Journal of NeuroVirology (1999) 5, 1–2

http://www.jneurovirol.com

Guest Editorial

Chemokine regulation of inflammatory-mediated nervous system diseases

Inflammatory diseases of both the central (CNS) and peripheral (PNS) nervous systems, with or without an autoimmune component, share a common feature of leukocyte infiltration. The characteristics of the infiltrate are partially governed by the adhesion molecules a particular inflammatory cell expresses allowing it to gain entry to the specific tissue site. However, it is becoming apparent that other molecular factors are involved in the migration, recruitment, and accumulation of leukocytes in either CNS or PNS. It is the accumulation of these inflammatory cells coupled with their activation state that determines whether the inflammatory response will lead to tissue damage. An important set of molecular mediators of this process are chemokines. Chemokines were first described as soluble products with the ability to induce directed chemotaxis of leukocytes. Now chemokines appear to be involved in many additional cellular processes (Karpus *et al*, 1997; Ward *et al*, 1998).

Chemokines are low molecular weight chemotactic peptides that are divided into four distinct subfamilies: C-x-C, C-C, C, and C-x_3-C, based on the position of the first two cysteines in the amino terminus as well as functional and genetic homologies. The C-x-C family members containing a receptor-binding glutamate-leucine-arginine (ELR) motif are primarily chemotactic for neutrophils and for endothelial cells (Strieter *et al*, 1995). C-x-C chemokines that lack this motif ('non-ELR C-x-C') are chemoattractant for activated T cells and block angiogenic effects of the ELR-bearing family members (Strieter *et al*, 1995). The C-C family members are primarily chemotactic for monocytes/macrophages, T lymphocytes, basophils and eosinophils (Davatelis *et al*, 1988; Schall, 1991; Taub *et al*, 1993). The C family prototypical member, lymphotactin, is chemotactic for T cells and NK cells (Hedrick *et al*, 1997). The sole member of the C-x_3-C family (neurotactin/fractalkine) consists of a chemokine domain tethered to a mucin stalk; a soluble chemokine can be generated by proteolysis or alternative processing of the mRNA precursor (Bazan *et al*, 1997). Although members of the chemokine subfamilies show considerable chemoattractant specificity for leukocyte subpopulations, there are many exceptions. It is clear that cellular chemokine specificity is dictated by the subset of chemokine receptors expressed on the cell surface at any given time (Baggiolini, 1998).

The importance of chemokines in the regulation of CNS and PNS disease processes has been approached using three different methodologies. The first of these was expression studies, in which chemokine mRNA and/or protein expression was correlated with clinical disease progression. In this way it was first demonstrated that CNS chemokine expression had a strong correlation with clinical experimental autoimmune encephalomyelitis (EAE) (Glabinski *et al*, 1997; Godiska *et al*, 1995; Hulkower *et al*, 1993). The second method used *in vivo* antibody treatments to demonstrate a direct role for chemokines in the development and progression of EAE (Karpus *et al*, 1995). The third approach is ongoing and that is to use mice with specific targeted chemokine mutations followed by phenotypic analysis of disease development and/or progression. In combination, these methods have shown a direct role for chemokines in CNS inflammatory disease development and progression.

This special issue is devoted to the discussion of chemokine regulation of CNS and PNS inflammatory diseases. The expression patterns of chemokine and chemokine receptors in CNS demyelinating diseases such as EAE and MS are reviewed by Glabinski and Ransohoff, and Hesselgesser and Horuk. Less is known about the role of chemokines in PNS demyelinating disease and Fujioka *et al* review the literature as well as provide original data showing expression of chemokines in experimental autoimmune neuritis (EAN). Xia and Hyman discuss the role of chemokine and chemokine receptor expression in Alzheimer's disease (AD). What is striking in AD is that there appears to be a substantial inflammatory involvement in a non-autoimmune mediated CNS disease. The role of chemokines in the pathology of herpetic stromal keratitis (HSK) is also discussed. Ocular herpes infection often leads to CNS pathology and therefore this particular paper by Kumaraguru *et al* provides information leading to the chemokine regulation of the initiating event in this process. The role of chemokines in virally-mediated CNS demyelinating disease has only recently been demonstrated (Asensio and Campbell, 1997; Lane *et al*, 1998). Three papers in the present issue provided additional evidence that virus-mediated CNS demyelinating diseases are regulated, at least in part, by chemokine expression. Additionally, Huffnagle and McNeil demonstrate a role for

chemokine regulation of *C. neoformans* induced CNS inflammatory disease. Luo *et al* show that a recently described IFN-γ-inducible C-x-C chemokine is expressed in the CNS of patients with CNS inflammatory disease, thus implicating this new chemokine in disease pathogenesis. Oh *et al* discuss astrocyte expression of chemokines and chemokine receptors as potential regulators of CNS disease. Glabinski *et al* provide evidence for IFN-γ inducible chemokines as regulators of relapsing EAE. Finally, Calabresi *et al* show a role for chemokines in human virus (HTLV-1) associated CNS disease.

