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Chemokines: coded messages for T-cell missions

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1. ABSTRACT

Chemokines and their receptors control leukocyte migration and homing throughout the body in both physiological and pathological conditions. In the context of the adaptive immune system, which requires high efficiency and control, chemokines and chemokine receptors represent a versatile code that orchestrates the "who, where and when" of the immune response by providing the spatio-temporal guidance for T-cell development, priming and effector functions. In addition to their chemotactic properties, chemokines can directly modulate T-cell responses by amplifying signals at the immune synapse and tuning Th1/Th2 polarization. In this review we will discuss the role of chemokines in T-cell biology, following an ideal pilgrimage that spans the key steps of the T-cell life.

2. INTRODUCTION

T lymphocytes strive all life long defending our body against pathogens. To accomplish this mission, they circulate continuously through lymphatic and blood vessels, collecting and integrating information about the presence or absence of invading pathogens or growing tumors. This information is provided by specialized cells, such as dendritic cells (DCs), B lymphocytes and macrophages, expressing at their surface pathogen- or tumor-derived antigenic peptides loaded onto MHC molecules (major histocompatibility complex). When a T cell finds an antigen-presenting cell (APC) carrying peptide-MHC complexes specific for its antigen-recognition receptor (TCR, T-cell receptor), it receives activation signals and starts to produce cytokines and proliferate. Although in this context each T cell may seem

to act in complete autonomy, lymphocytes belong to a complex and integrated system characterized not only by responsiveness, efficiency and rapidity but also by security and safety. Indeed, T cells interact with many different cells, both from innate and adaptive immunity, and are exposed to many soluble factors. All these signals participate in determining the T-cell fate.

The immune system piloting is therefore a very challenging task: the travel of different types of cells through the body as well as the precise positioning into organs has to be tightly controlled in order to allow timing interactions between cells. The orchestration of these complex interactions require a special code, which has to be common to all cell types, rich and versatile to avoid fatal gaps and precisely tune the message.

The chemokine system represents an ideal code: shared by all cell types involved in immune responses, it is mainly characterized by redundancy and pleiotropy. With more than 50 chemokines and 20 receptors identified to date, the chemokine system may tune and regulate the migration of immune cells not only spatially, but also temporally. Thus, chemotactic signals orchestrate the "who, where and when" of the immune system, under both homeostatic and inflammatory conditions.

Although the control of cell migration represents the *raison d'etre* of the chemokine system, evidence has been accumulated showing that chemokines may play several other roles in immunity and inflammation. In the specific case of T cells, chemokines may act as soluble costimulatory molecules to tune T-cell responses.

3. CHEMOKINES AND T-CELL DEVELOPMENT

Like all cells of hematopoietic origin, T lymphocytes must be generated during embryogenesis and continually re-generated throughout life in order to maintain the peripheral T-cell repertoire. Although T-cell progenitors are produced in the bone marrow, the organ that supports T-cell lineage differentiation and selection is the thymus. During maturation in the thymus T cells will acquire two crucial properties: self-restriction and self-tolerance. Indeed, in the thymus self-reactive T cells are negatively selected (clonally deleted) whereas T cells with moderate affinity for self-peptide-MHC are positively selected.

The self-renewing progenitors enter the thymus and, subsequently, migrate throughout distinct thymic microenviroments while differentiating into mature T cells, which finally exit to the periphery.

3.1. In and out of bone marrow

In the last decade several studies have been carried out in order to define the phenotype of the lymphoid hematopoietic ancestor within the pool of multipotent and self-renewing stem cells in the bone marrow. A general consensus has been reached on the identification of common lymphoid progenitors (CLPs), that are lineage $(lin)^-$ c-kit^{low}Sca-1^{low} IL-7Rα^+, and that can only generate T cells, B cells, NK cells and lymphoid dendritic cells (1, 2).

In the bone marrow, the hematopoietic stem cells (HSCs) are located in specialized microenvironments called niches, which provide signals for progenitor survival, proliferation and differentiation (3). The maintenance of HSCs in niches depends on the high amounts of CXCL12 that is secreted by bone-marrow reticular cells. The main receptor for CXCL12 is CXCR4, which is expressed by HSCs (4). CXCL12 is primarily implicated in progenitor retention in the bone-marrow niches and the use of CXCR4 antagonist, which reduces the sensitivity to CXCL12, as well as the increase of CXCL12 concentration in the peripheral blood (5) result in CLP mobilization from the bone marrow (6). In agreement, a recent study indicates a crucial and non redundant role for CXCR4 in facilitating localization of early lymphoid progenitors to thymus (7).

