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SDF-1 stimulates neurite growth on inhibitory CNS myelin

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ABSTRACT

Impaired axonal regeneration is a common observation after central nervous system (CNS) injury. The stromal cell-derived factor-1, SDF-1/CXCL12, has previously been shown to promote axonal growth in the presence of potent chemorepellent molecules known to be important in nervous system development. Here, we report that treatment with SDF-1α is sufficient to overcome neurite outgrowth inhibition mediated by CNS myelin towards cultured postnatal dorsal root ganglion neurons. While we found both cognate SDF-1 receptors, CXCR4 and CXCR7/RDC1, to be coexpressed on myelin-sensitive dorsal root ganglion neurons, the distinct expression pattern of CXCR4 on growth cones and branching points of neurites suggests a function of this receptor in chemokine-mediated growth promotion and/or arborization. These *in vitro* findings were further corroborated as local intrathecal infusion of SDF-1 into spinal cord injury following thoracic dorsal hemisection resulted in enhanced sprouting of corticospinal tract axons into white and grey matter. Our findings indicate that SDF-1 receptor activation might constitute a novel therapeutic approach to promote axonal growth in the injured CNS.

Introduction

Limited central nervous system (CNS) recovery (Ramón y Cajal, 1928) has been ascribed to multiple factors such as the absence of neurotrophins (Lu et al., 2004; Blackmore and Letourneau, 2005) or the formation of a lesion scar acting as a regeneration barrier at the site of injury (Stichel and Müller, 1998; Fawcett and Asher, 1999; Klapka and Müller, 2006). Furthermore, myelin-associated inhibitors, MAIs, were shown to contribute to regenerative failure (Schwab and Bartholdi, 1996; Fournier and Strittmatter, 2001; Filbin, 2003; Domeniconi et al., 2005). In postnatal mammalian CNS injury, Nogo-A (Chen et al., 2000; GrandPrè et al., 2000), myelin-associated glycoprotein (MAG, McKerracher et al., 1994; Tang et al., 2001), and oligodendrocyte-myelin glycoprotein (OMgp, Wang et al., 2002; Vourc'h and Andres, 2004), are efficient axonal outgrowth inhibitors. Interestingly, these molecules were described to abrogate axonal outgrowth upon interaction with a common tripartite receptor complex (Fournier et al., 2001; Filbin, 2003; Domeniconi et al., 2005) in a manner which largely depends on neuronal age and origin (McKerracher et al., 1994; Mukhopadhyay et al., 1994; DeBellard et al., 1996; Ng and Lozano, 1999). Recent studies documented that this impaired tolerance of inhibitory cues is related to the intrinsic state of the affected cells (Song et al., 1998; Ng and Lozano, 1999; Blackmore and Letourneau, 2005). In dorsal root ganglion (DRG) neurons, an increased sensitivity towards the myelin-associated axon growth inhibitor MAG coincides with a molecular switch at postnatal day three/four (P3/P4) which is characterized by decreased intracellular cAMP levels (DeBellard et al., 1996; Cai et al., 2001).

Cyclic AMP regulates numerous cellular processes through different signalling pathways (Antoni, 2000), and elevation of intracellular cAMP levels turned out to be a tool for increasing the regenerative capacity of neuronal cells (Cai et al., 1999; Neumann et al., 2002; Qiu et al., 2002).

One of the extrinsic factors which can promote cAMP-dependent alteration of axonal outgrowth behaviour was shown to be the chemokine SDF-1/CXCL12. Recent studies on guidance cues in embryonic neural development revealed an improvement in neurite outgrowth in the presence of potent neurorepellent molecules such as semaphorin 3A and slit after application of this chemokine (Chalasani et al., 2003, 2007). The α-chemokine SDF-1 is the only known ligand for CXCR4, a coreceptor of T-tropic HIV-1 strains (Oberlin et al., 1996; Nagasawa et al., 1998). While CXCR4- and SDF-1-deficient mice show similar developmental defects and die perinatally (Nagasawa et al., 1996; Ma et al., 1998; Lu et al., 2002), SDF-1 was recently shown to signal through an additional receptor, CXCR7/RDC1 (Balabanian et al., 2005).

In this study, we analyzed the ability of SDF-1α to overcome CNS myelin-associated outgrowth inhibition of myelin-sensitive postnatal

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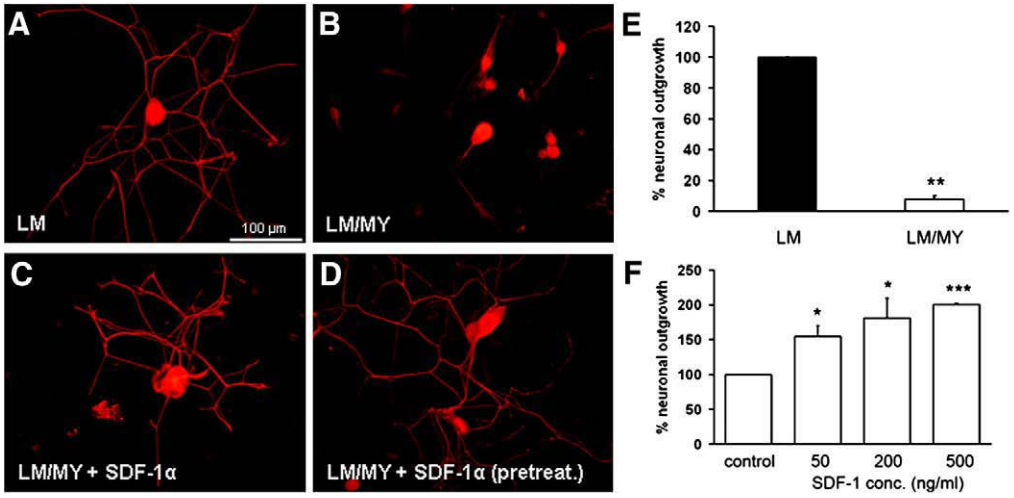

