Chemokines: role in inflammation and immune surveillance

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The majority of approximately 50 human chemokines fall into the group of either CXC or CC chemokines. In addition, there are two C chemokines, Ltn-α/XCL1 and Ltn-β/XCL2, in which two out of the four conserved cysts residues are missing, and a single CX3C chemokine, called fractalkine/CX3CL1, with three amino acids separating the two NH2 terminal Cys residues. Two nomenclature systems are used in the current literature, the traditional abbreviations dating back to the time of chemokine discovery, such as interleukin (IL)-8 and literature, the traditional abbreviations dating back to the time of chemokine discovery, such as interleukin (IL)-8 and interleukin-8 homologue in mice but not in rats or humans, and the lack of an IL-8 homologue in mice but not in rabbits or humans.

Downstream second messengers of G-protein signalling include phospholipase Cβ (PLCβ) isoforms, Ser/Thr kinases, phosphatidylinositol 3-kinase-γ (PI3Kγ) and e-Src related non-receptor tyrosine kinases. Cellular responses to chemokines are typically rapid in onset and transient in duration. The negative control mechanism elicited during chemokine receptor signalling is termed cellular desensitisation and is by itself also transient—that is, cells regain responsiveness to a given chemokine after a short period of culturing in chemokine depleted medium. Homologous desensitisation is mediated by G-protein coupled receptor kinases (GRKs), which block further signal transduction by phosphorylating Ser/Thr residues in the intracellular C terminal domains of ligand occupied chemokine receptors and other G-protein coupled receptors (GPCRs). Uncoupling from G-proteins is also observed in a process called heterologous desensitisation that involves phosphorylation of ligand free (non-engaged) chemokine receptors or other GPCRs by alternative protein kinases. GRK mediated receptor phosphorylation initiates β-arrestin binding, which leads to sequestration or clustering in specialised clathrin-rich membrane microdomains and endocytic uptake of chemokine-receptor complexes. Rapid internalisation allows the continuous redistribution of chemokine receptors on leucocytes for maintaining polarised chemokine sensing and directed cell migration along a chemokine gradient. Not all chemokine binding proteins induce cell migration, as exemplified by CXCR3-B (see above; reference 10), the “decoy” chemokine receptors D6,11 and the Duffy antigen related chemokine receptor (DARC). Furthermore, the signal transduction machinery of certain chemokine receptors can become uncoupled, as documented by the IL-10 mediated silencing of chemokine receptors in monocytes and dendritic cells (DCs).

Numerous chemokine receptors are highly promiscuous in their chemokine selectivity, and vice versa, numerous chemokines bind to more than one receptor. These redundant chemokine systems are most frequently associated with inflammation, which is in contrast with several monogamous chemokine systems with function in homeostatic

Abbreviations: DC, dendritic cell; GPCR, G-protein coupled receptor; G-proteins, GTP-binding proteins; GRK, G-protein coupled receptor kinase; IL, interleukin; LN, lymph node; PP, Peyer’s patch; Th, T helper
Chemokines in inflammation and immune surveillance

been shown to block CCR5.

MCP-3/CCL7, a potent agonist for CCR1, CCR2, and CCR3 has formed by the transmembrane regions of the chemokine receptor. The three fixation sites in the COOH terminal sites in chemokines that are essential for function include (1) the matrix regions participating in G-protein mediated signal transduction. The three chemokine binding, and the COOH-terminus. Other chemokines are also grouped into functional subsets. These findings indicate that several chemokines cannot be assigned unambiguously to either of the two functional categories and, therefore, may be referred to as “dual function” chemokines.

Recruitment of circulating leukocytes to sites of pathogen entry or inflammation involves two separate migration processes, termed extravasation and chemotaxis (fig 2). Adhesion to the luminal side of blood vessels, transendothelial migration, and subsequent chemotaxis of leukocytes are highly complex processes, which are controlled by “outside-in” and “inside-out” signalling events during cellular interactions of blood leukocytes with vascular chemokines and adhesion ligands. Triggering of chemokine receptors in leukocytes by endothelial associated chemokines is a requirement for extravasation and induces a rapid increase in integrin affinity/avidity, which results in firm but transient leukocyte adhesion.