3.2. In and out of thymus

T-cell progenitors must move from bone marrow niches to the blood (8), leave the circulation and finally enter in the thymus (9). Chemokines orchestrate T-cell trafficking to the thymus by providing directional cues for T-cell progenitors. During embryonic development, T-lymphoid precursor cells colonize the thymus *primordium*. This process occurs in human at 7 to 8 weeks of gestation and in mice at the embryonic day 11.5. The fetal thymus produces several chemokines, including CCL21, CCL25 and CXCL12 (10). Delayed fetal thymus colonization and decreased number of total fetal thymocytes occur in mice presenting a defective expression of CCL21 or in $CCR7^{-/-}$ mice (10). Similarly, mice deficient for CCR9, the receptor for CCL25, display a 3-fold decrease in thymic cell number compared to wild type animals (11). In contrast, $CXCR4^{-/-}$ bone marrow cells can enter the thymus but fail to differentiate (12).

T cells are continually generated throughout life from self-renewing HSCs localized in the adult bone marrow (13). T-cell precursors entry into the adult thymus is an intermittent rather than a continuous process (14), with waves of precursors invading the organ periodically. This process is based on feedback loops allowing thymic progenitors to sense the opening of the so-called thymic "gates" (15). A recent study provided a considerable indication for the molecular identity of these "gates", showing that the concentration of P-Selectin, which is related to the availability of intrathymic niches, may regulate homing of T-cell precursors to the thymus (16).

Although no chemokines have yet been directly linked to T-cell homing to the adult thymus, CXCL12, CCL21 and CCL25 mRNA increase in the adult thymus after intrathymic T-cell depletion (17), suggesting a possible role for these three chemokines in thymus colonization. Thymocyte precursors enter the adult thymus at post-capillary venules near to the cortico-medullary junction (CMJ) (18); at this site there is a significant production of CCL25, suggesting that CCR9 ligands may specifically influence $CD34^+$ progenitor entry into the organ (19). Similarly, CXCL12 is also produced at the CMJ

and immature T cells are able to respond to CXCL12 *in vitro*; nevertheless, in CXCL12 or CXCR4 knock-out mice thymocyte development proceeds normally (20). Recent studies have suggested that fetal liver CXCR4-deficient cells may enter the thymus but further expansion of T-cell precursors is affected, indicating a delayed role for CXCL12-CXCR4 interaction in the thymocyte maturation (7, 12). Indeed, during its maturation process, the T cell changes its localization into the thymus architecture, proceeding from CMJ to the cortex, then to the subcapsular zone and finally reaching the medulla. During this ripening promenade, the immature lymphocyte meets specialized thymic niches that support its evolution with several developmental cues, conferring to the uncommitted ancestor the T-cell identity.

Two main factors can influence thymocyte coordinated migration into the thymus: the adhesive matrix, that acts as substrate for thymocyte movement (21), and chemokines, that provide directional signals for thymocyte orientation (22). Elegant studies have been performed to identify chemokines specifically produced in different thymic niches. Nevertheless, the chemokine system is highly redundant in the thymus, like everywhere in the body, and the chemokine-receptor profile of thymocytes is extremely variable; consequentially, it would be difficult to make a detailed and exhaustive map of the T cell chemokine roads in the thymus. Although playing several roles during different T-cell maturation steps, CCR7, CCR9 and CXCR4 seems to be the pilots driving not only lymphocyte entry into the thymus but also their pilgrimage inside the organ. In addition CCL17 and CCL22, both CCR4 ligands, are expressed exclusively in the medulla, suggesting a pivotal role for these chemokines in regulating thymocyte movements toward thymic medulla (22).

Once mature, the newly generated T cells leave the thymus to start their circulation among blood and lymph. The refined mechanism that regulates T-cell egress from thymus is not totally understood but there is evidence that it could be regulated by a mixture of chemo-attractive and chemo-repulsive forces. Several reports have demonstrated the importance of the chemoattractant lipid sphingosine-1-phosphate (S1P) and $S1P_1$ receptor (a GPCR) in T-cell exit from the thymus. When ready to leave the thymus, T cells up-regulate $S1P_1$ receptor expression (23) and $S1P_1$-deficient T cells are indeed retained in the thymus (24). On the other hand, among the chemo-repulsive forces that would partially regulate thymic egression, CXCR4-CXCL12 interactions seems to be pivotal for both fetal and adult thymocyte egress (25, 26).

4. CHEMOKINES AND T-CELL PRIMING

After thymic egress, naïve T cells keep circulating between blood and secondary lymphoid organs until they meet antigen-specific APCs. This encounter occurs in a specialized area of the draining lymph nodes, referred to as the T-cell area. T cells enter the lymph node via high endothelial venules (HEV). This process is directly controlled by the CCR7 chemokine receptor, expressed on naïve T cells, and its ligands CCL19 and CCL21 (27), produced by DCs and HEV, respectively. CCL19 and CCL21 are essential not only as guidance, but also in converting the initial weak interaction between T cells and HEV into a strong arrest (28). CXCL12/CXCR4 interactions also participate during T cell extravasation to secondary lymphoid organs, although this process seems to be more relevant for memory T cells (29).

