# Migration of engrafted neural stem cells is mediated by CXCL12 signaling through CXCR4 in a viral model of multiple sclerosis.

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**Authors:** Kevin S Carbajal, Christopher Schaumburg, Robert Strieter, Joy Kane, Thomas E Lane

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**Public Summary:**
Multiple sclerosis (MS) is a human demyelinating disease characterized by multifocal regions of inflammation, progressive myelin loss within the central nervous system (CNS), and eventual failure to remyelinate damaged axons. These problems suggest deficiencies in recruiting and/or maturation of oligodendrocyte progentior cells (OPCs) and highlight cell replacement therapies to promote remyelination. We have used a model of viral-induced demyelination to characterize signaling cues associated with positional migration of transplanted remyelination-competent cells. Although successful transplantation of rodent-derived glial cell types into models of MS has been performed, the mechanisms by which these cells navigate within an inflammatory environment created by a persistent virus has not been defined. Infection of the mouse CNS with the neurotropic JHM strain of mouse hepatitis virus (JHMV) results in an immune-mediated demyelinating disease with clinical and histologic similarities to MS. Surgical engraftment of GFP+ neural stem cells (NSCs) into spinal cords of JHMV-infected mice with established demyelination results in migration, proliferation, and differentiation of the cells into OPCs and mature oligodendrocytes that is associated with increased axonal remyelination. Treatment with anti-CXCL12 [stromal derived factor-1alpha, (SDF-1alpha)] blocking serum resulted in a marked impairment in migration and proliferation of engrafted stem cells. Moreover, small molecule-mediated antagonism of CXCR4, but not CXCR7, impaired migration and proliferation, to an extent similar to that with anti-CXCL12 treatment. These data highlight the importance of the CXCL12:CXCR4 pathway in regulating homing of engrafted stem cells to sites of tissue damage within the CNS of mice persistently infected with a neurotropic virus undergoing immune-mediated demyelination.

**Scientific Abstract:**
Multiple sclerosis (MS) is a human demyelinating disease characterized by multifocal regions of inflammation, progressive myelin loss within the central nervous system (CNS), and eventual failure to remyelinate damaged axons. These problems suggest deficiencies in recruiting and/or maturation of oligodendrocyte progentior cells (OPCs) and highlight cell replacement therapies to promote remyelination. We have used a model of viral-induced demyelination to characterize signaling cues associated with positional migration of transplanted remyelination-competent cells. Although successful transplantation of rodent-derived glial cell types into models of MS has been performed, the mechanisms by which these cells navigate within an inflammatory environment created by a persistent virus has not been defined. Infection of the mouse CNS with the neurotropic JHM strain of mouse hepatitis virus (JHMV) results in an immune-mediated demyelinating disease with clinical and histologic similarities to MS. Surgical engraftment of GFP+ neural stem cells (NSCs) into spinal cords of JHMV-infected mice with established demyelination results in migration, proliferation, and differentiation of the cells into OPCs and mature oligodendrocytes that is associated with increased axonal remyelination. Treatment with anti-CXCL12 [stromal derived factor-1alpha, (SDF-1alpha)] blocking serum resulted in a marked impairment in migration and proliferation of engrafted stem cells. Moreover, small molecule-mediated antagonism of CXCR4, but not CXCR7, impaired migration and proliferation, to an extent similar to that with anti-CXCL12 treatment. These data highlight the importance of the CXCL12:CXCR4 pathway in regulating homing of engrafted stem cells to sites of tissue damage within the CNS of mice persistently infected with a neurotropic virus undergoing immune-mediated demyelination.

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