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Slit proteins, potential endogenous modulators of inflammation

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Recent studies suggest that molecules important for guiding neuronal migration and axon path-finding also play a role in modulating leukocyte chemotaxis. Neuronal migration and leukocyte chemotaxis may share some common regulatory mechanisms. Intracellular signal transduction mechanisms guiding neuronal migration and leukocyte chemotaxis are beginning to be elucidated. Studying molecular mechanisms modulating cell migration may provide new insights into understanding of endogenous inhibitors of inflammation. *Journal of NeuroVirology* (2002) **8,** 486–495.

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Introduction

Since the discovery of leukocyte chemotaxis by Leber in 1888 (reviewed in McCutcheon, 1946; Harris, 1954), this type of cell migration has been studied extensively (Boyden, 1962; Ramsey, 1972; Zigmond, 1974; Devreotes and Zigmond, 1988; Downey, 1994; Sanchez-Madrid and Angel del Pozo, 1999). Work in the last 20 years has demonstrated the importance of the chemokine family in leukocyte chemotaxis (reviewed in Murphy, 1994; Springer, 1994; Rollins, 1997; Baggiolini *et al*, 1997; Luster, 1998; Locati and Murphy, 1999). There are currently more than 40 chemokines that are structurally related small proteins with 70 to 100 amino acid residues. Chemokines are classified into several families according to their structural features: CXC chemokines such as IL-8 (interleukin-8) and SDF-1 (stromal cell–derived factor-1), CC chemokines such as RANTES (regulated upon activation in normal T cells expressed and secreted) and MCP-1 (monocyte chemotractant protein-1), C chemokine (such as lymphotactin), and CX3C chemokine (such as fractalkine). Although many CC chemokines are of broad spectrum, CXC chemokines often are more restricted.

Chemokines play multiple roles, not only in normal development but also in the pathogenesis of a large number of diseases such as atherosclerosis (Yla-Herttuala *et al*, 1991; Nelken *et al*, 1991; Boring *et al*, 1998; Gerszten *et al*, 2000), allogeneic transplant rejection (Pattison *et al*, 1994; Kondo *et al*, 1996), virally induced vascular diseases (Streblow *et al*, 1999), as well as tissue injury repair (Furie and Randolph, 1995) and tumor development (Sharpe *et al*, 1990; Smith *et al*, 1994; Strieter *et al*, 1995; Dilloo *et al*, 1996; Moore *et al*, 1998). In tumoriogenesis, both tumor-induced angiogenesis and tumor metastasis involve cell migration (Koch *et al*, 1992b; Smith *et al*, 1994; Strieter *et al*, 1995; Boshoff *et al*, 1997; Tachibana *et al*, 1998; Moore *et al*, 1998). Activation or increased production of chemokines has been found in a number of inflammatory disorders, not only in the organs outside of the nervous system but also in certain neurodegenerative disorders (for example, Koch *et al*, 1992a; reviewed in

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Segerer *et al*, 2000; Luster, 2001, 2002). Inhibition of chemokines has shown therapeutic potentials in animal models (Harada *et al*, 1994; Gong *et al*, 1997; Barnes *et al*, 1998). Therefore, much effort has been directed towards obtaining reagents that can block chemokines or their receptors (Baggiolini and Moser, 1997; Nelson and Krensky, 1998; Baggiolini, 1998; Luster, 2001; Izikson *et al*, 2002).

Extensive studies on chemokines show that these chemotactic factors act through seven-transmembrane receptors coupled to G proteins (GPCRs). Many chemokine receptors signal through Gi-type proteins. Activation of the receptors by chemokines often involves calcium mobilization and stimulation of phosphoinositide-specific phospholipase C (PI- PLC) (for reviews, see Murphy, 1994). However, our understanding of signal transduction pathways downstream of chemokine receptors is still limited. It is not known about how these pathways are regulated by other ligand-receptor pathways. Although some viral-derived chemokine inhibitors have been reported (Smith *et al*, 1997; Kledal *et al*, 1997), very little is known about endogenously produced chemokine inhibitors.