In vivo imaging experiments have shown that lymphocytes entering the T-cell zones move randomly over densely packed networks of dendritic cells (DCs) and fibroblastic reticular cells (FRCs) (30, 31). This motility is driven by CCR7-binding chemokines and may be pivotal for T cells to find their proper partners among numerous other cells. Besides CCL21, other chemokines produced in lymph nodes may coordinate specific encounters between cells. Thus, CCL3 and CCL4 seem to be involved in recruitment of naïve $CD8^+$ T cells, which can upregulate CCR5 expression during inflammation, to sites where they can receive help from $CD4^+$ T cells (32).

The encounter between naïve T cells and antigen-specific APCs initiates a variety of biochemical and cellular responses resulting in T-cell activation and proliferation. The interaction between a single T-cell–APC pair can be sustained for several hours (33), and is accompanied by the organization of a specialized junction – referred to as the immunological synapse (IS) – between the two cells. The IS is a high-order, dynamic structure formed at the T-cell plasma membrane, as a consequence of the interaction between TCRs and pMHC molecules displayed at the APC surface (34). Spatio-temporal segregation of second messangers, integration and balancing of signaling are likely the main IS functions. Indeed, the polarized and compartmentalized nature of the T-cell IS may facilitate local signaling, leading to specific cellular responses at specific location and times. In addition, physiological T-cell activation is generally achieved by very few antigenic complexes on the APC, suggesting that signaling amplification by costimulatory molecules is an important requirement for T-cell priming. Another role of the IS is favoring polarized secretion of soluble mediators toward the T-cell partner/target. In a polarized IS-forming T cell, trafficking of vesicles is directed to the T-cell–APC contact region and this may be important to facilitate T-cell functions.

Although the contribution of costimulatory molecules to IS formation has long been recognized, only recently chemokine receptors have been described as new T-cell costimulatory molecules (35). During T-cell activation, recruitment of CCR5 and CXCR4 chemokine receptors into the IS, by a mechanism requiring chemokine secretion by APCs, results in prolonged T-cell–APC interaction, and facilitates T-cell activation by reinforcing T-cell–APC pair attraction and delivering costimulatory signals (36). TCR activation leads to a major change in the signaling of chemokine receptors that, in this condition, couple preferentially to

G_q/G_{11} instead of G_i (36), thus inducing cell adhesion rather than chemotaxis (37, 38), either by enhancing LFA-1 affinity (39, 40) or by overriding G_i-mediated chemotactic signaling. In addition, G_q-mediated signaling also triggers the translocation of nuclear factor of activated T cells (NFAT) to the nucleus (41), providing another additional mechanism by which chemokine-receptor engagement at the IS may enhance T-cell activation. Whether other chemokines can costimulate T-cell activation when released by APCs into the IS is an important issue to be determined.

A dual role for chemokines in T-cell activation has been therefore proposed (35): while the presence of chemoattractant forces when T cells are searching for the right partner may indeed prevent T-cell–APC pairing, production of chemokines by the APCs, and subsequent accumulation and trapping of G_q-coupled chemokine receptors at the IS, may represent a strategy to reinforce T-cell–APC interaction and facilitate T-cell activation.

It has been proposed that some chemokines are subordinate to TCR signaling being unable to reverse the TCR-stop signal, whereas other chemokines override the TCR-mediated stop signal and have an immunosuppressive potential. Dustin and coworkers indicated CXCR4 and CCR5 ligands among the subordinate chemokines, whereas CXCR3 and CCR7 ligands among the dominant immunosuppressive chemokines (42). It is likely that the overall effect of chemokines over IS assembly would be the result of a combination of quantity and quality of the chemokines secreted by APCs and present in the milieu where interactions are taking place.

After priming, activated T cells must leave the lymph node T-cell area and exert their functions. One of the initial events is therefore the downregulation of CCR7 and the upregulation of other chemokine receptors specific for the target tissue. As already described for the thymus, S1P and its receptor regulate lymphocyte egress from lymph nodes. Notably, $S1P_1$ receptor is rapidly and transiently downregulated after antigenic stimulation of naïve T cells, contributing to sustained stimulation and efficient activation in lymph node (24). Some $CD4^+$ T cells do not leave lymph nodes immediately and provide help to B cells: T lymphocytes upregulate expression of CXCR5, and therefore become directed to the follicle, where CXCL13 is produced (43). Conversely, other activated T cells are recruited in peripheral tissues to fight invading pathogens.

