Through the looking glass: the diverse in vivo activities of chemokines

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Just over a decade ago, a small group of scientists was struggling to understand the significance of a human monocyte-derived neutrophil chemotactic factor (MDNCF)/neutrophil-activating factor (NAF), which possessed peptide sequence similarity to other putative host defense cytokines (1, 2). The early structural and biological studies of this factor, which was later named interleukin-8, provided the foundation for our current understanding of the chemistry and functions of a large group of signaling factors, the products of the chemokine superfamilies (3). These early investigators, perhaps, failed to anticipate the magnitude of the topic they had begun to study: the term “chemokine” is now taken to encompass 4 different structural families, comprising over 50 ligands that interact with at least 17 different receptors (Figure 1).

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BCA-1 may play a dual role, promoting both B-cell homing during normal conditions and the pathologic accumulation of B cells in Helicobacter-induced disease. The present studies also provide some of the first information correlating bacteria and/or bacterially derived products with the local expression of a specific chemokine and with ensuing B-cell accumulation. This study is a sequel to early investigations that indicated that the receptor for BCA-1 (CXCR5) is highly expressed on circulating blood B lymphocytes and on Burkitt’s lymphoma cells, and that mice deficient in this receptor do not have normal follicle and germinal center formation in the spleen and Peyer’s patches (15–17). Thus, the precedent for BCA-1/CXCR5 expression and the elicitation of B cells had been established, but the potential contribution of this ligand/receptor pair in the pathology of specific diseases had not been well explored. It should be underscored that the biology of B-cell homing and chemotaxis is not well understood and that all of the above studies have provided significant insight toward defining this biological phenomenon.

As manuscripts relating to the structure, function, and in vitro cell biology of chemokines fill volumes of scientific journals, investigations like those by Mazzucchelli et al. begin to address the physiological relevance of chemokines. Taking a broad view of the field, chemokine researchers have developed a wealth of recombinant proteins, neutralizing antibodies, and genetically altered mice; with these tools, they have learned something about a few members of the chemokine family, but very little about most of them. As the last decade has provided researchers with a plethora of ligand and receptor targets to study, the next decade will likely provide a more complete understanding of the complex role that chemokines play in vivo in homeostasis and disease.

As Alice said after reading the poem “Jabberwocky” in Through the Looking Glass and What Alice Found There, “It seems very pretty, but it is rather hard to understand!” (You see she didn’t like to confess, even to herself, that she couldn’t make it out at all.) “Somehow it seems to fill my head with ideas only I don’t exactly know what they are!”