MULTIPLE STEP LEUCOCYTE MIGRATION CONTROL

Chemotactic activity and the “four Cys residue” fingerprint arrangement prompted the term chemokines to designate this novel group of chemotactic cytokines. In addition to the CXC, CC, XC, and CX3C classification, chemokines are also grouped into functional subsets. Inflammatory chemokines control the recruitment of effector leucocytes in infection, inflammation, tissue injury, and tumours. Many of the inflammatory chemokines have broad target cell selectivity and act on cells of the innate as well as the adaptive immune system. Homoeostatic chemokines, in contrast, navigate leukocytes during haematopoiesis in the bone marrow and thymus, during initiation of adaptive immune responses in the spleen and lymph nodes, and in immune surveillance of healthy peripheral tissues. Recent findings indicate that several chemokines cannot be assigned unambiguously to either of the two functional categories and, therefore, may be referred to as “dual function” chemokines.

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After crossing the endothelial barrier, perivascular leukocytes will chemotax in response to a chemokine gradient, allowing more precise localisation of the leukocytes within the tissue (see fig 2). Importantly, chemokines forming a gradient in the tissue do not need to be identical to those controlling attachment of leukocytes to microvascular endothelial cells. As mentioned above, chemokine binding quickly leads to neutralisation and endocytosis of engaged receptors, thereby allowing continuous redistribution of...
Chemokine receptors and de novo chemokine sensing. At the site of chemokine production where chemokine concentrations are highest, homologous desensitisation may impede leucocyte migration and, in the presence of alternative chemokine gradients, may allow their further relocation. Some T cells and maturating (inflammatory) DCs exit the tissue site to reach secondary lymphatic tissues and blood (see fig 2). For instance, naive T cells and B cells within LNs and Peyer’s patches (PPs) that remain uninvolved in local immune processes return to peripheral blood by means of efferent lymphatic channels. Similarly, immune surveillance T cells (see below) may also exit healthy epithelial tissues via afferent lymphatic channels, local LNs, and the thoracic duct to reach blood circulation. The molecules controlling this reverse (abluminal to luminal) transmigration across the lymphatic endothelium are poorly defined but chemokines and adhesion molecules may also be involved. Recent data indicate a role for sphingosine-1-phosphate (S1P) receptors in the exit of lymphocytes from the thymus and LN, but the underlying mechanisms are not yet understood. Similarly, CD38 was shown to affect DC traffic into and out of tissues by modulating chemokine receptor function, and blockage of the multiple drug resistance protein (MDR)-1 prevented the exit of skin DCs. Desensitisation of chemokine receptors by the high local concentration of chemokines in LNs may also play an important role in releasing lymphocytes from these sites. With regard to afferent lymphatic vessels, expression of secondary lymphoid tissue chemokine (SLC)/CCL21 was shown to be essential for guiding mature, CCR7 expressing DCs to local LNs. However, it is not known at all whether naive, effector, or immune surveillance T cells use a similar mechanism for tissue exit. Finally, the chemokine binding protein D6 marks afferent lymphatic vessels, suggesting involvement in lymphatic leucocyte traffic.