5. CHEMOKINES AND T-CELL EFFECTOR FUNCTIONS

Recruitment of effector T cells into inflamed tissues is driven by chemokines, produced either by infiltrating inflammatory cells or by tissue injured cells. For example, T-cell homing in the skin, where CCL17 is expressed by endothelial cells and CCL27 is secreted by skin keratinocytes, depends on expression of CCR4 and/or CCR10 (44, 45), together with ligands for P and E selectin (such as cutaneous lymphocyte antigen CLA). This skin-tropism may represents a "default" pathway, that may be suppressed by gut-homing instructions, when present (46); furthermore this homing restriction depends on the origin of DCs that prime T lymphocytes (47). Indeed, T-cells activation in Peyer's patches or in mesenteric lymph nodes is followed by T-cells expression of CCR9 and α4β7 integrin and drives the homing to the small intestine, where CCL25 is highly expressed in the epithelium and also presented on the postcapillary venules of the lamina propria (48).

Because the aim of the immune system is to eliminate invading pathogens and considering that every enemy has his weaknesses, T cells have adapted their effector strategy to the source of the antigen. Therefore, during T-cell priming, $CD4^+$ T cells can be polarized toward distinct effector cells: Th1, Th17 and Th2. A corresponding type 1 and type 2 polarization exists also in $CD8^+$ T-cells responses (49, 50).

Each effector T-cell subset is driven into specific locations by different chemokines. Although the analysis of chemokine receptors expressed by Th1 or Th2 T lymphocytes purified from human blood shows high heterogeneity (51), combinatorial expression of chemokine receptors defines physiologically significant subsets of T cells and allows tissue- and subset-dependent targeting of effector cells during chemotactic navigation. Moreover, chemokines modulate the expression of cytokines that induce Th1/Th2 polarization, thus promoting lymphocyte activation and/or differentiation (52). Therefore chemokines receptors allow not only T cell selective recruitment but also amplification of effector T cell polarization during immune response shaping. Moreover, chemokines control the trafficking of $CD4^+CD25^+$ regulatory T cells (Treg), the lymphocytes deputed to switch off immune responses.

5.1. Th1 cells

Th1 cells are a subset of T lymphocytes, committed by IFN-γ and IL-12 and suppressed by IL-4 to destroy cancer cells or intracellular pathogens (such as viruses and some bacteria). They predominantly secrete IL-2, IL-3, TNF-α and IFN-γ, activate phagocytes, favor the production of opsonizing and complement-fixing IgG1 and IgG3, and control cellular responses; moreover Th1 cells are involved in DTH (delayed-type hypersensitivity) response and in autoimmune diseases (53).

Among chemokine receptors, Th1 cells are characterized by CXCR3, CXCR4, CCR5 (54, 55), CCR7 and CX3CR1 expression.

The common expression of CCR5 on Th1 cells (56) and monocytes (57), the precursors of macrophages, allows the co-recruitment of these major players of chronic inflammatory responses into tissues. Chemokines are not only important in attracting T cells into tissues, but they can directly modulate T-cell responses, too. Thus, CCL3, a ligand of CCR5, enhances IFN-γ production (58), whereas Th1 cytokines production is enhanced by CXCL10 (through CXCR3-A), and inhibited by CXCL4 (through CXCR3-B) (59, 60).

5.2. Th17 cells

Recently, it has been identified a new subset of T lymphocytes, the Th17 cells (61-63), whose development is induced by TGF-β and IL-6 (64), stabilized and amplified by IL-23 and suppressed by IL-4 and IFN-γ (65). Th17 cells predominantly secrete IL-17, IL-22 (66), IL-6 and TNF-α and activate cells involved in destroying extracellular bacteria and in chronic inflammation (67); moreover Th17 cells are implicated in autoimmune diseases, such as multiple sclerosis and psoriasis.

Human $CD4^+$ Th17 cells, from blood of healthy donors, are identified as uniquely bearing the $CCR2^+CCR5^-$ phenotype (68). Recently, Th17 cells in the gut of subjects with Cronh's disease have been characterized (69). These cells show an excellent ability to help B cells, low cytotoxic potential and reduced susceptibility to suppression by autologous Treg cells. Human Th17 cells share CXCR4, CXCR6, CCR5 and CCR4 expression with Th1 or Th2 clones, whereas CXCR3-A, CXCR3-B, CCR3, CCR8 and CCR9 expression is lacking; however Th17 cells selectively express CCR6, functionally active in migration. This population $CD4^+$ $CCR6^+$ is present also in peripheral blood and tonsils. Th17 cells are the only memory cells that continue to express CCR6 even after prolonged antigen activation, with important implications for the long-term maintenance of influx and pathogenic role of Th17 cells into inflamed tissues (69).

5.3. Th2 cells

Th2 cells are a subset of T lymphocytes committed to orchestrate immune responses against extracellular pathogens (such as helminthes). Th2 polarization is induced by IL-4 and suppressed by IFN-γ and IL-12. Th2 cells secrete IL-4, IL-5, IL-9 and IL-13, activate eosinophils and B cells (helping class switching to IgE) and control phagocyte-independent responses; moreover, they are involved in allergy (53). Th2-cytokine production is enhanced by CCL2 (58) and CXCL4 (through CXCR3-B), and inhibited by CXCL10 (through CXCR3-A) (59, 60).