Slit: A molecular cue for axon guidance and neuronal migration

A number of neuronal guidance cues have been found in the nervous system (reviewed in Tessier-Lavigne and Goodman, 1996; Raper and Tessier-Lavigne, 1999). Recent studies on a family of secreted proteins, the Slit proteins, have uncovered molecular cues guiding neuronal migration. First identified in *Drosophila* (Nusslein-Volhard *et al*, 1984; Rothberg *et al*, 1988, 1990), slit gene family in mammals has at least three members, slit1, -2, and -3. They encode secreted proteins containing four leucine-rich repeat (LRR) regions at N-terminal region, followed by nine epidermal growth factor (EGF) repeats, a laminin G domain (previously also known as the a laminin G domain with similarities to agrin, laminin, and perlecan [ALPS] domain), and a cysteine-rich C-terminal region. slit genes have been shown to encode ligands for the Roundabout receptor (Robo) (Battye *et al*, 1999; Brose *et al*, 1999; Kidd *et al*, 1999; Li *et al*, 1999; Nguyen Ba-Charvet *et al*, 1999; Yuan *et al*, 1999). Slit can promote axon branching (Wang *et al*, 1999b) and repel axons in the spinal cord and in the brain (Brose *et al*, 1999; Kidd *et al*, 1999; Li *et al*, 1999; Nguyen Ba-Charvet *et al*, 1999). Slit proteins are capable of guiding the movement of at least two populations of tangentially migrating neurons in the CNS: those migrating from the anterior subventricular zone (SVZa) to the olfactory bulb (Wu *et al*, 1999; Hu, 1999) and those migrating from the striatal primordium to the neocortex (Zhu *et al*, 1999). Slit protein acts as a chemorepellent whose concentration gradient guides neuronal migration (Wu *et al*, 1999). The activities of Slit in both axon guidance and neuronal migration led to the conclusion that these two phenomena in the nervous system share common guidance mechanisms (Wu *et al*, 1999; Zhu *et al*, 1999).

Activities of Slit proteins in the nervous system and in the immune system

It is not clear whether mechanisms underlying cell migration that operate in the nervous system are conserved in the immune system. At the cellular level, the environment in which leukocytes migrate seems to be different from the tightly packed environment within which axons and neurons navigate. Furthermore, the morphology of migrating neurons with a rather long leading process and a trailing process appears to be distinct from that of the leukocytes. At the molecular level, receptors for all known neuronal guidance cues, including a C. elegans homolog of DCC (UNC-5), deleted in colorectal cancer (DCC), Eph, neuropilin, Robo, and plexin, are proteins containing a single transmembrane domain (Leung-Hagesteijn *et al*, 1992; Cheng and Flanagan, 1994; Keino-Masu *et al*, 1996; Chan *et al*, 1996; Tessier-Lavigne and Goodman, 1996; Leonardo *et al*, 1997; Ackerman *et al*, 1997; He and Tessier-Lavigne, 1997; Kolodkin *et al*, 1997; Feiner *et al*, 1997; Chen *et al*, 1998; Giger *et al*, 1998; Winberg *et al*, 1998; Kidd *et al*, 1998, 1999; Zallen *et al*, 1998; Brose *et al*, 1999; Li *et al*, 1999; Yuan *et al*, 1999; Takahashi *et al*, 1999; Tamagnone *et al*, 1999; Bashaw and Goodman, 1999; Mueller, 1999). In contrast, seven-transmembrane GPCRs mediate responses not only to all chemokines but also to other known chemotactic factors in vertebrate animals (Hwang, 1990; Murphy, 1994; Rollin, 1997; Baggiolini *et al*, 1997; Luster, 1998; Locati and Murphy, 1999) and in *Dictyostelium* (Klein *et al*, 1985, 1988; Devreotes and Zigmond, 1988; Parent and Devreotes, 1996, 1999; Chen *et al*, 1996). It is, therefore, not obvious whether neuronal guidance cues can play important roles in the immune system.

We previously reported the expression of Slit and Robo outside the mammalian nervous system (Li *et al*, 1999; Yuan *et al*, 1999) and speculated possible roles for Slit in the immune system (Wu *et al*, 1999; Zhu *et al*, 1999). Our recent studies show that Slit is capable of inhibiting leukocyte migration induced by chemokines (Wu *et al*, 2001). Both human Slit2 and *Xenopus* Slit protein were found to inhibit leukocyte chemotaxis induced by chemokines such as SDF-1, and chemotaxis of differentiated HL-60 cells induced by *N*-formyl peptide f-Met-Leu-Phe (fMLP) was also inhibited by Slit protein. These results demonstrated the functional interaction between Slit-Robo and chemokine–chemokine receptor signal transduction pathways. These studies indicated functional interaction between two distinct families of guidance molecules,

one working through single transmembrane receptors and the other through seven-transmembrane GPCRs. These studies have implications on modulation of pathways involving heterotrimeric G proteins and demonstrate conserved guidance mechanisms for neurons and leukocytes. Furthermore, these findings have biological and therapeutic implications in neuronal migration as well as multiple processes involving chemokines. Our results with Slit and chemokines suggest that modulation of pathways involving heterotrimeric G proteins is important in guiding cell migration.

