

Summaries

Introduction

Raffaele Badolato and Silvano Sozzani

Lymphocyte trafficking: from immunology paradigms to disease mechanisms

Summary

Gao Ping, Ji Ming Wang, O. M. Zack Howard, and Joost J. Oppenheim

Biology of chemokines

This overview of chemokine biology covers how chemokine interaction with their receptors and initiate a sequence of internalization of receptor-ligand complexes, signal transduction pathways, and activates directional migration or desensitize cells. The biological consequences of chemokines include crucial roles in development, organogenesis, cellular trafficking, angiogenesis, and inflammatory responses associated with innate and adaptive immunity. We have discussed in brief how viral pathogen mimic chemokine ligands and or receptors and thus preempt or usurp host defenses mechanisms to their own advantage. Finally, we have outlined how inactivation of chemokine genes reveals their specialized roles in host defense. This book represents a major effort to fill in the vast gaps in this overview and provide more detailed, documented and convincing exposition of these and other chemokine activities we failed to touch on altogether.

Summary

Gabriela Constantin and Carlo Laudanna

Lymphocyte – endothelial cell interaction

Lymphocyte recirculation is essential to immune system function and is strictly dependent of the capability of lymphocytes to interact with the endothelial cells. Lymphocyte recognition of the endothelium follows a multi-parametric logic based on the concurrent involvement of adhesion molecules and activating factors. Integrin-dependent arrest of circulating lymphocytes is critical to the subsequent trans-endothelial migration and is finely regulated by complex intracellular signaling events generated by apical chemokines and, likely, by selectins. The simple elegance of the combinatorial model of lymphocyte recruitment not only models the process at mechanistic level but also provides a conceptual framework accounting both for qualitative and quantitative variations of pro-adhesive micro-vascular cues whose combination determines the diversity of lymphocyte recruitment and of the whole immune response.

Key words: Adhesion, integrins, selectins, chemokines, homing, lymphocytes, leukocytes, cell trafficking, signal transduction, integrin affinity, chemotaxis, lymphoid organs, immunity.

Summary

Mara Messi and Federica Sallusto

Chemokine receptor expression in effector and memory T cell subsets

Chemoattractant receptors have emerged as the most important determinants for T lymphocyte migration and positioning in both the afferent and efferent phase of the adaptive immune response. The recruitment of different types of lymphocytes to lymphoid and non-lymphoid tissues under steady state or inflammatory conditions is governed by the regulated expression of receptors on lymphocyte subsets, and the circumstances of ligand expression in tissues. In addition, chemoattractant receptors serve as important markers for functional subsets of effector and memory T cells, because cell migration is closely linked to functional roles. In this chapter we will first consider the process of naive T cell activation and differentiation with particular emphasis on the coordinate regulation of effector function and migratory capacity. Then, we will describe the property and role in the immune response of memory T cell subsets that are identified according to the expression of different chemokine receptors.

Key words: Th1, Th2, central memory, effector memory, IFN- γ , IL-4, skin, gut, lymph node.

Summary

Silvano Sozzani, Annalisa Del Prete, Karel Otero, Amerigo Santoro, William Vermi and Fabio Facchetti

Migration of dendritic cell subsets

Dendritic cells (DC) are professional antigen presenting cells that play a pivotal role in the activation of adaptive immunity. Tissue invasion by pathogens induces the recruitment of blood DC to the site of infection and to their subsequent migration to secondary lymphoid organs. This complex process relies on the expression and regulation of chemotactic receptors on the surface of migrating DC and on the activation of adhesion molecules that allow DC to properly interact with both blood and lymphatic vessels. In the absence of correct tissue localization, DC fail to promote proper immune responses. DC represent a heterogeneous population of cells that differ for their ability to interact with pathogens, the production of cytokines, the induction of adaptive immunity and for their migration properties and tissue localization. The attempt of this chapter is to review the migration pathways of DC subsets.

Key words: Dendritic cells, chemokines, endothelial cells, adhesion molecules, signal transduction.

Summary

Angela Gismondi and Angela Santoni

Migration of NK cells

Natural Killer (NK) cells represent a distinct population of circulating and tissue resident lymphocytes which play an important role in the early phases of immune responses against microbial pathogens, by exhibiting cytotoxic functions and secreting a number of cytokines and chemokines.

NK cells comprise 5-20% of peripheral blood lymphocytes and are present in spleen, liver, bone marrow, whereas are rare in thymus, and lymph nodes. Moreover, they are the most abundant class of lymphocytes in the mucosal tissues of maternal uterus and are rapidly recruited in the the parenchima of injured organs during inflammation, viral infections and tumor growth.

NK cell migration across endothelium and into the tissues is governed by integrated signals initiated by a plethora of chemotactic factors and adhesion molecules belonging to selectin, integrin, and immunoglobulin families as well as chemokines. The differences in chemokine receptor expression together with distinct adhesive properties, imply that NK cell subsets and activated NK cells have different routes of circulation and trafficking patterns.

