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Chemokine Research Moves On

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It is difficult to set a start date for the study of chemokines, but as early as 1898 chemotaxis of neutrophils associated with interstitial nephritis was described and linked to soluble substances [1]. Many reports followed describing chemical factors that induced chemotaxis related to inflammation [2,3], aggregate formation in *Dictyostelium discoideum* [4], and sperm motility[5]. In 1967 Peter Ward described the factors produced by bacteria that were chemotactic for neutrophils[6], while others reported that chemotactic factors could be purified from serum, such as C5a[7],[8]. Though these proteins are highly chemotactic, they are not officially identified members of the “family of chemokines”, which denotes those chemotactic factors with partial sequence homology to platelet factor 4 (PF4). Monocyte chemotactic protein-1 (MCP-1) was first described in 1973 and referred to as LDCF for leukocyte-derived chemotactic factor[9] and when purified to homogeneity in 1989 as the predominant monocyte chemoattractant in culture fluids of phytohaemagglutinin-stimulated human mononuclear leukocytes [10] it was shown to have sequence homology to PF4. In mouse this protein was first cloned as JE, a PDGF inducible early response gene[11] and five years later was shown by Rollins to have cytokine-like properties[12]. The human MCP-1 was purified to homogeneity in 1989.

Another protein in this family of early response genes was first described by my laboratory in the early 80's as factor secreted by melanoma tumor cells that enhanced their growth [13,14]. We purified this melanoma growth stimulatory activity (MGSA) factor to homogeneity in 1986, [15,16]. Amino-terminal sequencing revealed MGSA had homology to connective tissue activating protein III (CTAPIII) and members of the platelet factor IV(PF4) family of genes, and from this information the full length MGSA cDNA was cloned and sequenced in 1988 [15,17]. Interestingly, the same cDNA was identified by subtractive hybridization of transformed and non-transformed cells cloned and identified as *gro* (for growth related oncogene) by Anisowicz [18]. Moreover, when Cochran identified JE, KC was also identified as a PDGF inducible early response gene [11], and this gene was later fully sequenced and shown to be a murine homolog of MGSA/*gro* by Oquendo et. al. [19]. In 1989 another murine homolog of MGSA/*gro* was identified as MIP-2 by Wolpe *et al* [20], while the rat orthologs, CINC1–3, were subsequently identified[21].

Other neutrophil activating proteins produced by monocytes were described by a number of groups as early as 1987 [22–25]. Interleukin-8 (IL-8) was first characterized by several groups including Schmid and Weissman, by Yoshimura, and by Walz as neutrophil activating factor 1 (NAF-1)[23,26,27], and by Matsushima as monocyte-derived neutrophil chemotactic factor (MDNCF) [28,29]. Like MGSA/*gro*, IL-8 had some sequence homology to PF4 and β -thromboglobulin. In 1990, Balentien *et al* demonstrated that MGSA/*gro*

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competes with IL-8 for binding sites on neutrophils[30]. One of the receptors for MGSA/gro and IL-8 was cloned and sequenced by Murphy and Tiffany in 1991[31]. The cloning and characterization of other chemokine receptors rapidly followed [32,33].

As early as 1985 Luster et al described the γ -Interferon inducible early-response genes with homology to PF4 [34] and then in 1987 published the biochemical characterization of interferon-inducible protein 10 (IP-10), a gene with now identified as CXCL10 [35–37]. The murine homolog of IP-10 was identified first as CRG-2[38]. Another member identified as mig [39], for which the human homolog is CXCL9.

The identification of these proteins with homology to platelet factor IV occurred rapidly from a number of laboratories. In 1988 Sherry et al cloned the first of what later became known as the CC chemokines, murine macrophage inflammatory protein-1 (MIP-1 α) [40]. By 1989 MIP1 β and hLD78 [41,42], hRANTES [43,44], mTCA3 [42], hNAP-1 [45], c9E3 a chicken PF4 family [46] had all been cloned. All these proteins were recognized as members of the PF4/CTAPIII/ β -thromboglobulin superfamily [47].