The observation that functional interaction between Slit and chemokines requires the single-pass transmembrane Robo receptor for Slit and the GPCRs for the chemokines suggests a novel approach to regulate signal transduction pathways activated during inflammation. Chemokines are known to activate a number of downstream components (Downey, 1994; Ganju *et al*, 1998; Rodriguez-Frade *et al*, 1999). Chemokine signaling can be inhibited at any step, beginning from ligand binding (Mashikian *et al*, 1999), receptor polarization or distribution (Nieto *et al*, 1997; Djellas *et al*, 1998; Servant *et al*, 1999), receptor coupling to G proteins (Arai and Charo, 1996; Kuang *et al*, 1996), release of the $\beta\beta$ subunits of G proteins (Neptune and Bourne, 1997; Arai *et al*, 1997; Neptune *et al*, 1999), activation of effectors such as Ca^{2+}, focal adhesion kinase (FAK), MAP kinase, or inosital 1,4,5-triphosphate (PI3) kinase (Bacon *et al*, 1996; Ganju *et al*, 1998), function and distribution of integrins (Lauffenburger and Horwitz, 1996), to the organization of actin cytoskeleton (Mitchison and Cramer, 1996). At present, it is not clear at which step(s) the Slit pathway interacts with the chemokine pathway(s). However, recent studies on the intracellular signaling pathways downstream of the Slit receptor, Robo, have demonstrated an important role of a new family of GTPase-activating proteins (GAP) proteins, Slit-Robo GAP (srGAP), as well as Cdc42 in neuronal guidance (Wong *et al*, 2001, 2002a, 2002b). These genes are also expressed in leukocytes (Wu and Havlioglu, unpublished results). These studies provide potential new target genes for studying functional interaction between Slit and chemokine pathways.

Potential implication of Slit in inflammatory nervous system disorders

Because Slit is not unique among the neuronal guidance cues, we propose that other neuronal guidance cues may also play a role in modulating migration of other cell types, including leukocyte chemotaxis in the immune system. Chemokines play multiple roles, including inflammatory responses (reviewed in Rollins, 1997; Luster, 1998), leukocyte activation (Bokoch, 1995), lymphocyte trafficking, and lymphoid organ homeostasis (Springer, 1994; Forster *et al*, 1996; Mackay, 1996; Baggiolini, 1998; Ward, Bacon and Westwick, 1998; Melchers *et al*, 1999; Jung and Littman, 1999; Cyster, 1999). The potential roles of chemokine activation in the inflammatory disorders outside of the nervous system have been extensively covered by a number of excellent reviews. Here we will discuss the potential implication of Slit protein in the inflammatory responses in the nervous system.

Similar to the eye and testes, the central nervous system (CNS) in mammals has evolved complex mechanisms to protect its structure and function from damaging inflammatory responses. There are several layers of anatomical and physiological barriers. These include the unique organization of the blood-brain barrier (BBB), the lack of conventional lymphatic drainage of the brain, the absence of potent antigen-presenting cells, and the down-regulatory roles of neurons on major histocompatibility complex (MHC) expression in the CNS, with paucity of class I and II MHC molecules on resident cells (Aloisi, 1999; Bradl, 1996; Frohman *et al*, 2001; Lawrence and Kim, 2000).

It is known that immune cells and factors can enter the brain parenchyma in the absence of any pathogen. However, only a very small percentage of peripherally injected cytokines can cross the BBB as demonstrated for IL-2 and chemokines (Lawrence and Kim, 2000). Nonetheless, the CNS is under constant surveillance by the immune system. Perivascular and meningeal macrophages are replaced continuously by blood-derived macrophages that may act as first-line scavengers (Lassman, 1999). Small numbers of dendritic-like cells have been detected in some CNS-associated compartments, such as the meninges and the choroid plexus. Human immunodeficiency virus (HIV)-infected T lymphocytes and monocytes are often found in the stroma, as well as in supraepithelial regions of the choroid plexus (Antel, 2000). Numerous resident cells such as microglia, cerebral endothelial cells, and astrocytes acquire the expression of immune accessory molecules and they function as antigen-presenting cells. Healthy neurons may have a number of mechanisms to escape the recognition by immune cells and avoid autoimmune responses. These may include suppression of MHC expression in neurons. In healthy CNS, MHC class II molecules are only present on perivascular cells, leptomeninges, and choroid plexus. MHC class II is induced on microglia and perivascular cells in response to trauma, ischemia, infection, inflammation, and neurodegeneration. MHC class II expression is controlled by neurons. Neurotrophins (especially nerve growth factor [NGF]) play a role in down-regulating MHC class II on microglia (Aloisi, 1999; McCluskey and Lampson, 2000). Functional damage to neurons and loss of bioelectric activity renders neurons susceptible to recognition and

elimination by cytotoxic CD8+ T lymphocytes (Lassman, 1999).

