory $CD4^+$ and $CD8^+$ TCM cells continuously enter secondary lymphoid tissues (e.g LNs) *via* high-endothelial venules

and survey local dendritic cells for the presence of cognate antigen. T_{CM} cells express CCR7 and CD62L enabling their entry and localisation within LNs.

Effector memory T cells (T_{EM} cells): Circulating memory $CD4^+$ and $CD8^+$ T_{EM} cells that do not express CCR7 and CD62L and, therefore, are excluded from secondary lymphoid tissues. T_{EM} cells are also excluded from healthy peripheral tissues but express variable combinations of receptors for inflammatory chemokines guiding them to site of inflammation where the corresponding chemokines are produced.

Memory precursor T cells (T_{MP} cells): Alternatively called stem-cell memory T (T_{SCM}) cells and memory precursor effector T (T_{MPEC}) cells). T_{MP} cells share a $KLRG1^{low}T\text{-}bet^{low}IL\text{-}7Ra^{hi}$ phenotype, survive contraction phase of adaptive immune responses, and give rise to long-lived circulating and possibly tissue-resident memory T cells.

Peripheral tissue immune surveillance T cells (T_{PS} cells): The combination of $CD3^+$ T cells present in healthy peripheral tissues, including tissue resident memory and circulating $\alpha\beta$ T cells, $\gamma\delta$ T cells and NK T cells.

Resident memory T cells (T_{RM} cells): $CD4^+$ and $CD8^+$ T cells with long-term residence in healthy tissues forming part of the local immune surveillance system. T_{RM} cells often express CD69 ± CD103, are generated during ongoing adaptive immune responses and are in disequilibrium with circulating memory T cells.

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Highlights

Chemokines orchestrate immune cell trafficking, and thus the site of chemokine production can define the local immune cell composition.

Healthy peripheral tissues host a highly complex network of immune surveillance cells, including macrophages, antigen-presenting cells and functionally diverse subsets of T cells and innate lymphoid cells. Homeostatic chemokines responsible for their recruitment, tissue retention and/or immune effector function have remained ill-defined.

Peripheral tissue chemokines orchestrate the function of the local immune surveillance system and, therefore, are essential contributors to tissue health and longevity.

In human skin, CCR8 and its ligand CCL1 are thought to play a critical role in the migration and maintenance of resident immune surveillance cells.