Key words: NK cells; uterine NK cells; adhesion molecules; integrins; chemokine receptors; chemokines; migration; chemotaxis; lymphocytes homing; signal transduction; protein tyrosine kinases (pTKs).

Summary

Nicholas W. Lukacs and Matthew Schaller

Lymphocyte trafficking and chemokine receptors during pulmonary disease

Although a number chemokine receptors that have been described that mediate the accumulation of T lymphocytes to the lung during disease progression, there continues to be a paucity of data regarding their specific function during certain pulmonary diseases. Questions persist on whether the differential receptor display on T cell subsets described in *in vitro* experiments, represent those that cause accumulation during disease. The diversity of chemokine production and the promiscuous pattern of chemokine-chemokine receptor interactions have made the identification of individual chemokine or chemokine receptor targets for therapeutic intervention extremely difficult. Interestingly, several of the "lead" candidates for targeting during chronic asthmatic disease are receptors that appear to bind a single or at most two chemokines, including CXCR4, CCR4, CCR6, and CCR8. Choosing the proper targets for specific disease phenotypes will only occur after careful coordinated animal modeling experiments coupled with translational research efforts in human disease.

Summary

Ineke M. Dijkstra and Richard M. Ransohoff

Lymphocyte migration to the brain

Lymphocyte migration into the central nervous system (CNS) is tightly regulated and involves passing of different blood-CNS barriers, which requires the presence of various molecules. In this chapter, we discuss current understanding of molecular mechanisms for lymphocyte entry into the CNS in health and disease. Moreover, varying mechanisms at specific CNS anatomical sites are addressed. Most experimental evidence supporting the currently suggested trafficking mechanisms is derived from studying multiple sclerosis (MS) and its animal models, both characterized by extensive lymphocyte infiltration in the CNS. Under healthy conditions infiltration of lymphocytes is limited to the cerebrospinal fluid (CSF) and suggested to play a role in immunosurveillance. The inflamed CNS provides lymphocytes with additional cues, by upregulation of adhesion molecules and the expression of chemokines, enabling further entry into the CNS parenchyma.

Key words: Central nervous system, Neuroinflammation, Blood-Brain-Barrier, Choroid plexus, Adhesion molecule, Chemokine, Chemokine receptor, Multiple Sclerosis, Experimental Autoimmune Encephalomyelitis, Intravital Microscopy, Immune surveillance.

Summary

Takashi Wada, Hitoshi Yokoyama, Shuichi Kaneko and Kouji Matsushima
Lymphocyte migration to the kidney

Evidence is accumulating to show the pivotal role of lymphocyte infiltration in the kidney in the pathogenesis of various renal diseases. Cytokines, chemokines, adhesion molecules and growth factors underlie molecular mechanisms of lymphocyte trafficking and their activation in the inflammatory renal diseases. Interactions between infiltrating inflammatory cells and resident renal cells involved in the phase-specific renal disorders eventually lead to the development of renal fibrosis. The selective intervention of these molecules might have the therapeutic potential to modulate renal inflammatory responses, thereby halting the progression of renal diseases. This review focuses on specific interaction between certain proinflammatory mediators, especially chemokines and lymphocyte migration to the kidney in the pathogenesis of human and experimental renal diseases.

Key Words: Lymphocyte, kidney, chemokine, chemokine receptor, inflammation, fibrosis.

Summary

Nadia Giarratana, Giuseppe Penna, Susana Amuchastegui, Roberto Mariani and Luciano Adorini
Leukocyte Migration to Pancreatic Islets: a Critical Step in the Pathogenesis of Type 1 Diabetes

Type 1 diabetes (T1D) is a Th1 cell-mediated autoimmune disease characterized by leukocyte infiltration into the pancreatic islets targeting insulin-producing β cells. Thus, a critical check-point in the pathogenesis of T1D is represented by the migration of pathogenic Th1 cells to the pancreas, where they can meet and contribute to destroy islet β cells. Migration of pathogenic cells to the pancreas appears to be induced by the capacity of pancreatic β cells themselves, as well as other islet cell types, to produce chemokines potentially able to attract effector cells involved in β cell death. This could occur via ligation of toll-like receptors (TLRs), surface molecules able to recognize distinct pathogen components that are expressed by mouse and human islet cells. TLR engagement by pathogen-derived ligands markedly enhances proinflammatory chemokine production by islet cells. Thus, the association between infections and T1D could reflect the triggering of signal transduction via TLRs expressed by islet cells, in particular TLR3 and TLR9, leading to an enhanced production of proinflammatory chemokines by islet cells that contributes to create the conditions for an autoimmune attack.

Key words: Chemokines, Toll-Like receptors, vitamin D analogs, islet cells, NOD mice.

