More mileage out of myelin

By Tracey Baas, Senior Editor

A team led by U.K. researchers has shown that retinoid X receptor agonists can enhance remyelination of demyelinated axons in rodents by increasing the differentiation of oligodendrocyte precursor cells into oligodendrocytes.¹ This remyelination activity could spark interest in repurposing the agonists, which are on the market and in the clinic for cancer.

In individuals with demyelinating disease such as multiple sclerosis (MS), loss of myelin is often repaired by a natural regenerative process in which a type of stem cell called adult oligodendrocyte precursor cells (OPCs) migrate to injured areas, differentiate into oligodendrocytes and restore myelin. However, as the disease progresses, the process of rebuilding is unable to keep pace with the disease-induced damage, leading to chronic lesions and neurologic deterioration.

The team came across RXRs as part of a search for key genes involved in CNS remyelination. In rodents whose axons had been focally demyelinated by toxin, the team found that genes associated with myelination and Rxr signaling were more highly expressed during the natural regeneration process. *Retinoid X receptor-γ* (*Rxrg*; *Rxrγ*), one of three types of RXRs, was one of the most upregulated genes.

The group corroborated the importance of *RXRG* expression in MS by using postmortem brain sections from MS patients. Indeed, *RXRG* was expressed predominantly in oligodendrocyte lineage cells within the active borders of lesions but not in cells within the chronic inactive core, suggesting that *RXRG* plays a role in myelin repair.

Next, in explants from mice with toxin-induced demyelination, the Rxr agonist 9-*cis*-retinoic acid (9cRA) led to the generation of more remyelinated axons than saline.

Critically, in aged rats, in which remyelination is inherently inefficient and mimics the progressive decline in remyelination seen in MS patients, 9cRA accelerated the rate of remyelination following toxin-induced demyelination.

"If OPC differentiation and remyelination could be enhanced in chronic lesions, it would be truly clinically relevant," said Thomas Lane, professor of molecular biology and biochemistry and director of the MS Center at the **University of California, Irvine**.

The findings were published in *Nature Neuroscience*, and the team

included researchers from the **University of Cambridge**, **The Queen's Medical Research Institute**, **Pierre and Marie Curie University**, **Louis Pasteur University** and **Tokyo Medical and Dental University**.

Co-lead authors were Robin Franklin, professor of neuroscience and director of the MS Society Cambridge Centre for Myelin Repair at the University of Cambridge, and Charles ffrench-Constant, professor of medical neurology and director of the Multiple Sclerosis Society Centre for MS Research at **The University of Edinburgh**.

Model behavior

One important question raised by researchers contacted by SciBX was the potential clinical relevance of the toxin-induced MS model used in the *Nature Neuroscience* paper. Researchers were split on whether this model provided a better picture of the utility of RXR agonists than the more widely used experimental autoimmune encephalomyelitis (EAE) model.

"By using a toxin-induced MS model, the researchers know exactly where lesions will develop, allowing them to capture specific injured tissue with laser microdissection," said Bruce Trapp, chairman of neurosciences at **Cleveland Clinic's** Lerner Research Institute and a founder and CSO of **Renovo Neural Inc.** "The researchers also know the exact time when the lesions form, allowing them to collect precise kinetic data and characterize whether therapeutic intervention enhances remyelination. Their model unequivocally shows that 9cRA accelerates remyelination."

The downside, Trapp said, is that the toxin model "lacks the immunopathic component that is observed in MS. The EAE model of MS relies on brain inflammation to induce demyelination and shows an etiology more similar to that of MS. But with EAE, you don't know when the lesions form and you don't know their location, so there are pros and cons with each model. While EAE is useful to evaluate anti-inflammatory therapeutics, it may not be helpful to assess remyelination."

Franklin thinks the toxin-induced model is well suited to identify compounds that are regenerative.