Fig. 1. SDF-1α mediates neurite outgrowth on adult CNS myelin substrate. On a laminin substrate cultured postnatal (P6) DRG neurons show extensive neurite outgrowth (A, E), whereas neurite outgrowth was significantly impaired on a culture substrate containing CNS myelin (B, E). The addition of SDF-1α to DRG cultures plated on a CNS myelin substrate results in improved neurite outgrowth (C). Further preincubation of the neurons with SDF-1α prior to plating of the cells on myelin leads to a significant and dose-dependent increase in the proportion of outgrowing neurons (D, F) when compared to myelin controls lacking the chemokine supplement (B, F). LM, laminin; LM/MY, laminin/myelin. Results in (E, F) are shown as mean ± SEM and are derived from three independent experiments ($n = 3$) each in which the percentage of neurons displaying three or more neurites with a length of at least the cell body diameter was determined. Values are normalized for numbers of untreated cells growing out on laminin (E) or on myelin (F), respectively. *$p < 0.05$, **$p < 0.01$; ***$p < 0.001$ (student's t-test).

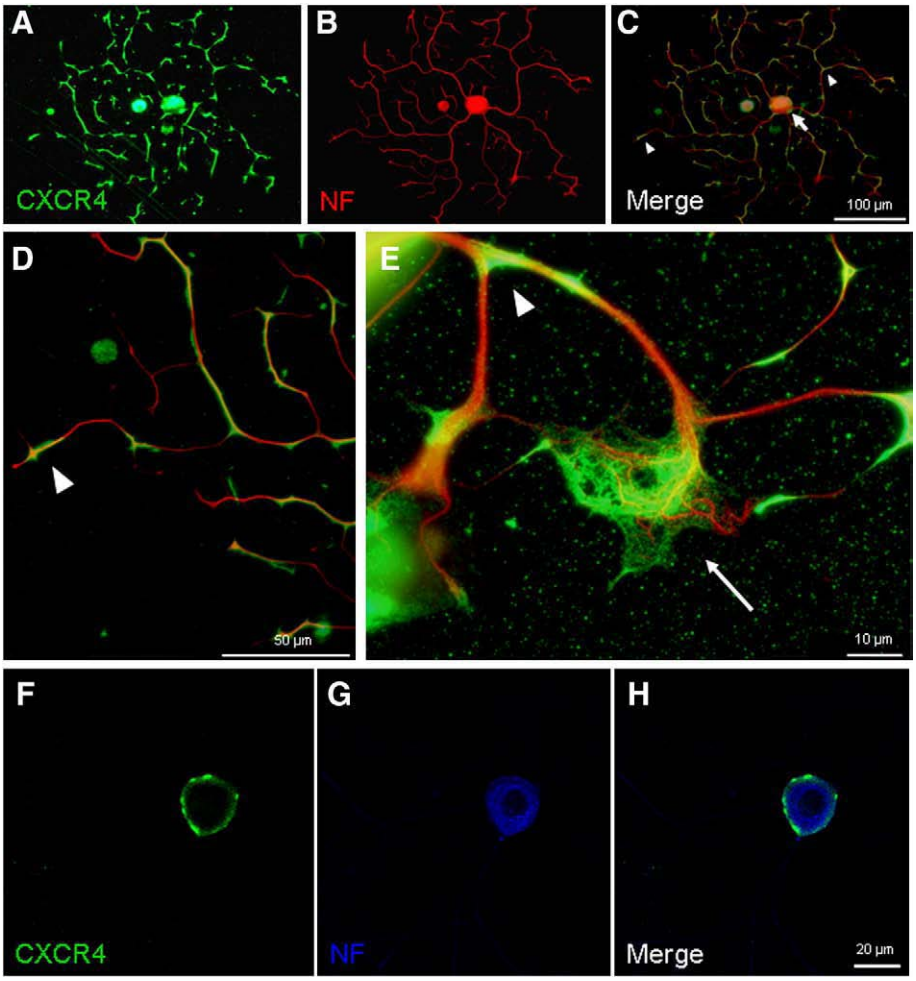

Fig. 2. CXCR4 is expressed on DRG neurons. The cognate receptor to SDF-1, CXCR4, is expressed on cultured DRG neurons, where it is located in a characteristic pattern on neurofilament (NF)-positive cell bodies and neurites (A–C, in C arrow and arrowheads, respectively). CXCR4-immunoreactivity on neurites is prominent near branching points (D, E, arrowheads) and at growth cones (E, arrow). Cell surface localization of CXCR4 is confirmed by confocal laser scan microscopy (F–H). Pictures chosen for presentation are representative of at least five independent experiments ($n \geq 5$).