This whirlwind of purification and cloning of factors related to β -thromboglobulin and platelet factor IV resulted in several conferences for discussion of how to deal with the nomenclature of these factors. A group first met at the Royal College of Surgeons in the UK in December of 1988 [48] and the second International Symposium on Chemotactic Cytokines was held in the same place in 1990[49]. It was not until the meeting of the Third International Symposium on Chemotactic Cytokines held in Baden-bei-Wien, Austria that the name chemokines was agreed upon for naming these factors[50]. By this time the receptors for the chemokines were being cloned and characterized. It was decided that the receptors would be numbered to match the chemokines to which they bind, with CXC, CC, CX3C and C chemokine subgroups being used to designate the various chemokines and their receptors based upon the conservation of the cysteine residues in the chemokines. We held the first Gordon Research Conference on Chemotactic Cytokines in 1994 and this meeting has continued to serve as a forum for exchange of the latest information on chemokines and their receptors for scientists in academia as well as industry.

The last 20 years of chemokine research has led to extraordinary new findings, revealing key roles for chemokines in inflammation, development and organogenesis, angiogenesis, hematopoiesis, atherosclerosis, wound healing, chronic inflammation, viral infection, homeostasis, autoimmunity and cancer. With the break through discovery in the early 90's that chemokine receptors serve as co-receptors for HIV infection, to the recent demonstration that chemokine receptors are important for West Nile viral infection, we have continued to unravel the significance of this family of proteins and their receptors. We have determined that chemokines and their receptors are key for the formation of atherosclerotic lesions, and that chemokines play key roles in establishing the 'pre-metastatic niche' and in creating an environment that promotes tumor progression. New chemokines, chemokine receptors, and chemokine-like factors continue to be discovered and characterized. We have come to understand that some atypical chemokine receptors may not couple to the heterotrimeric G proteins, but still play important functional roles (DARC, CCR6, CXCR7, CCRL1). We have learned quite a bit about receptor signal transduction, receptor trafficking, receptor transcription, and receptor function in health and disease. Efforts continue to develop useful chemokine antagonists for therapy.

In tribute to the over 20 years of chemokine research, *the Journal of Experimental Cell Research* invited us to produce a special edition on chemokines. While it was not possible to include a chapter for the all varied and important functions of chemokines and their receptors, this edition includes contribution from some of the leaders in the field detailing

the state of chemokine research in many areas: Chemokines as mediators of normal function and disease, Chemokine/integrin signaling during motility, Chemokines as mediators of angiogenesis and neovascularization, CXCR3 in T cell function, Chemokine-like receptors, CCR6 as a mediator of immunity in the lung and gut, Chemokines in cancer-related inflammation, Heterophilic chemokine receptor interactions in chemokine signaling and biology, Post-translational processing of chemokines, Chemokine oligomerization in receptor and GAG interactions, Atypical chemokine receptors, and finally Chemokines as targets for therapy. I apologize to all who were not able to include their story due to page limitations. Many outstanding scientists have worked together to contribute to our knowledge of the myriad biological roles of chemokines.

Hopefully in the next decade we will develop a better understanding of how diverse chemokine receptors sense and respond to a chemokine gradient and generate the myriad of signaling networks to execute directed motility. We hope to better understand how chemokine receptors facilitate the maturation and differentiation of leukocytes, how atypical receptors modulate the levels and localization of chemokines, how receptor trafficking and interaction with novel adaptor proteins affect signaling, and how the receptors interact with GAGs and other receptors to produce unexpected responses to chemokines. Finally, we anticipate that additional research will lead to successful clinical trials with chemokine antagonists so that we can positively impact outcomes for chronic obstructive pulmonary disease, rheumatoid and osteoarthritis, diabetes, atherosclerosis, acquired immune deficiency syndrome, transplantation, cancer, multiple sclerosis, and many other disorders affected by chemokines.

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