Among chemokine receptors, Th2 cells are characterized by CCR4 (54, 55), CCR7, CCR8 (70, 71) and CXCR4 at higher levels than in Th1 cells (72, 73). The chemokine receptor CCR3 was initially thought to be a receptor that control the trafficking of Th2 cells; however, subsequent studies have revealed that while it is expressed on all eosinophils, it is only present on a minority of Th2 cells. CCR3-deficient mice have a profound defect in eosinophil migration but Th2 cell trafficking appears to be intact and CCR3-deficient mice can mount a tissue-specific allergic response (74, 75).

5.4. Regulatory T cells

After antigen elimination, effector T-cell activation must be suppressed to maintain immune tolerance. This containment job is done by Treg cells, a $CD4^+CD25^+$ subset of T cells. Bone marrow is a preferential site for migration and maintenance of the $CD4^+$ Treg pool, which express CXCR4 and are retained into the bone marrow through CXCL12-induced signals (76). However, Treg selectively migrate and accumulate where immune-suppression is required (77). Regulated expression of specific chemokine receptors and adhesion molecules controls Treg trafficking from lymphoid organs to periphery. Treg cells exert their function, at least in part, in the lymph nodes, during T-cell activation, where they are attracted by CCL19, the CCR7 ligands (78). The appropriate localization of Treg cells at the site of the immune response is essential for their immuno-regulatory activity and, indeed, Treg cells share the same chemokine receptors with their targets, the effector T cells (79). Thus, Treg cells migrate efficiently to ligands for CXCR3, CCR2, CCR4, CCR5 and CCR6 (80-82). CCL22/CCR4 has been shown to drive Treg homing to allografts, allowing long-term allograft survival (83), but also Treg attraction into specific tumor microenvironments, where elevation in the Treg cell number has been correlated with a bad prognosis (84).

5.5. Cytotoxic T lymphocytes

Because of their pivotal role in antiviral and anti-tumor immunity, $CD8^+$ T cells are protagonists of adaptive immune responses, but they need help by $CD4^+$ T cells to perform all their functions properly (85, 86). Inflammation leads to CCR5 expression by naïve $CD8^+$ T cells, permitting their recruitment to sites of $CD4^+$ T-cell interaction with DCs, where CCL3 and CCL4 are produced (32). This chemokine-driven cell clustering appears to be fundamental for development of proper long-term $CD8^+$ T-cell memory.

Inflammatory chemokine receptors such as CXCR3, CCR5 and CX3CR1 are expressed on activated CD8+ T cells and enable these lymphocytes to migrate into the periphery (87-89). CCR5 and CXCR3 are expressed by the majority of effector cytotoxic T cells infiltrating the lesion of oral lichen planus; moreover the localization of CCL5 and CXCL10 within the cytolytic granules of these infiltrating $CD8^+$ T cells strongly suggests a self-recruiting mechanism for accumulation of $CCR5^+$ and/or $CXCR3^+$ T cells (87). In addition to their classical role as chemoattractants, chemokines stored in cytolytic granules have been suggested to participate in fighting HIV-1. CCL3, CCL4 and CCL5 are localized in the cytolytic granules of HIV-1-specific $CD8^+$ cytotoxic T lymphocytes and secreted by CTL as a macromolecular complex containing sulphated proteoglycans. This association appears to have a functional significance, because heparan sulphate facilitates CCL5-mediated inhibition of HIV-1 infection of monocytes (90).

A subset of cytotoxic CD8 T cells with high cytotoxic potential expresses CXCR1, a receptor that may control their recruitment into sites of innate immune system activation in response to viral infections. CXCR1 thus defines a "rapid-responder" subset of CD8 T cells that bridges the gap between the innate and acquired immune responses, being CXCL8 one of the earliest and most abundantly produced chemokines after innate immune recognition of pathogens (91). Interestingly, the membrane-bound CX3CL1 enhances migration of

CX3CR1-expressing cells to other chemokines, such as CCL4 and CXCL8, acting on the same cells (89).

5.6 Memory T cells

Most of the pathogens that can invade our body are endemically present in our environment. It is therefore very advantageous for the immune system to "remember" every enemy that it has met and the optimal strategy used to fight it. So, a fraction of activated T lymphocytes generated and expanded during the primary response, persists in our body as memory T cells and circulate between both lymphoid and extra-lymphoid tissues, in order to identify antigens and control secondary responses.

Memory T cells are divided in two subsets depending on CCR7 expression (92). The $CCR7^+$ subset – central memory T cells (T_{CM}) – is able to home to lymph nodes and, if stimulated by antigen-specific DCs, generate new effector T cells. Moreover, T_{CM} cells express receptors for inflammatory chemokines and therefore they can migrate into peripheral inflamed tissues. The other subset of T memory cells – effector memory T cells (T_{EM}) – does not express CCR7 and it is excluded from lymphoid organs. $CCR7^-$ memory T cells can be rapidly recruited to inflamed peripheral tissues, where they perform immediate effector functions (such as cytokine secretion or cytotoxicity).

