

Charles Mackay and Bernhard Moser

Traffic of T lymphocytes

Summary

T cells form an integral part of the adaptive arm of immunity and are characterized by a clonotypic T cell antigen receptor (TCR) composed of either V α - and V β -gene segments ($\alpha\beta$ T cells) or V γ - and V δ -gene segments ($\gamma\delta$ T cells). Here, we focus on $\alpha\beta$ T cells, which make up the majority of T cells within blood and peripheral tissues of healthy individuals. They are further divided into numerous subsets defined by their mode of antigen recognition (expression of CD4 *versus* CD8), by their antigen experience (naïve *versus* effector/memory T cells), by their state of differentiation (non-polarized *versus* differentiated T cells) and by the longevity. Here, we give an update on the current understanding of the molecular mechanisms controlling the positioning and relocation of mature T cells. Accordingly, T cells in peripheral blood and tissues can be subdivided by their distinct migration properties defined by the combination of chemokine receptors and adhesion molecules they express and by their responsiveness to chemokines. The chemokine systems controlling T cell recruitment to sites of inflammation and disease are targets for therapeutic intervention.

Key words: T cell, priming, migration, homing, naïve cells, memory cells, effector cells, lymph node, spleen, peripheral tissue

William W. Agace and Bernhard Homey

Lymphocyte homing to peripheral epithelial tissues

Summary

Leukocyte trafficking provides important immune functions to the host. For more than a decade the tissue-specific homing pathways of effector memory T cells have been appreciated. With the rapid identification of chemokine ligands and their receptors together with the unraveling of the complex chemokine networks during homeostasis and inflammation important insights into the underlying mechanism of tissue-specific migration of lymphocytes have recently been achieved. In this overview, current concepts on the role chemokines and their receptors on lymphocyte trafficking into epithelial surfaces are summarized and recent observations on the imprinting of tissue-specific homing capacities by the local microenvironment are highlighted.

Key words: chemokine, chemokine receptor, gut associated lymphoid tissue, lamina propria, IgA, dendritic cell, intraepithelial lymphocyte, tropism, intestine, $\alpha_4\beta_7$, skin, cutaneous lymphocyte associated antigen, homeostasis, inflammation

Chenggang Jin and Craig T. Morita

Chemokine biology of NK cells and $\gamma\delta$ T cells

Summary

Natural killer (NK) cells and $\gamma\delta$ T cells mediate immunity against intracellular pathogens and malignant tumors. Chemokines and chemokine receptors play important roles in the migration and function of these immune cells. Chemokine receptors on NK and $\gamma\delta$ T cells direct them to specific anatomic locations or to sites of infection. For example, the local expression of CCL25

guides the migration of $\gamma\delta$ T cells to the small intestine via the chemokine receptor CCR9 whereas CCR10 guides murine dendritic $\gamma\delta$ T cells to skin. The expression of the "neutrophilic" chemokine receptors, CXCR1 and CXCR2, by NK and effector $\gamma\delta$ T cells allows their rapid recruitment to inflamed sites where CXCL8 is produced. NK and $\gamma\delta$ T cells not only express a range of chemokine receptors but also produce chemokines such as CCL3, CCL4, CCL5, and CXCL8. The production of inflammatory chemokines by NK and $\gamma\delta$ T cells plays an important role in their effector functions through the recruitment of both innate and adaptive immune cells.

Key words: chemokines, chemokine receptors, NK cells, T-cell antigen receptors gamma-delta, memory V γ 2V δ 2 T cells, CXCR1, CXCR2

Federica Sallusto, Alfonso Martín-Fontecha and Antonio Lanzavecchia
Dendritic cell traffic control by chemokines

Summary

The capacity to migrate to sites of inflammation and from there to the T cell areas of secondary lymphoid organs is a fundamental aspect of dendritic cell (DC) biology. DC precursors and DCs in their immature stage express receptors for inflammatory chemokines and are attracted to sites of inflammation where they capture antigen and receive maturation stimuli by microbial products and inflammatory cytokines. Mature DCs switch the pattern of chemokine receptors expressed and migrate to lymphatics and T cell areas guided by CCR7. Upon stimulation by microbial products DCs also produce large amounts of chemokines that contribute to the initial phases of inflammation and attract naive T cells in secondary lymphoid organs. The encounter of naive T cells with antigen-carrying stimulatory DCs induce their activation, and differentiation to effector cells. The pathways of DC migration in vivo are highly regulated and represent interesting targets for immune intervention.

Key words: dendritic cells, interferon-producing cells, migration, chemokine receptor, chemokine, Toll like receptor, CCR7, naive T cell, lymph node

Mario Mellado, Carlos Martínez-A., José Miguel Rodríguez-Frade
Chemokine receptor-mediated signal transduction

Summary

Chemokines signal through interaction with seven-transmembrane, G protein-coupled receptors. The way in which chemokines exert their functions no longer adjusts to the simple view in which one chemokine binds to one receptor coupled to a G protein-mediated signaling pathway. Here we will examine recent findings showing how a chemokine interacts with several chemokine receptors specifically expressed on the surface of a cell. We will consider how this interaction should be seen in the context of the variety of chemokine and non-chemokine receptors and stimuli that participate in the net cellular response. Finally, we will analyze how this response can be mediated through distinct types of G proteins or non-G protein-related pathways.

