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Pillars of Immunology

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Attracting Attention: Discovery of IL-8/CXCL8 and the Birth of the Chemokine Field

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In the days when almost every biomedical science building has ubiquitous posters on the walls highlighting the various chemokines, their receptors, their alternative names, and the cell types they recruit, it is hard to imagine what it was like before these molecules were identified and understood. By the early 1980s, it was appreciated that certain substances could be chemoattractants for inflammatory cells. These substances included the bacterial peptide fMLF, the complement anaphylatoxin C5a, and the lipid mediator leukotriene B_4. However, these substances did not show selectivity in their ability to uniquely recruit particular leukocyte subsets. There were hints, however, that neutrophil-specific chemotactic activity did exist. For example, in 1980, Merrill et al. demonstrated that human alveolar macrophages, when activated by adhesion to tissue culture plastic or when stimulated with aggregated IgG or zymosan particles, released a substance that, by gel filtration, had a size of ∼10 kDa and was able to attract neutrophils (1). The chemotactic activity of this substance was sensitive to trypsin, suggesting a protein product, but this activity was not further purified or cloned at the time. Fast forward a few years, and the sequences of the cDNAs encoding IL-1α and IL-1β were both identified (2, 3), paving the way for studies on the effects of rIL-1 on inflammation in vivo and in vitro. By 1984, IL-1, or substances later identified as IL-1, were shown to be induced by LPS stimulation and to have the capacity to promote neutrophil chemotaxis in vitro (4–6). In 1986, it was reported that s.c. injections of IL-1 could cause acute inflammatory responses, including rapid margination of neutrophils in vivo (7). Thus, at this point in time, it appeared that the cytokine IL-1 was a chemoattractant. The breakthroughs in the initial discovery of chemokines came in 1987 with two important collaborative papers.

In August of 1987, a collaborative study between Drs. T. Yoshimura and K. Matsushima working in the laboratories of Drs. E. Leonard and J. Oppenheim at the National Cancer Institute, respectively, showed that highly purified or rIL-1 had no chemotactic activity for neutrophils. Furthermore, the groups demonstrated that the chemotactic activity for neutrophils seen in LPS-stimulated monocytes could be separated from IL-1 and was attributed to a protein of ∼10 kDa (8). In a subsequent paper, which we are highlighting in this *Pillars of Immunology* series, these same investigators and their colleagues demonstrated that they could purify a substance from LPS-stimulated monocytes using anion exchange chromatography, gel filtration, and HPLC on cation-exchange and reverse-phase columns. This substance as a purified 7 kDa band with an amino acid composition that was unique from IL-1, as determined by N-terminal amino acid sequencing performed by Dr. E. Appella's laboratory (9). They originally called this substance "human monocyte-derived neutrophil chemotactic factor." Of importance, this report showed that, at an optimum concentration of 10 nM, the substance could attract human neutrophils with a potency similar to fMLF but showed no ability to attract human monocytes. They also identified what would come to be known as the CXC conserved cysteine residue motif in the N-terminal region of the molecule. Thus, this report originally published in the *Proceedings of the National Academy of Sciences USA* is regarded as the first identification of the chemotactic cytokine (or chemokine) that would eventually be known as neutrophil-activating protein and, later, IL-8. Given that the significance of this publication at the time was in the identification of a chemokine that was specific for neutrophils, it is somewhat ironic that the impetus to change the name to IL-8 came when it was shown that this same protein could also attract a subset of T cells (10). It should also be noted that the laboratories of Dr. M. Baggilioni (11) and J. Van Damme (12) reported purification of the identical protein shortly after publication by Yoshimura et al. Drs. Yoshimura and Matsushima also went on to independently characterize the monocyte-recruiting activity of the chemokine we now know as MCP-1/MCP-1 or CCL2 (13, 14). Thus, the chemokine field was born.

Over the next several years, the improvements in protein purification and molecular cloning led to the discoveries that the numerous chemotactic substances with unique names, an alphabet soup of abbreviations and a myriad of specificities, were all attributable to the growing family of molecules known as chemokines. It also became appreciated that chemokines act by binding high-affinity seven-transmembrane G protein–coupled receptors, according to the structure of the chemokine subfamilies. In an effort to coalesce and simplify these expanding data, the International Union of Immunologic Societies/World Health Organization Subcommittee on Chemokine Nomenclature recommended a systematic nomenclature based on the conserved cysteine residue structures of the subfamilies (15), which gave IL-8 the designation of CXCL8 and identified its specific receptors as CXCR1 and CXCR2.

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Abbreviation used in this article: ELR, glutamic acid, leucine, and arginine.

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Shortly after the discovery that cytokines like IL-1 and TNF-α could induce IL-8/CXCL8 in monocytes, laboratories, including the laboratory of coauthor Dr. Steven L. Kunkel, began to realize that structural cells, such as fibroblasts, endothelial cells, and hepatocytes, could release IL-8/CXCL8 (16–18). It was quickly shown that IL-8/CXCL8 could contribute to host defense but also to inflammatory diseases and neutrophil-mediated tissue damage [reviewed in (19)]. Having access to rIL-8/CXCL8 allowed for studies of IL-8/CXCL8 impact on numerous cell types. Indeed, IL-8/CXCL8 had angiogenic activity on endothelial cells as well (20); the angiogenic activity was mediated by the amino acid motif of glutamic acid, leucine, and arginine (ELR) within the N terminus of the CXC family of chemokines, whereas ELR-negative CXC chemokines were actually angiostatic (reviewed in Ref. 21). Development of Abs against IL-8/CXCL8 allowed for studies using human disease samples, and it became clear that this chemokine was overexpressed in multiple forms of cancer, respiratory diseases, and tissue fibrosis (reviewed in Ref. 22–24). This rapidly expanding literature sparked the interest of coauthor Dr. B. Moore and led her to move to the University of Michigan to work in collaboration with Dr. R. Strieter. Here, they confirmed the importance of ELR^+ CXC chemokines in regulating tumorigenesis of prostate cancer cells (25). The idea that chemokines could regulate behaviors of nonmotile structural cells, such as alveolar epithelial cells, led to her work showing the importance of MCP-1/CCL2 and other CCR2 ligands in regulating lung fibrosis (reviewed in Ref. 26). Thus, three decades later, a large number of laboratories, including those of the coauthors, are indebted to the resourceful and collegial collaboration that discovered IL-8/CXCL8 (9) and birthed the field of chemokine biology. We are confident that the next 30 years will yield even more insights into this fascinating family of proteins.

Disclosures

The authors have no financial conflicts of interest.

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