**CHEMOKINES DEFINE “MIGRATORY” T CELL SUBSETS**

Two types of Ag-experienced T cell subset are produced during adaptive immune responses: large numbers of short lived effector T cells and a minor fraction of long lived memory T cells (fig 3). Effector T cells are equipped with receptors for inflammatory chemokines and adhesion molecules that are greatly upregulated during inflammation and, thus, these cells efficiently home to sites of pathogen entry and disease. As an example, fig 4 shows a list of chemokines that were found to be present in the synovial fluid and inflamed tissue of joints with rheumatoid arthritis, and similar situations are found in other acute and chronic inflammatory diseases. Clearly, no known chemokine system is singularly responsible for recruitment of effector cells to inflammatory sites. Also, during the evolution of the disease the composition of inflammatory chemokines induced at these locations may change and thus may affect the composition of the recruited inflammatory cells. Inflammatory responses at early stages are often dominated by neutrophils and monocyte/macrophages, which is reflected by the predominance of chemokines targeting cells of the innate immune system. During later stages, additional...
CHEMOKINES IN INFLAMMATION AND IMMUNE SURVEILLANCE

Figure 4 Complex composition of chemokines and chemokine receptors in rheumatoid arthritis. (A) As an example, inflammatory cells in the affected synovial tissue express Th1 typical chemokine receptors CXCR3 and CCR5 but not the CCR3, which is more prominent on Th2 cells. (B) A multitude of chemokines were detected in the synovial fluid and inflamed synovial tissue. The chemokines are listed according to their receptor selectivity and target cells. Of note, the condition of rheumatoid arthritis leads to the generation of all chemokines necessary for recruitment of the full complement of effector cells. BCA, B cell attracting chemokine; ELC, EBI-1-ligand chemokine; ENA, epithelial cell derived neutrophil activating protein; GCP, granulocyte chemotactic protein; GRO, growth related oncogene; IP, interferon α inducible protein; LARC, liver and activation regulated chemokine; MIP, monocyte chemoattractant protein; Mig, monokine induced by interferon γ; MIP, macrophage inflammatory protein; RANTES, regulated on activation, normal T cell expressed and secreted; SDF-1, stromal cell derived factor 1; SLC, secondary lymphoid tissue chemokine.

Chemokines are responsible for the recruitment of effector T cells, and in autoimmune diseases, such as rheumatoid arthritis, the steady influx of macrophages and T and B cells is maintained by continuous production of corresponding chemokines. The multitude of inflammatory disease associated chemokines is mirrored by the profile of chemokine receptors present on cells within the inflammatory infiltrates (see fig 4). It is interesting to note that several homeostatic chemokines, with primary function in secondary lymphoid tissues (B cell attracting chemokine (BCA)-1/CXCL13, EBI-1-ligand chemokine (ELC)/CCL19 and CCL21) have also been detected in rheumatoid arthritis and several other chronic inflammatory diseases. These chemokines are frequently associated with extranodal follicular structures resembling B cell follicles or even LNs, which is in agreement with their role in LN neogenesis. In addition, these chemokines orchestrate cellular contacts between T cells, B cells, and DCs for the generation of effector cells and, thus, may contribute to disease chronicity. However, currently no direct correlation has been found between the presence of such lymphoid structures and the severity of local inflammation.

Development of low molecular weight compounds for blocking chemokine receptors has become a major goal of the pharmaceutical industry. Obvious targets are receptors that control leucocyte recruitment to inflammatory sites, such as in rheumatoid arthritis, or those with human immunodeficiency virus (HIV)-1 coreceptor function, and several mostly polycyclic lead compounds are currently being examined. Thus far, research has focused on blocking single chemokine receptors. However, given the apparent redundancy of the inflammatory chemokine system (for example see fig 4), compounds with multiple receptor selectivity need to be considered as more efficient anti-inflammatory agents.