Interestingly, $CCR7^+$ naïve T cells may differentiate in $CCR7^+$ T_{CM} cells and successively, at the second exposure of antigen, in $CCR7^-$ T_{EM} cells (93); nevertheless, $CCR7^+$ naïve T cells may become $CCR7^-$ effector T cells and retain this phenotype while patrolling peripheral tissue as T_{EM} cells, but at some stage they re-express CCR7 to migrate to the lymph nodes via the afferent lymph (94, 95). This migration of activated T cells from the tissue back to the lymph node may have important implications for the generation, polarization and control of immune responses.

6. CHEMOKINES AND T-CELLS IN RENAL DISEASES

The attraction of leukocytes to sites of inflammation and infection is an essential component of the host response to invading pathogens. Although crucial host defense proteins, chemokines can also be detrimental in certain inflammatory diseases, such as asthma, atherosclerosis, rheumatoid arthritis and multiple sclerosis, where the recruited inflammatory cells induce tissue damage.

In addition to inflammatory and autoimmune diseases, chemokines and chemokine receptors play important roles in a wide range of human pathologies, including immunodeficiencies, infections, and cancer (96-98). However, an extensive discussion of chemokines in diseases goes beyond the aim of the review. Here we will focus on chemokines in T cell-mediated kidney diseases.

6.1. Inflammation

The host response to acute infection or injury commonly consists of an exuberant neutrophilic inflammatory response. As is often the case in inflammation, this is a double-edged sword, and this robust protective response can also be deleterious to the host. Host response to many acute tissue insults, such as ischemia, induces a neutrophil-rich inflammatory response that significantly contributes to tissue injury. Ischemia-reperfusion injury is thought to contribute to many important pathologic conditions.

Renal ischemia-reperfusion injury (IRI) is the main cause of intrinsic renal failure, determining a mortality greater than 50% (99). Although neutrophils were traditionally indicated as the predominant inflammatory mediators, recent reports highlight the critical implications of T cell in renal IRI (100). An elegant study performed by Rabb and colleagues demonstrated that T cell deficient mice (*nu/nu)* are insensitive to renal injury post-ischemia and the damage is restored after naive T cell adoptive transfer (101). The effector mechanisms that support T cell tissue injury are still debated. Nevertheless there is accumulating evidence that Th1/Th2 balance is crucial for the pathogenesis of renal IRI (102).

Th1 responses are well described in several renal pathologies. The chemokine receptor CXCR3 is implicated in recruitment of Th1 T cells into the organ, as shown by the fact that CXCR3 deficient mice display a reduced recruitment of Th1 cells into inflamed kidneys (103).

Crescentic glomerulonephritis (GN), a form of acute GN that finally leads to acute renal failure, is a clear manifestation of Th1 predominant nephritogenetic immune responses (104). Among chemokines, CCL2 has been associated to renal GN, mediating cell infiltration and interstitial fibrosis (105). Nevertheless, other CC chemokines, such as CCL3 and CCL5, which have been detected in crescentic lesions (106), may recruit and activate T cells and macrophages (106).

The membrane-bound chemokine CX3CL1, which is highly expressed in inflamed kidneys, seems to be a good candidate for lymphocyte and monocyte recruitment into the organs in several types of human renal inflammations (107).

6.2. Autoimmunity

Infiltration of effector T cells and activated macrophages into tissue is characteristic of a multitude of prominent human autoimmune diseases, including Type 1 Diabetes, multiple sclerosis, and rheumatoid arthritis. Among the T lymphocytes, a prominent role is played by Th1 and Th17 $CD4^+$ T cells and, in some disease, by cytotoxic $CD8^+$ T lymphocytes. Thus, the chemokines involved in the pathogenesis of autoimmune diseases are mainly CCR2, CCR5, CXCR3, and CX3CR1 ligands.

Approximately 30% of patients with type 1 diabetes develop diabetic nephropathy, a progressive renal disease, characterized by glomerulosclerosis and proteinuria. Infiltration of imflammatory cells, driven by chemokines such as CCL2 and CX3CL1, seems to play a crucial role in the development of the disease (108).

Lupus nephritis is one of the serious complications of Systemic Lupus Erythematodes, an autoimmune disease characterized by the production of pathogenic auto-antibodies and tissue deposition of immune complexes. An elegant study of a murine lupus nephritis model established the key role of CCL5 in autoimmune kidney injury. Authors demonstrated that CCL5 is expressed in the kidney cortices of autoimmune MRL-*Fas*^{lpr} mice prior to renal injury and increases with the severity of nephritis. Furthermore, CCL5 promoted the influx and propagation of macrophages and specific T-cell subsets into the MRL-*Fas*^{lpr} kidney, directing the extravascular migration of leukocytes and priming these cells to initiate tissue damage (109).