During viral infection or development of certain autoimmune disorders of the nervous system, activated T cells can cross BBB and initiate both protective and unwanted inflammatory responses. When BBB is damaged, a large number of T cells and other inflammatory cells enter the CNS by encountering perivascular macrophages. Activation of microglia and astrocytes also play an important role in the immune responses in the CNS. Activated microglia has phagocytic activity and they also synthesize cytokines and mediators. Activated microglia express B7, intercellular adhesion molecule (ICAM)-1, and CD40 molecules and astrocytes also may expres B7 and CD40 (Aloisi, 1999; Antel, 2000; Aloisi, 2000a, 2000b; Becher *et al*, 2000).

In addition to the role of chemokines in the development of the nervous system (for example, see recent papers by Klein *et al*, 2001; Zhu *et al*, 2002 and references within), accumulating evidence suggests that chemokines and their receptors may play an important role in the inflammatory responses in the CNS (Bajetto *et al*, 2001; Izikson *et al*, 2002). These include encephalitis, encephalomyelitis, meningitis, CNS ischemia, CNS reperfusion injury, CNS trauma, CNS tumors, multiple sclerosis, Alzheimer's diseases, and HIV dementia (reviewed in Karpus, 1999; Glabinski and Ransohoff, 1999; Fujika *et al*, 1999; Hesselgesser and Horuk, 1999; Xia and Hyman, 1999; Mennicken *et al*, 1999). However, little is known about endogenous inhibitors of chemokine activation in the CNS. Our recent studies show that Slit is expressed in the postnatal meninges and active in chemorepulsion (Wu and Rao, unpublished observation), suggesting a potential role of Slit in protective mechanisms against leukocyte infiltration into the CNS. In addition, Slit proteins expressed inside CNS may also play a role in modulating inflammatory responses in the CNS.

In a number of scenarios, it is possible that Slit may be of potential therapeutic benefits. For example, multiple sclerosis is an autoimmune disease mediated by leukocyte infiltration. Chemokine expression is up-regulated in multiple sclerosis and its animal models (Ransohoff *et al*, 1993, 1996; Miyagishi *et al*, 1995; Godiska *et al*, 1995; Hvas *et al*, 1997; Glabinski and Ransohoff, 1999; Hesselgesser and Horuk, 1999). Inhibition of chemokine receptors is protective against the induction of experimental allergic encephalomyelitis, a mouse model of multiple sclerosis (Karpus *et al*, 1995). An inhibitor such as Slit may thus be of use in ameliorating multiple sclerosis. Because the chemokine receptor CXCR4, in the absence of CD4, has been shown to mediate neuronal apoptosis induced by HIV-1 gp120 and the chemokine SDF-1 (Hesselgesser *et al*, 1998; Meucci *et al*, 1998), our results on Slit inhibition of SDF-1 signaling through CXCR4 (Wu *et al*, 2001) suggest that Slit may be used to reduce neuronal apoptosis. Up-regulation of chemokine receptors has also been proposed as a potential player in the pathogenesis of Alzheimer's disease either by exacerbating inflammatory responses or by apoptosis (reviewed in Xia and Hyman, 1999; Hesselgesser and Horuk, 1999), forming a basis for suggesting a beneficial effect of Slit and other chemokine inhibitors in Alzheimer's disease.

Several chemokine receptors, including CXCR4 and CCR5, have been shown to be coreceptors for HIV-1 (Cocchi *et al*, 1995; Feng *et al*, 1996; Oberlin *et al*, 1996; Bleul *et al*, 1996, 1997; Dragic *et al*, 1996; Deng *et al*, 1996; Choe *et al*, 1996; Doranz *et al*, 1996; Simmons *et al*, 1997). Because inhibition of receptor signaling can block HIV infection (Alfano *et al*, 1999; Wang and Oppenheim, 1999), the finding of Slit inhibition of signaling through chemokine receptors, including CCR5 and CXCR4, suggests a possible application of Slit in acquired immunodeficiency syndrome (AIDS). This may open a new avenue in drug research for Slit or its derivatives to be used as a therapeutic reagent in inhibiting HIV infection by inhibiting its coreceptors CXCR4 and CCR5 (Wu, *et al*, 2001). The studies on the interplay between chemokine pathways and other signal transduction pathways are only at the beginning. Mechanisms underlying the complex regulation of chemokine signaling inside and outside the nervous system await further investigation with combined molecular, biochemical and functional approaches.

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