Key words: GPCR, chemokine, receptor, homodimerization, heterodimerization, G protein, JAK, STAT, SOCS, inflammation4

Lixin Liu and Paul Kubes

Chemokines in leukocyte transendothelial migration

Summary

Chemotactic migration of leukocytes from the blood stream across endothelium into the underlining tissues is crucial to inflammation and many other aspects of immunity in the body. Chemokines are a family of chemotactic cytokines and key players in inducing leukocyte transendothelial migration. Recent studies suggest that chemokines interact with endothelial cells and activate integrins on rolling leukocytes to trigger firm adhesion to endothelium, a prerequisite for transmigration. Chemokine-induced leukocyte transendothelial migration and subsequent chemotaxis in tissue are enhanced by prior selectin-ligand interactions. Intracellular signalling molecules, particularly those in p38 mitogen-activated protein kinase signalling pathway, play a key role in mediating chemokine-induced leukocyte transendothelial migration and in chemotaxis in tissues of inflammation.

Key words: chemokines, leukocytes, transmigration, endothelial cells, inflammation, cellular interactions, selectins, integrins, signal transduction

Mariagrazia Uguccioni and Basil O. Gerber

Natural chemokine antagonism and synergism

Summary

In homeostasis as well as in inflammation, various chemokines are often expressed concomitantly and simultaneously, creating a veritable chemokine "milieu". Recently, evidence has been accumulating that collectively suggests a previously unrecognized regulatory role for this milieu in leukocyte trafficking. On one hand, these effects can be negative through receptor inhibition exerted by either native or protease-modified chemokines, which mainly act by competitive antagonism. On the other hand, a positive regulation seems to apply as well in the form of synergism. These synergistic effects seem to stem from either interactions between chemokine receptors, or from the formation of heteromeric complexes that are composed of the native chemokines themselves. Here, we summarize the data currently available on these regulatory effects, and discuss the known or presumed molecular mechanisms as well as the possible consequences of these novel types of regulation.

Key words: chemokine, G protein-coupled receptor, synergy, antagonism, cooperativity, priming, protease, expression, regulation

Ning Zhang and Joost J. Oppenheim

Crosstalk between chemokine, opioid and vanilloid receptors

Summary

Chemokine receptors serve as a bridge between the immune and neural systems. Neuropeptides, such as opioids, inhibit chemokine receptor function on leukocytes by activating Gi protein and calcium-independent protein kinase C. Conversely, during inflammation, chemokines similarly regulate neuronal sensing. Activation of chemokine receptors on neurons desensitizes the

analgesic μ -opioid receptor and concomitantly enhances the sensitivity of a pain receptor, TRPV1, via protein kinase C-dependent phosphorylation, resulting in hyperalgesic effects.

Key words: chemokine receptors, opioid receptors, Vanilloid receptors, receptor crosstalk, pain, inflammation, hyperalgesia, analgesia, protein kinase C, GiPCR, calcium influx.

Osamu Yoshie

Antimicrobial and related activities of chemokines

Summary

Chemokines are now known to play pivotal roles in both innate and acquired immunity primarily through their chemotactic activity for various leukocyte classes and subsets. The family of antimicrobial peptides, also called natural antibiotics, constitutes the important immediate effector molecules against invading microorganisms. Accumulating evidence has revealed that the families of chemokines and antimicrobial peptides have substantially overlapping functions. While a number of antimicrobial peptides are chemotactic for selected classes and subsets of leukocyte, many chemokines have a substantial microbicidal activity against a broad spectrum of microorganisms. Furthermore, CXCL16, a transmembrane-type chemokine, was originally identified as a scavenger receptor termed SR-PSOX (scavenger receptor that binds phosphatidylserine and oxidized lipoprotein). Subsequently, a number of chemokines have been shown to display a similar binding activity for typical scavenger receptor ligands including oxidized lipoprotein and bacteria [1]. Thus, the family of chemokines may have substantial functional overlaps with the families of antimicrobial peptides and scavenger receptors. The overlapping functions of these distinct molecular families may have an evolutionary basis stemming from an ancient mode of recognition of pathogens and may represent a certain aspect of the pattern recognition of innate immunity.

Alexandra Lucas, Dana McIvor and Grant MacFadden

Virus-encoded chemokine modulators as novel anti-inflammatory reagents

Summary

Many viruses encode and express immunomodulatory proteins that protect the virus from attack by elements of the innate and acquired immune response systems. Some of these viral anti-immune regulators are expressed as secreted proteins that engage extracellular elements of the chemokine system. We review here viral chemokine binding proteins and chemokine mimics that have been tested as anti-inflammatory reagents in animal models of diseases which are known to be mediated by upregulation of chemokines. The potential for the development of such viral chemokine modulators as novel therapeutics for immune-based or inflammatory disorders is discussed.

Paola Romagnani, Laura Lasagni and Sergio Romagnani

Chemokine receptors in tissue cells and angiogenesis

Summary

Chemokines are not only essential for the recruitment of leukocytes in the inflamed tissues, but they also play other important functions. First, they are involved in several steps of

embryogenesis. Secondly, a number of chemokine receptors are constitutively expressed by resident epithelial cells from different tissues, where they can be responsible for proliferation, cell migration, maintenance and renewal of epithelia, apoptosis, and wound healing response. Moreover, chemokines are active on vasculature-associated pericytes and smooth muscle-like microvessel mural cells, thus contributing even at this level to the process of wound healing. Of particular importance is the function of some chemokines in the control of angiogenesis. Indeed dysregulated production of angiogenic chemokines may ultimately lead to tumor progression. Chemokines can also regulate some pathophysiologic processes in the central nervous system and in the migration and differentiation of osteoclasts.

Key words: chemokine receptors, angiogenesis, pericytes, tumor

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