Editorial

Understanding the ingenuity of chemokines and their receptors

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Several articles in this issue are devoted to various aspects of chemokines and their receptors. Although this topic is not new to the Journal, it is a rapidly growing area that requires frequent review. Recent reviews have focused on their role in cell trafficking as it relates to allergic disease pathophysiology.[1-6] Chemokine receptors belong to a much larger family of G protein–coupled 7-transmembrane receptors (Fig 1) that include rhodopsin, adrenergic receptors, histamine receptors, and others that snake in and out of the cell membrane (hence the name *serpentine* and the cover art). Relatively unknown until the 1980s, the chemokine field has exploded in the last 2 decades, leading to the need for a major change in nomenclature in 2000 to account for the 20 or so receptors and about 50 known ligands.[7] Along with this surge of new knowledge comes the understanding that chemokines and their receptors do much more than simply facilitate cell migration. Indeed, biologic functions beyond alteration of leukocyte adhesion and migration attributed to chemokines include cell growth and proliferation, microbial pathogenicity, tumor metastasis, and inflammation. Another aspect that has clearly evolved in our understanding of chemokines is the selective induction of release of stereotypic patterns of chemokines during different inflammatory and immunologic responses and the equipping of tissue-resident and migratory cells with subsets of chemokine receptors, allowing an extreme fine tuning of cellular responses that are elicited downstream of chemokine production. The reader is referred to a series of outstanding recent reviews published elsewhere that have summarized many of these aspects of chemokine and chemokine receptor biology.[8-13]

In the Current Reviews article, Schaller et al[14] review the role of respiratory viral infections and chemokines in asthma. This article does an excellent job of summarizing both the knowledge and holes in our understanding of how viruses, such as RSV, influenza, rhinovirus, and adenovirus, can alter, initiate, or predispose to diseases like asthma, bronchiolitis, and chronic obstructive pulmonary disease. Because specific chemokine and chemokine antagonists are not yet available, the current state-of-the-art investigations in human subjects involve analysis of induction of patterns of chemokines and examination of parallel patterns of chemokine receptors during induced or naturally occurring viral infections of the airway. Available data, as reviewed in this article, strongly implicate CCL3 (macrophage inflammatory protein 1α), CCL5 (RANTES), CCL11 (eotaxin), and CXCL8 (IL-8) in viral predisposition to asthma and asthma exacerbations. The authors deftly review parallel literature in mouse models, which, although helpful from the standpoint of having access to specific antagonists or knockouts, are yet of unclear use in defining or predicting similar patterns of chemokine biology in viral inflammation of human airways. This drawback, along with the issues that not all human chemokines and chemokine receptors have mouse orthologs and that not all viruses capable of infecting human airways can infect mouse airways, adds additional pitfalls to these approaches. Nevertheless, with chemokine and chemokine receptor antagonists well into development,[8,15] the ultimate proof of chemokine involvement in disease should be soon forthcoming.

In the Molecular Mechanisms review, Pease and Williams[16] adeptly review chemokines and their receptors in allergic disease. They provide an outstanding updated perspective and summary regarding chemokine and chemokine receptor interactions, how such interactions lead to a cellular signal, and how chemokines act on a variety of cell subsets involved in allergic inflammation, including dendritic cells, T cells, mast cells, basophils, and eosinophils. Another admirable aspect of this review is that it reviews available human data on the role of chemokines and their receptors in allergic diseases and allergen challenge models and how mouse models have been used to

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FIG 1. A "human" model of a chemokine receptor shown binding a yellow-clothed "extracellular" chemokine. Concept and photograph by Andrea Meiser, PhD, National Heart and Lung Institute, Imperial College London. Reproduced with permission from www1.imperial.ac.uk/medicine/about/divisions/nhli/respiration/leukocyte/chemo/.

explore mechanistic involvement of chemokines and their receptors in these responses. Table I in this article provides a handy summary of those chemokine receptors implicated in allergic inflammation pathophysiology. Finally, this review touches on a number of strategies being used to antagonize chemokines and their receptors, especially in the context of those relevant to allergic inflammation, supplementing other recent reviews on this topic.[8,17-19] It also pairs nicely with the Images in Allergy and Immunology piece by Fiset and Hamid[20] that provides numerous striking examples of how selected chemokines display altered expression in the airways and skin during acute and chronic allergic conditions. These reviews of eosinophil-active chemokines are timely given that in the previous issue of the Journal, Klion et al[21] provided a workshop summary on approaches to the treatment of hypereosinophilic syndromes, and as part of the discussion of future approaches to the treatment of these disorders, chemokine receptors, such as CCR3, are mentioned.

Feeney et al,[22] in this issue, provide an example of how cells and chemokine receptors have evolved to deal with the consequences of HIV infectivity. These investigators describe a case study of a perinatally HIV-infected individual who is now 15 years old who generated an atypically strong anti-HIV T-cell response and remains symptom free with undetectable virus after more than 5 years off antiretroviral therapy. This adolescent was found to have heterozygosity for the so-called Δ32-CCR5 mutation (a 32-bp deletion in the gene encoding for the CCR5 coreceptor used for HIV entry). This represents the first description of such a case, even though adults with nonprogressive HIV disease having the Δ32-CCR5 homozygous mutation have been previously reported.[23] In a Letter to the Editor in this issue of the Journal, Shearer et al[24] describe the rationale for the use of biologic inhibitors of HIV entry. In particular, PRO 542 (a recombinant CD4-IgG2 molecule) and PRO 140 (a humanized antibody against CCR5) are examined for their ability to inhibit pretreatment HIV isolates of patients enrolled in the Pediatric AIDS Clinical Trials Group protocol 351. Although the sample size is small, this preliminary report is extremely encouraging in that both the CD4-targeted and CCR5-targeted protein-based therapeutics inhibited with impressive potency the *in vitro* growth of 2 types of HIV viruses from infected children (those with R5 and R5X4 tropism), lending credence and enthusiasm to the use of mAbs and Ig infusion proteins as alternative molecular treatments for HIV-infected patients. Similar biologic approaches, as well as small molecules, are likely to be used for other inflammatory conditions as well, and as physicians, we eagerly await the potential benefits that future chemokine-related therapies could someday offer to our patients.

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