6.3. Transplantation

Organ transplantation is often the only effective treatment for the large number of patients with end-stage kidney, liver, heart or lung disease. Although a transplant is often life saving, it ushers in a new set of problems and potential diseases for the organ recipient. These include organ ischemia-reperfusion injury, acute rejection, and chronic organ dysfunction from chronic rejection. These processes involve recruitment of leukocytes into the transplanted organs, with neutrophil recruitment dominating ischemia-reperfusion injury whereas lymphocytes and monocyte recruitment involved in rejection. Chemokines and chemokine receptors are clearly involved in all of these processes ultimately leading to complications of transplantation (110, 111).

Organ ischemia-reperfusion injury, acute rejection, and chronic rejection lead to increased expression of multiple chemokines that are surprisingly similar in all organs after transplantation (112). However, organ specific differences do exist, so one cannot fully generalize the response to all transplanted organs (113). In the limited studies looking at chemokine expression following human organ transplantation the expression of CXCL8 has been associated with ischemia-reperfusion injury (114), while CCL2, CCL3, CCL4, CCL5, CXCL9, CXCL10, and CXCL11 have been associated with acute rejection (115).

An interesting study performed on human renal biopsies investigated the *in situ* expression of chemokines and chemokine receptors after renal transplantation (116). This inquiry demonstrated that the allograft mRNA expression of CCL5, CXCL10 and CXCL11 is up-regulated in patients with acute allograft rejection compared to patients without rejection. This variation in chemokine expression profile is associated with an increased recruitment of CXCR3 and CCR5 positive cells into renal allograft and with acute rejection (116).

6.4. Cancer

Although chemokine receptors are predominantly expressed on leukocytes, they are also expressed at lower levels on many other cell types. On tumor cells, these receptors are found at increased levels and they may participate in metastasis, tumor growth and survival. Furthermore, tumors secrete chemokines with angiogenic activity, which may play a role in maintaining an adequate blood supply to the tumor.

It is a shared opinion that chemokines may influence the type of immune responses - Th1 or Th2 - in the tumor, by selectively recruiting T lymphocytes and monocytes. In a recent paper on human renal cell carcinoma (RCC), Kondo and colleagues indicated that CXCL9, CXCL10 and CXCL11 play important roles in recruiting Th1 cells, into the tumor and that upregulation of Th1-associated chemokine expression correlates with a favorable prognosis after curative surgery of RCC patients (117). A previous study characterizing tumor-infiltrating lymphocytes, obtained from RCC patients before and after radical nephrectomy, showed that this cell polulation is predominately composed of CD4+ Th1 polarized effector memory cells that express CXCR3 and CCR5 (118).

RCC is characterized by a significant propensity for metastases, and, in addition, patients do not respond to conventional therapy. Alternative therapeutic approaches, such as immunotherapy, may thus represent successful strategies for RCC treatment. Strieter and colleagues proposed an interesting therapeutic model that combined systemic IL-2 with an intratumor CXCR3 ligand (CXCL9). In a mouse model, this immuno- cocktail led to significant reduction in tumor growth and angiogenesis, increased tumor necrosis, and enhanced intratumor infiltration of CXCR3+ mononuclear cells (119).

7. PERSPECTIVES

Chemokines and their receptors play an essential role in each step of the T cell life, coordinating development in primary lymphoid organs, homing to, migration and placement within secondary lymphoid organs as well as priming in secondary lymphoid organs, patrolling through the whole body, infiltration in inflamed tissues and the final withdrawal at the end of the mission (Figure 1). Thus, dysregulated expression of chemokines and their receptors is involved in the development of many human immune-mediated or immune-related diseases, including autoimmune and chronic inflammatory diseases as well as immunodeficiency and cancer. Chemokine receptors are considered among the most druggable targets in the immune system and there has been considerable effort in both the public and private sectors to develop drugs to modulate their activities.