"Axon destruction in MS is partially due to inflammation; this is certainly true in the acute lesion and is why effective immunosuppression is neuroprotective," said Franklin. "However, there is a second type of axon degeneration that occurs in the chronic lesion and arises from an entirely different mechanism that is independent of inflammation and relates to the loss of trophic axonal support provided by the myelinating cell. It is this second type of axonal loss that remyelination therapies—neuroregenerative therapies—aim to prevent."

"Because there is no perfect model, it would be crucial to see how RXR agonists affect remyelination in several of the different MS models available," said Lane. "In many of the commonly used MS models, the rodents do not have chronic lesions like those seen in individuals with MS."

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University of California, Irvine

Trapp agreed. "Until there is a better animal model of MS, several models should be used for evaluation, including those with chronic lesions," he said. "At Renovo Neural, we use a cuprizone-induced demyelination mouse model that shows acute lesions at 6 weeks and chronic lesions at 12 weeks."

Using these models, Renovo Neural is testing molecules that increase numbers of OPCs and/or induce oligodendrocyte differentiation.

A delicate dance

Until now, RXR agonists have been used exclusively in the cancer space. These include Targretin bexarotene, which is marketed by **Eisai Co. Ltd.** to treat cutaneous T cell lymphoma (CTCL); **Kowa Co. Ltd.**'s peretinoin (NIK-333), which is in Phase II/III testing to treat liver cancer; and NRX4204 from **Vitae Pharmaceuticals Inc.** and partner **NuRx Pharmaceuticals Inc.**, which is in Phase I to treat cancer. These compounds are relatively nonspecific RXR agonists.

Regardless of model employed, Trapp thinks further work needs to detail the molecular pathways that RXR agonists affect and to develop more finely tuned agonists. Part of the issue, he said, is that "the receptor is found in multiple cell types in the brain, and broad modulation of RXRs might lead to as yet unknown side effects in the CNS."

RXRs are nuclear receptors that work through heterodimeric association with other nuclear receptors. RXR heterodimer partners include liver X receptor (LXR) and peroxisome proliferation-activated receptor (PPAR), both of which have been described in oligodendrocyte lineage cells.²⁻⁴

PPAR already has been identified as a target in MS. In an EAE mouse model, the PPAR agonist Actos pioglitazone blocked the development of autoimmune-associated T helper type 17 (Th17) cells, suggesting that the drug might help prevent flare-ups of relapsing-remitting MS.⁵

Actos is an insulin sensitizer marketed by **Takeda Pharmaceutical Co. Ltd.** to treat type 2 diabetes.

Ultimately, Trapp wanted the authors of the *Nature Neuroscience* paper to show "which RXR heterodimers are most specific to OPCs and oligodendrocytes and possibly identify compounds that can activate these specific heterodimers to cause oligodendrocyte differentiation and myelin repair."

Ongoing studies by Franklin and ffrench-Constant are looking for heterodimer interactions of RXRG.

Lane thinks the ideal MS treatment will be "both immunosuppressive, dampening the immune system to prevent the damage, and

neuroregenerative, repairing lesions that have already formed. This will most likely involve a therapeutic cocktail."

Trapp agreed. "A therapeutic strategy that combines immunosuppression and neuroregeneration would be the most attractive. With the neuroregenerative aspect, it will be important to include compounds that inhibit the inhibitors of remyelination, such as LINGO-1 and NOGO, and also compounds that enhance remyelination, so the identification of 9cRA as an RXRG agonist is an important lead," he said.

An antibody against LINGO-1 (leucine-rich repeat neuronal protein 1) from **Biogen Idec Inc.** is in Phase I to treat MS.

GlaxoSmithKline plc is running a Phase I trial of an antibody against NOGO (reticulon 4; RTN4; NOGO-A) to treat amyotrophic lateral sclerosis (ALS), while **Novartis AG** has an anti-NOGO antibody in Phase I testing to treat spinal cord injury (SCI).

9cRA has not been patented, and the authors are working with more potent, undisclosed RXRG agonists.

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