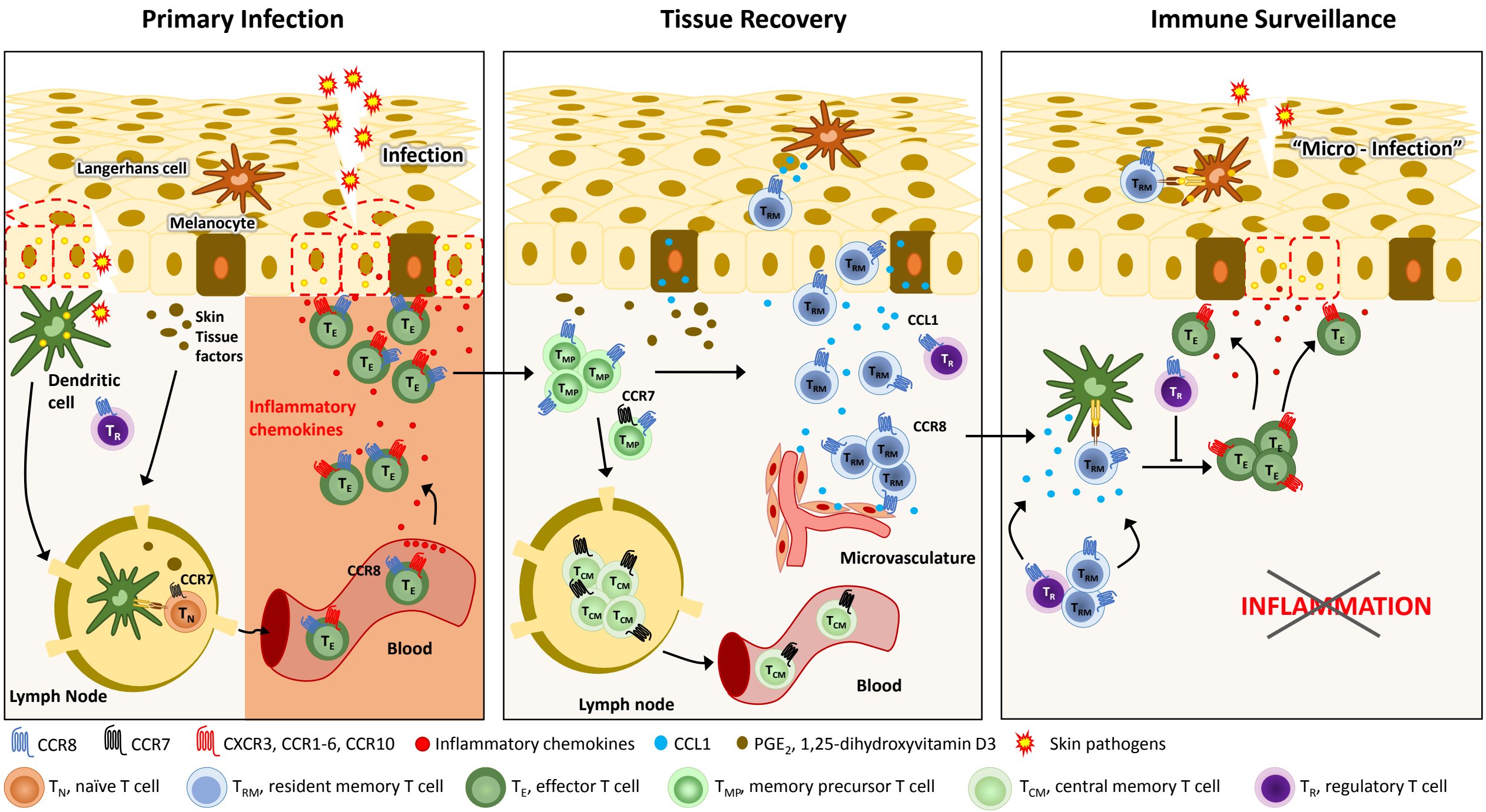
Outstanding Questions

- Are homeostatic chemokine systems, such as CCL1-CCR8 in human skin, necessary for TRM recruitment, localization and/or retention, survival or memory responses to local antigens?
- What is the role of tissue non-specific chemokine receptors present on TRM cells? Do they synergize with receptors for homeostatic chemokines or are they mainly involved in controlling immune cell mobilization in response to local infections?
- How do tissue factors, including vitamins, imprint tissue residency / survival? Do they also work on other lymphocyte populations (e.g. ILCs, $\gamma\delta$ T cells)?
- Since numerous memory $\alpha\beta$ T cells in human skin are not tissue-resident (i.e. do not express tissue residence markers CD69 ± CD103), what chemokine networks regulate their recirculation?
- Can peripheral tissue chemokine networks be manipulated to promote tissue-specific immunity, e.g. Treg cell recruitment in the case of autoimmune diseases or localization and/or maintenance of memory T cells in response to vaccination?

Table 1. Chemokine receptors involved in peripheral tissue T cell traffic

Chemokine receptor	Cellular expression	Ligands	Function in tissue lymphocyte traffic	Refs
CXCR4 (ACKR3)	Haematopoietic and non-haematopoietic stem cells, thymocytes, leukocytes, tissue cells	CXCL12	CXCR4 is a chemokine receptor whereas ACKR3 binds and internalizes CXCL12, thereby regulating extracellular CXCL12 concentrations. The CXCL12-CXCR4/ACKR3 axis controls bone marrow stem cell and progenitor localization, thymocyte development, plasma B cell homing as well as tissue (brain, heart, vasculature) development and repair. CXCR4 also functions as co-receptor for HIV-1	[3, 25, 26, 28]
CXCR6	αβ T, γδ T, NKT, NK, plasma cells	CXCL16	CXCL16 is either membrane-bound (cell-cell adhesion) or soluble (chemotaxis). CXCR6 associated with memory T cell and /NK cell compartments in liver and skin.	[30-33]
CCR6	αβ T, γδ T, Treg, ILCs, NKT, NK, B, immature DCs	CCL20	CCL20 is present at low levels in healthy skin but is massively upregulated during inflammation. Besides inflammatory involvement, CCR6 contributes to the maintenance of memory γδT17 cells in healthy skin and draining LNs.	[39-41]
CCR8	Human skin lymphocytes (αβ T, γδ T, NKT, NK). Mouse thymocytes, TH2 and Treg	CCL1 CCL8 (mouse) CCL18 (human)	CCL1, the primary ligand for CCR8, is constitutively expressed in human skin and rapidly released by activated skin TRM cells. Murine CCL8 and human CCL18 are alternative ligands for mouse and human CCR8, respectively. Murine CCR8 is primarily a T cell-associated chemokine receptor with expression on skin-homing Th2 and Treg cells. CCR8 on human skin T cells is discussed in the main text.	[94, 121, 138, 139]
CCR9	Thymocytes, intestinal (αβ T, γδ T)	CCL25	CCL25 is primarily produced in small intestinal tissues. CCR9 is present almost exclusively on intestinal αβ T cells, γδ T cells and plasmablasts but its function in intestinal T cell traffic, including T cell recruitment and maintenance of memory T cell compartment appears to be redundant.	[43]
CCR10	Effector T, B, ILCs, melanocytes	CCL27 CCL28	CCL27 and CCL28 share mutually exclusive expression pattern, CCL27 being present in the skin whereas CCL28 is being expressed in colon and secretary organs. CCR10 expressing $CD8^+$ T cells and Treg cells support survival of T cells as well as $CCR10^+$ ILCs. CCR10 on melanocytes/melanoma cells may control their skin retention.	[55-57]

CX3CR1	Monos, LCs, mΦ, NK, αβ T, γδ T, platelets, neurons	CX3CL16	CX3CL1 exists in two forms, membrane-bound (cell adhesion) or secreted (chemotaxis). Expression of CX3CR1 on macrophages (microglia, LCs) and intestinal DCs was shown to support local immune surveillance functions. Graded surface levels of CX3CR1 were used to distinguish effector/memory T cells subsets, including long-lived recirculating and LN-sessile memory T cells.	[60, 61]


Primary Infection
Tissue Recovery
Immune Surveillance
Langerhans cell
Melanocyte
Infection
Skin Tissue factors
Dendritic cell
Inflammatory chemokines
CCR7
CCR8
Lymph Node
Blood
CCL1
Microvasculature
Lymph node
"Micro - Infection"
INFLAMMATION
CCR8
CCR7
CXCR3, CCR1-6, CCR10
Inflammatory chemokines
CCL1
PGE2, 1,25-dihydroxyvitamin D3
Skin pathogens
TN, naïve T cell
TRM, resident memory T cell
TE, effector T cell
TMP, memory precursor T cell
TCM, central memory T cell
TR, regulatory T cell

McCully et al., Figure 2