Selective Leukocyte Chemoattractants Emerge from the Primeval Sup(ernatants)

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It is frequently said that a field has grown explosively. The field of leukocyte trafficking, and the roles of chemokines in that process, justify the simile, which implies immediate expansion with an overwhelming impact. Since the publication of this article (1), almost 18 years ago, there have been 26,517 citations of “chemokines” in PubMed (compared with 1,289 before). The extraordinary development of this field is rooted in its history (2): the community of inflammation researchers was primed to receive this information and to act upon it. From accounts of “laudable pus” two millennia ago, through articulation of a cellular theory of inflammation by William Addison and Augustus Volney Waller (known also for Wallerian degeneration) and culminating in Metchnikoff’s seminal distinction of macrophages from microphages (granulocytes), it seemed plausible that inflammatory leukocyte chemoattractants would operate with scrupulous specificity.

This report (1) from Teizo Yoshimura, Kouji Matsushima, Joe Oppenheim, and Ed Leonard is deceptively simple, starting with the question “is IL-1 (IL-1) the neutrophil chemoattractant produced by LPS-stimulated human monocytes?” At the time, it was established that LPS injection evoked neutrophilic inflammation, that LPS-stimulated cells made IL-1, and that intradermal IL-1 could elicit neutrophilic tissue infiltrates. Accordingly, it had been proposed that IL-1 was directly chemotactic for neutrophils (3). A background question concerned inflammatory reactions more generally. Orthodox concepts held that products of bacterial pathogens (such as the cell wall-derived peptide fragment f-met-leu-phe (fMLP)) or of the tissue reaction to infection (such as C5a) were the prime movers of inflammatory infiltrates. Yet, these classical chemoattractants acted equally toward monocytes and neutrophils, while the immediate response to bacterial invasion involved only the latter. What, therefore, were the determinants of cellular specificity in inflammation?

Yoshimura et al. (1) began by demonstrating a sensitive assay for the neutrophil chemoattractant in supernatants of LPS-stimulated monocytes. This chemotactic activity was produced rapidly (within 3 h) and exhibited a shallow dose-response curve, with very high concentrations of LPS eliciting not much more chemoattractant beyond that evoked by 10 ng/ml LPS. These observations suggested that monocytes reacted very rapidly to LPS with production of a neutrophil chemoattractant and that the response was simultaneously sensitive and robust.

Through chromatography on Sephacryl S-200, it became evident that neutrophil chemotactic activity was distinct from IL-1 and was ~10 kDa in molecular mass. Confirmatory studies using HPLC added relatively little, except for the suggestion that there might be more than one physicochemically similar neutrophil chemoattractant in the culture supernatant. In that distant era, recombinant DNA technology was applied only to show that rIL-1α (from two sources) or rIL-1β lacked neutrophil chemotactic activity. Further analysis with HPLC chromatofocusing showed that the neutrophil chemotactic activity had an isoelectric point of ~8.5. This partially purified factor was analyzed in “checkerboard” experiments to demonstrate chemotaxis as differentiated from chemokinesis (the factor was active only when present in excess in the bottom well of a chemotaxis chamber).

The final sentence of the article was tantalizing, hinting that the partially purified factor was attractant for neutrophils but not for monocytes. Yoshimura et al. alluded in the Discussion to close similarities between their factor and that reported (4) 7 years earlier: a selective neutrophil chemoattractant produced by zymosan-stimulated alveolar macrophages.

The promise of this research was quickly realized, with further purification of the protein by Schröder et al. (5) and cloning of a cDNA encoding the factor (6), all within 2 years. This family of proteins had been under intense investigation by others (7–11) at about the same time. The converse discovery (12, 13) (a factor that attracted monocytes but not neutrophils) followed shortly. The outlines of the field were drawn in these first few years of investigation: selective chemoattraction in the service of inflammation and host defense (14, 15); signaling through pertussis toxin sensitive Gαi-linked receptors, phosphoinositol 3-kinase and calcium flux (16); regulation of cell proliferation and survival (suggesting the developmental role demonstrated subsequently) (9, 17); rapid expansion of the family by differential or subtractive hybridization cloning (18, 19); an implication in neurobiology, with pyrogentic activity (20) of one early member; complex in vivo effects on leukocyte-endothelial interactions (21); putative roles in human disease (22); regulation of phagocyte effector functions (8); and production of chemokines by cytokine-stimulated cells (23) (implying the cytokine-chemokine-chemokine cascades demonstrated in later work). On the dark side, this one small protein gained at least four names within months of its birth, presaging the need for the stultifying, anonymized nomenclature now in use (24). It is amazing, with the perspective of an additional 1.5 decades, to consider how this initial burst of creative research shaped the field and how different the world of inflammation now seems. The status of this article (1) as a borderline citation...
classic (94 references in Google Scholar) understates its authentic stature: this was the time when chemokines began to emerge from primordial supernatants and eventually transformed the ancient field of inflammation research.

References


