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Triggering myelin repair in MS

By Tim Fulmer, Senior Writer

Researchers at the **Cleveland Clinic** and the **University of California, Irvine** have shown that knocking out *CXC chemokine receptor 2* on oligodendrocytes improves myelin repair in two different mouse models of multiple sclerosis.[1] The team thinks the receptor is an ideal target because it plays a role in two aspects of the disease: CNS inflammation and demyelination. However, finding antagonists that can cross the blood brain barrier could prove challenging.

The role of CXC chemokine receptor 2 (CXCR2; IL8RB) in recruiting immune cells to sites of peripheral inflammation has been established for more than a decade, but recent findings have revealed an additional role in the CNS. There, the receptor is expressed on at least two cell types involved in multiple sclerosis (MS): proinflammatory neutrophils, which infiltrate the CNS from the periphery, and oligodendrocytes, which are the CNS cells responsible for myelinating neurons.[2–4]

In previous studies, genetic knockout or blockade of Cxcr2 decreased pathology and demyelination in MS mouse models, suggesting that antagonizing the target could help treat the disease not only by blocking neutrophil-mediated inflammation but also by triggering remyelination by oligodendrocytes.

To test that hypothesis, a group led by Richard Ransohoff and Thomas Lane generated autoimmune encephalomyelitis (EAE) mouse models of MS that lacked Cxcr2 on oligodendrocyte precursor cells but still expressed the receptor on neutrophils. Ransohoff is director of the Neuroinflammation Research Center at the Cleveland Clinic, and Lane is a professor of molecular biology and biochemistry and an associate director of the Institute for Immunology at the University of California, Irvine.

As expected, the brains of the genetically modified EAE mice had lesion areas and inflammatory pathology similar to brains of wild-type EAE controls. However, the genetically modified mice showed significantly better myelin repair than the wild-type mice ($p<0.05$). Thus, knocking out *Cxcr2* exclusively in the CNS was sufficient to trigger remyelination even in the presence of local tissue injury and inflammation caused by neutrophils and other immune cells.

That finding was confirmed by a time-course study in a second MS mouse model, which showed that CNS-specific deficiency of Cxcr2 led to significantly accelerated remyelination at days 7 and 10 compared with that seen in wild-type controls ($p<0.05$).

Finally, in an *in vitro* brain slice model of myelination and remyelination, an antibody against CXCR2 significantly accelerated remyelination compared with control rabbit IgG ($p<0.01$). The findings were published in *The Journal of Neuroscience*.

According to Robert Miller, professor of neuroscience and vice dean for research at **Case Western Reserve University School of Medicine** and a member of the **Myelin Repair Foundation**, an ideal MS therapeutic would do two basic things: "control or dampen the inflammatory pathology that drives the disease and enhance repair of damaged myelin to improve neural function."

By accomplishing that two-pronged attack, a CXCR2 antagonist "could act at multiple stages in the disease process and prevent, as well as reverse, myelin damage. Currently there are no drugs that specifically reverse damage in MS," said Benjamin Segal, professor of neurology and director of the Program in Neuroimmunology and Multiple Sclerosis at the **University of Michigan Medical School**.

> **"Currently there are no drugs that specifically reverse damage in MS."**
> ***—Benjamin Segal, University of Michigan Medical School***

Both Segal and Miller said a clear next step is to develop CXCR2 antagonists that can penetrate the blood brain barrier to target both infiltrating immune cells and oligodendrocytes.

There are no disclosed brain-penetrant CXCR2 antagonists in clinical development. Instead, pharmas and biotechs are developing peripherally acting antagonists for pulmonary disorders such as chronic obstructive pulmonary disease (COPD) and cystic fibrosis (CF).[5–7]

Ransohoff told *SciBX* he is working with Lane and Miller to develop and characterize compounds capable of targeting CXCR2 in the CNS. He also plans to generate additional mouse models with conditional *Cxcr2* knockout in other cell types, including leukocytes and other stages of the oligodendrocyte developmental lineage.

"Those models will further clarify the expression pattern of CXCR2 in the CNS and better define its role in the progression of MS," he said.

The findings in *The Journal of Neuroscience* are not patented, according to Ransohoff.

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