Summary

Christopher A. Haskell, Richard Horuk
Controlling Leukocyte Trafficking in Disease

It is widely recognized that the therapeutic control of leukocyte migration could be an ideal mechanism by which to control human disease. For the last decade, there has been extensive research and development on using chemokine receptor antagonists to reduce the extent of

migration into inflammatory lesions. The control of homeostatic, or basal, leukocyte trafficking is an emerging area of drug development, and approaches to modulate this process are also discussed. This article provides a brief overview of the clinical programs that are investigating small molecule antagonists targeting specific chemokine receptors. In addition, there are a number of emerging tools that may allow for the promiscuous targeting of multiple receptors, including modified chemokines, viral proteins and dual receptor peptide antagonists. The current state and potential for these approaches are also presented.

Key words: Chemokine, leukocyte, monocytes, lymphocyte, dendritic cell, antagonist, dual receptor antagonist, inflammatory, homeostatic, antibody, multiple sclerosis, transplant, FTY-720.

Summary

Amos Etzioni

Leukocyte adhesion deficiency (LAD)

The crucial role of the $\beta 2$ -integrin subfamily in leukocyte emigration was established after leukocyte adhesion deficiency (LAD) I was discovered. Patients with this disorder suffer from threatening bacterial infections. In its severe form, death usually occurs in early childhood unless bone marrow transplantation is performed.

The LAD II disorder clarifies the role of the selectin receptors and their fucosylated ligands such as SLeX. In vitro and in vivo studies establish that this family of adhesion molecules is essential for neutrophil rolling, the first step in neutrophil emigration through the blood vessel. Clinically, patients with LAD II suffer from a less severe form of disease, resembling the moderate phenotype of LAD I. This may be due in part to the ability of LAD II neutrophils to emigrate when blood flow rate is reduced and to the observed normal T and B lymphocyte function in LAD II as opposed to LAD I.

LAD III emphasizes the importance of the integrin activation phase in the adhesion cascade. Although the primary defect is still unknown, it is clear that the molecule activation processes for all hematopoietic integrins are defective, leading to severe infection as observed in LAD I and to marked increase tendency for bleeding problems.

Key words: Adhesion, Leukocyte, Integrin, Selectins, Chemokines, LAD syndrome, Fucose , Sialyl Lewis X, Rap1.

Summary

Gerben Bouma, Adrian J. Thrasher and Siobhan Burns

Wiskott-Aldrich Syndrome as a model of cytoskeleton defects

Dynamic rearrangement of the actin cytoskeleton is key for many leukocyte functions during the generation of normal immune responses. The Wiskott-Aldrich Syndrome protein (WASp) is an important cytoskeletal regulator in haematopoietic cells, integrating multiple signals from cell surface receptors to temporally and spatially control actin polymerisation. Mutations in the encoding gene give rise to Wiskott-Aldrich Syndrome (WAS), a human X-linked immunodeficiency disease in which functional defects have been described for most non-erythroid haematopoietic cells. Here we discuss our current understanding of how WASp-deficiency impacts leukocyte function. This model disorder serves to highlight the importance

of the cytoskeleton for normal immunity and the relevance of cytoskeleton defects for human disease.

Key words: Wiskott-Aldrich syndrome, Wiskott-Aldrich syndrome protein, Immune response, Actin cytoskeleton, Cell migration, Leukocyte homing, Immunodeficiency.

Summary

Raffaele Badolato, Vanessa Bonomi und Laura Tassone
From CXCR4 mutations to WHIM syndrome

WHIM syndrome is a paradigmatic hematopoietic disorder which is characterized by abnormal leukocyte trafficking among lymphoid organs, thereby emphasizing the immunoregulatory role of chemokines and chemokine receptor. The identification of heterozygous mutations of CXCR4 in the majority of patients with autosomal dominant transmission of WHIM syndrome has revealed the pathogenesis of this primary immunodeficiency. CXCR4 mutations in WHIM patients result in the loss of the last 10-19 residues of the intracellular C- terminal tail where numerous serine and threonine residues are located. Several studies have shown that loss of the CXCR4 intracellular tail prevents its internalization and desensitization in response to CXCL12/SDF1, suggesting that C-terminal region is involved in the regulation of its ligand-dependent endocytosis. Because of the defective CXCR4 internalization leading to continuous activation of the receptor and prolonged leukocyte adhesion to microvascular endothelium, leukocytes and hematopoietic precursors are actively retained in the bone marrow of WHIM patients. In this context, senescent neutrophils, which express the highest levels of CXCR4 and are particularly responsive to CXCL12, are attracted and sequestered in the bone marrow where CXCL12 is markedly expressed. Enhancement of CXCR4-mediated responses of B lymphocytes may account for the defect of B cell homeostasis and for the hypogammaglobulinemia.

Keywords: Warts, Hypogammaglobulinemia, neutropenia, CXCR4, CXCL12, chemotaxis, lymphocytes, myelokathexis, bone marrow, recurrent infections, primary immunodeficiency.



<http://www.springer.com/978-3-7643-7308-5>

Lymphocyte Trafficking in Health and Disease

Badolato, R.; Sozzani, S. (Eds.)

2006, X, 253 p., Hardcover

ISBN: 978-3-7643-7308-5

A product of Birkhäuser Basel