Acknowledgements

We hope that this special issue on chemokine regulation of CNS and PNS inflammatory diseases inspires further discussion and research toward understanding the roles of these soluble mediators in the induction and progression of these diseases, with the ultimate goal of targeting these molecules for specific treatment. I would like to thank the authors for their stimulating contributions and more importantly the Journal of NeuroVirology editorial staff, particularly June Vieth without whose help I could not have assembled this special issue.

Dr William J Karpus
Department of Pathology,
Northwestern University Medical School,
303 E Chicago Avenue, W127,
Chicago, Illinois 60611, USA

References

Asensio VC, Campbell IL (1997). Chemokine gene expression in the brains of mice with lymphocytic choriomeningitis. *J Virol* **71:** 7832–7840.

Baggiolini M (1998). Chemokines and leukocyte traffic. *Nature* **392:** 565–568.

Bazan JF, Bacon KB, Hardiman G, Wang W, Soo K, Rossi D, Greaves DR, Zlotnik A, Schall TJ (1997). A new class of membrane-bound chemokine with a CX_3C motif. *Nature* **385:** 640–644.

Davatelis G, Tekamp-Olson P, Wolpe SD, Hermsen K, Luedke C, Gallegos C, Coit D, Merryweather J, Cerami A (1988). Cloning and characterization of a cDNA for murine macrophage inflammatory protein (MIP), a novel monokine with inflammatory and chemokine properties. *J Exp Med* **167:** 1939–1944.

Glabinski AR, Tani M, Strieter RM, Tuohy VK, Ransohoff RM (1997). Synchronous synthesis of α- and β-chemokines by cells of diverse lineage in the central nervous system of mice with relapses of chronic experimental autoimmune encephalomyelitis. *Am J Pathol* **150:** 617–630.

Godiska R, Chantry D, Dietsch GN, Gray PW (1995). Chemokine expression in murine experimental allergic encephalomyelitis. *J Neuroimmunol* **58:** 167–176.

Hedrick JA, Saylor V, Figueroa D, Mizoue L, Xu YM, Menon S, Abrams J, Handel T, Zlotnik A (1997). Lymphotactin is produced by NK cells and attracts both NK cells and T cells in vivo. *J Immunol* **158:** 1533–1540.

Hulkower K, Brosnan CF, Aquino DA, Cammer W, Kulshrestha S, Guida MP, Rapoport DA, Berman JW (1993). Expression of CSF-1, c-fms, and MCP-1 in the central nervous system of rats with experimental allergic encephalomyelitis. *J Immunol* **150:** 2525–2533.

Karpus WJ, Lukacs NW, Kennedy KJ, Smith WS, Hurst SD, Barrett TA (1997). Differential CC chemokine-induced enhancement of T helper cell cytokine production. *J Immunol* **158:** 4129–4136.

Karpus WJ, Lukacs NW, McRae BL, Strieter RM, Kunkel SL, Miller SD (1995). An important role for the chemokine macrophage inflammatory protein-1α in the pathogenesis of the T cell-mediated autoimmune disease, experimental autoimmune encephalomyelitis. *J Immunol* **155:** 5003–5010.

Lane TE, Asensio VC, Yu N, Paoletti AD, Campbell IL, Buchmeier MJ (1998). Dynamic regulation of alpha- and beta-chemokine expression in the central nervous system during mouse hepatitis virus-induced demyelinating disease. *J Immunol* **160:** 970–978.

Schall TJ (1991). Biology of the RANTES/SIS cytokine family. *Cytokine* **3:** 165–183.

Strieter RM, Polverini PJ, Kunkel SL, Arenberg DA, Burdick MD, Kasper J, Dzuiba J, Van Damme J, Walz A, Marriott D, Chan SY, Roczniak S, Shanafelt AB (1995). The functional role of the ELR motif in CXC chemokine-mediated angiogenesis. *J Biol Chem* **270:** 27348–27357.

Taub DD, Conlon K, Lloyd AR, Oppenheim JJ, Kelvin DJ (1993). Preferential migration of activated $CD4^+$ and $CD8^+$ T cells in response to MIP-1α and MIP-1β. *Science* **260:** 355–358.

Ward SG, Bacon K, Westwick J (1998). Chemokines and T lymphocytes: more than an attraction. *Immunity* **9:** 1–11.