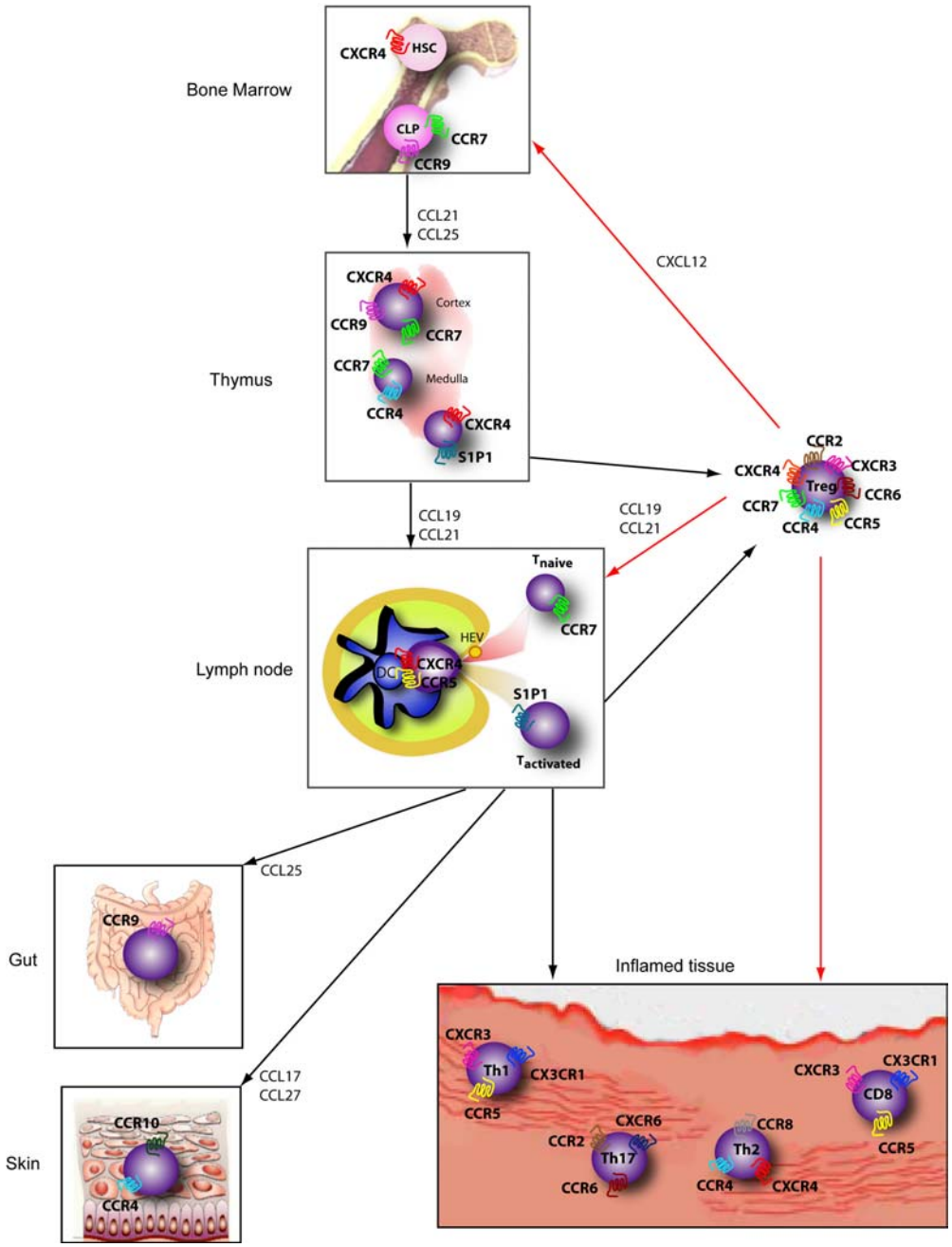

Figure 1. A simplified view on the main roles of chemokines and chemokine receptors in T-cell life. In the bone marrow, the maintenance of $CXCR4^+$ human stem cells (HSC) in niches depends on the high amounts of CXCL12 that is secreted by reticular cells. Common lymphoid progenitors (CLP) express CCR7 and CCR9 and their ligands, namely CCL21 and CCL25, are involved in recruitment of thymocytes into the thymus. The up-regulation of $S1P_1$ receptor by mature T cells allows them leaving the thymus and joining blood and lymph circulations. Circulating naïve T cells express CCR7 and are attracted into lymph nodes by its ligands CCL19 and CCL21. These interactions are also involved in the T-cell search for DCs in the lymph nodes, where T-cell priming occurs. During priming, as well as during T-cell activation in peripheral tissues, chemokines may facilitate T-cell activation working as soluble costimulatory molecules released at the IS. Activated T cells leave the lymph node through S1P-dependent signals and migrate to skin, gut and other peripheral tissues in a chemokine-controlled manner (chemokines controlling recruitment of effector T cells in inflamed tissues are not shown, because this depends on the tissue and the type of T cells involved; however, this information can be easily deducted by the chemokine receptor expression on specific T-cell subtypes). Regulatory T cells (Treg), which can be generated either in the thymus or in lymph nodes, can inhibit T-cell responses in tissues because they may express a variety of chemokine receptors allowing their co-recruitment with effector T cells. In addition, Treg homing into lymph nodes or bone marrow is driven by CCL19 or CXCL12, respectively.

As a result, chemokine-receptor antagonists have already made their way into the clinic, although several problems related to redundancy and pleiotropy of the system have still to be solved. We believe that a deeper understanding of the complex communication between the chemokine and the immune system will allow finding new and better drugs to fight human diseases.

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