In contrast to naive T cells, memory T cells are believed to provide rapid and superior protection against pathogens they have encountered during previous immune responses. Classically, memory T cells are further subdivided into functional subgroups: Th cells are mostly major histocompatibility complex (MHC) class II restricted and produce type 1 interferon γ or type 2 (IL-4, IL-5, IL-13) cytokines whereas subsets of regulatory T cells inhibit T helper responses possibly by cell to cell contact and/or IL-10/TGFβ secretion. Cytolytic T cells are mostly MHC class I restricted and kill target cells by perforin and granzyme dependent processes. Here we wish to emphasise an alternative classification of memory T cells based on their primary residence in distinct body compartments. The three main memory T cell compartments are peripheral blood, secondary lymphoid tissues (spleen, LNs, PPs), and healthy peripheral (extralymphoid) tissues, and the three subsets of T cells residing in these locations are termed effector memory T (TEM) cells, central memory T (TCM) cells, and peripheral immune surveillance T (TSP) cells, respectively (see fig 3). TCM cells are characterised by a LN-homing address code that includes the expression of the chemokine receptor CCR7 and the adhesion molecules CD62L or α4β7 for continuous recirculation through the spleen, LNs, and PPs. A subset of TCM cells—folicular B helper T (TFH) cell—is abundant in LNs and has the chemokine receptor CXCR5 for efficient homing to the B cell compartment. In humans, TCM cells (and TFH cells) have been described as being not differentiated—that is, as being unable to produce inflammatory cytokines or lytic enzymes. This is in contrast with TSP cells that immediately initiate effector functions in response to stimulation. Furthermore, due to lack of CCR7 but presence of receptors for inflammatory chemokines, TSP cells are excluded from LNs and PPs but, instead, behave as innate cells, such as blood monocytes and granulocytes, which are ready to participate in inflammatory responses. It is important to emphasise that this distinction is not strict—that is, TCM cells have the capacity to reacquire CCR7 during restimulation. Collectively, the primary residence of TCM cells is in the secondary lymphoid tissues where they participate in responses to recall antigens whereas TSP cells circulate in blood and wait to be recruited to inflammatory sites.

The third class of memory T cell, called TPS cells, are characterised by their preferential localisation in healthy (extralymphoid) peripheral tissues including normal skin and the respiratory and gastrointestinal tracts (see fig 3). Importantly, TPS cells—unlike TCM and TEM cells—have the capacity to respond to chemokines expressed constitutively in healthy peripheral tissues. As a result, they are largely excluded from peripheral blood and secondary lymphoid tissues (spleen, LNs, and PPs). We wish to emphasise that the large majority (>95%) of T cells reside outside of peripheral blood at any given moment, indicating that TPS cells cannot be studied by examining T cells isolated from peripheral blood. The rare TPS cells found in peripheral blood may be on their way to a distinct peripheral site that produces the homeostatic chemokine(s) to which they respond. Similar to blood TCM cells (and naive T cells) that constantly provide rapid and superior protection against pathogens they have encountered during previous immune responses.
recirculate through secondary lymphoid tissues, TPS cells preferentially home to potential sites of pathogen entry (skin, lungs, and gut) for immune surveillance purposes. In contrast to TCM cells that need the LN environment for stimulation, it has been proposed that TPS cells fulfill their defensive function directly at the site of pathogen entry.

We know much about the highly sophisticated network of chemokines and adhesion molecules involved in the control of inflammatory cells of both the innate and adaptive immune system, and we have some ideas about the regulatory molecules controlling leucocyte traffic within the spleen and LNs. In contrast, we are still at the very beginning of understanding the molecular basis for maintaining the steady state (inflammation unrelated) traffic of peripheral sentinel cells. Inflammatory chemokines are abundant at inflammatory sites and, thus, are relatively accessible for study. Homoeostatic chemokines, in contrast, are produced in low concentrations and are meant to control constitutive recruitment of TPS cells in numbers that are many fold lower than effector cells known to “flood” inflammatory sites. Probably, this may explain the more problematic nature of understanding the trafficking preferences and function of peripheral blood T cells. The identification of skin selective TPS cells suggests that additional TPS cells with homing preferences for alternative peripheral sites, such as healthy airways, lung, and the gastrointestinal and urogenital tracts, may exist. Detailed analysis of the expression of homoeostatic chemokines by the microvasculature feeding these sites may lead the way to understanding the trafficking preferences and function of peripheral immune surveillance T cells.

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