Review Article

Chemokines and Interleukins – The Chemodirectors of Immunity

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Abstract

Chemokines are tiny proteins that regulate the movement of cells. In mammals, a large family of these compounds has been identified, with almost 50 members. There are four groups within this family, each distinguished by the spacing of two N-terminal cysteines, which form disulphide bonds with two other cysteine residues to generate the tertiary structure that chemokines are known for. Interleukins (IL) are a type of cytokine that was once considered to be produced only by leukocytes but has now been discovered to be produced by a variety of different bodily cells. They are involved in immune cell activation and differentiation, as well as proliferation, maturation, migration, and adhesion. They have anti-inflammatory and pro-inflammatory effects as well. Interleukins' major function is to control growth, differentiation, and activation during inflammatory and immunological reactions. Interleukins are a wide category of proteins that connect to high-affinity receptors on cell surfaces and can cause a variety of responses in cells and tissues. They work in both a paracrine and autocrine manner.

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Chemokines are a large family of small secreted proteins that control the trafficking of specific leukocyte subpopulations both in physiological and pathological process. They belong to a family of cytokines. It has been noted that these mediators play an important role in embryonic development, hematopoiesis, angiogenesis, host defense, inflammation, immunity, AIDS, and cancer. According to the arrangement of the cysteine residues near the amino terminus, chemokines are classified into four families: CC, CXC, C, and cx3C. Chemokines interact with seven transmembrane domain receptors coupled to trimeric G protein and activate multiple intracellular signaling pathways that eventually lead to cytoskeletal rearrangements and cell mobilization. In addition to their roles in cell recruitment, chemokines may induce leukocyte activation (degranulation and synthesis of proinflammatory mediators) and control lymphocyte differentiation and effector function. The chemokines can be broadly classified into inflammatory and lymphoid. The inflammatory chemokines are induced by pathogens and proinflammatory stimuli in both resident tissue cells and leukocytes.

Their receptors are expressed on phagocytes such as neutrophils, eosinophils, and monocytes, in immature dendritic cells (DCs) and in some stages of T cell development. These chemokines play a role in innate immunity (i.e., in the body defense against pathogens) and in inflammation. In general, mice with deletions in a gene encoding a single inflammatory chemokine or receptor exhibit a mild or no apparent phenotype unless exposed to specific inflammatory situations w6,7x. Lymphoid chemokines are constitutively expressed in discrete microenvironments within lymphoid tissues, skin, and mucosa. They are involved in basal leukocyte trafficking and homing, as well as in development. Their receptors are expressed on T cells, on B cells, and in mature DCs. These chemokines direct the positioning of lymphocytes to the specific T cell and B cell areas

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of secondary lymphoid organs. This facilitates the interactions between DC–T cells and T cells–B cells at the appropriate localizations, necessary for the development of an immune response.

The development and differentiation of immune cell precursors occur in the primary lymphoid organs—the bone marrow and thymus—and these processes are under the fine control of chemokines. T cell development in the thymus depends on the interaction of epithelial-derived CCL21, CCL25, and CXCL12 with CCR7, CCR9, and CXCR4, respectively, expressed on T cell progenitors. T cell progenitors first enter the thymus in response to CCL21, CCL25, and CXCL12, which are produced by the thymic epithelium and neighboring structures. Double-negative thymocytes are guided past the corticomedullary junction by CCR7- and CXCR4-mediated signals. CCR9 expression then guides these cells into the subcapsular zone. Subsequent developmental progression from double-positive through single-positive thymocytes occurs in concert with their migration into the medulla, which is dependent on CCR7 and perhaps another yet to be defined chemokine. Mature thymocytes then upregulate the sphingosine-1-phosphate (S1P) receptor 1, which allows them to ultimately migrate out of the thymus and into the blood in response to S1P produced by thymic pericytes at the corticomedullary junction.

CXCL12/CXCR4 interactions are necessary for normal bone marrow development of multiple immune cell lineages, including B cells, monocytes, macrophages, neutrophils, natural killer cells, and plasmacytoid DCs. CXCL12/CXCR4 interactions promote the retention of both developing and mature immune cells within the bone marrow. Thus, blockade of CXCR4 signals using antagonists leads to abnormal and increased mobilization of neutrophils into the peripheral blood. As neutrophils mature in the bone marrow, their expression of CXCR4 progressively decreases, permitting neutrophil release from the bone marrow and their positioning in the blood and peripheral tissues. Normal downregulation of CXCR4 appears to play an important role in controlling bone marrow residence of neutrophils under homeostatic conditions, but other chemokines may be involved. When compared with wild-type neutrophils in gnotobiotic mice, CXCR2-deficient neutrophils exhibit enhanced bone marrow retention and reduced numbers in the peripheral blood. However, this likely plays a minor role in neutrophil homeostasis because neutrophils doubly deficient in both CXCR2 and CXCR4 exhibit the CXCR4-deficient phenotype of constitutive mobilization. Indeed, the primary importance of CXCR4 in neutrophil homeostasis has been illustrated in patients with warts, hypogammaglobulinemia, infections, and myelokathexis syndrome. This syndrome is most commonly caused by mutations in CXCR4 that enhance responsiveness to CXCL12 either by impairing CXCR4 internalization and chemokine-induced desensitization or by leading to enhanced or sustained chemokine signaling. Neutrophils are unable to normally decrease responsiveness to CXCL12 and are therefore trapped within the bone marrow, resulting in peripheral neutropenia. In contrast to granulocytes, homeostatic release of monocytes from the bone marrow is dependent on both CXCR4 and CCR2 signaling.

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Conflicts of interest

There are no conflicts of interest.