Gene immunotherapy protects against multiple sclerosis in mice

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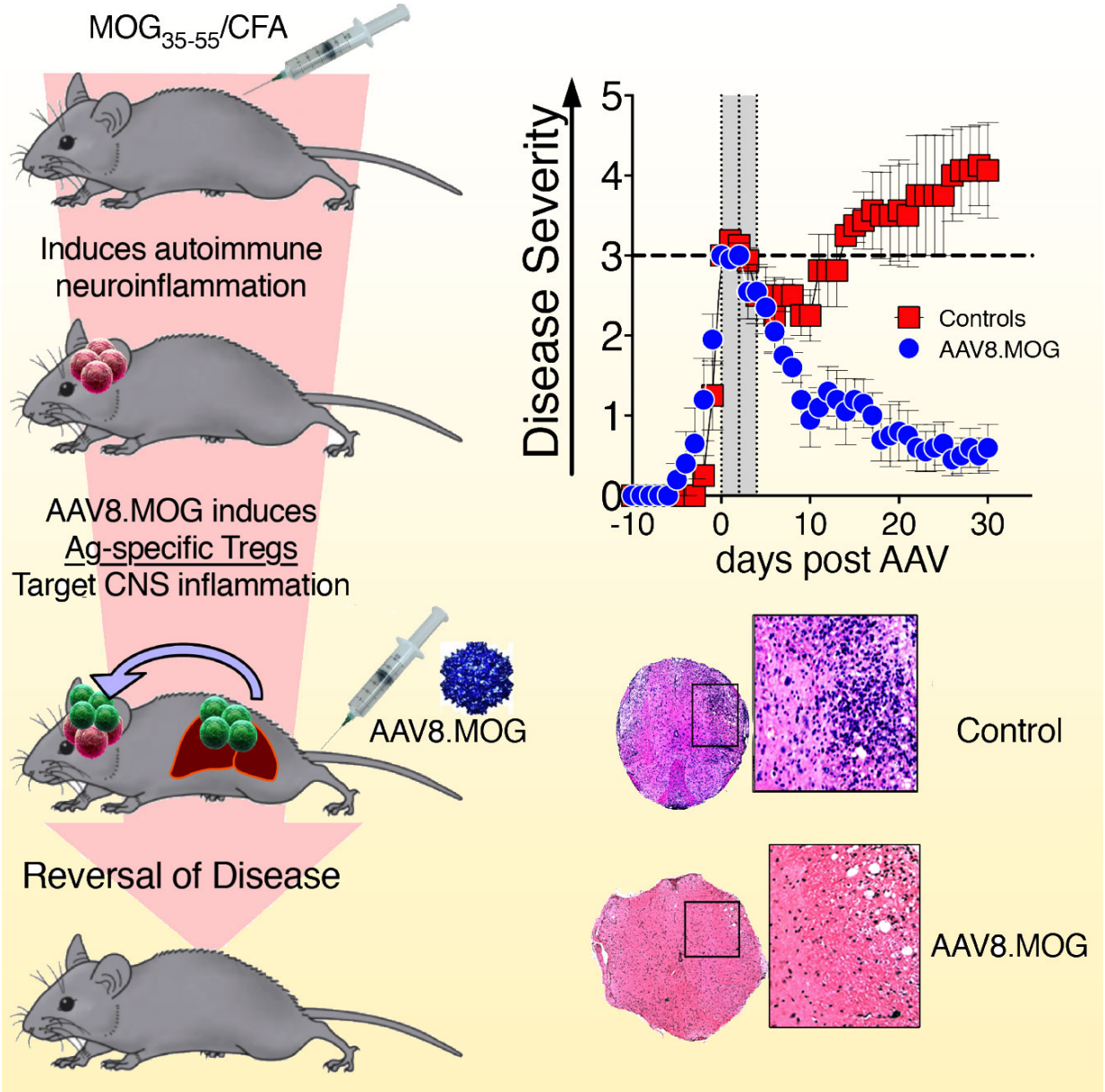

This visual abstract depicts the work of Keeler et al., who developed a gene immunotherapy for multiple sclerosis in mice. Credit: Keeler et al.

A potent and long-lasting gene immunotherapy approach prevents and reverses symptoms of multiple sclerosis in mice, according to a study published September 21st in the journal *Molecular Therapy*. Multiple sclerosis is an autoimmune disease in which T cells destroy the myelin sheath—the material that surrounds and protects nerve cells in the brain and spinal cord. The researchers used a viral vector to deliver a gene encoding a myelin sheath protein to the liver, thereby inducing robust and durable immune tolerance in mice by preventing T cells from attacking the myelin sheath.

"Using a clinically tested gene therapy platform, we are able to induce very specific regulatory cells that target the self-reactive cells that are responsible for causing disease," says senior study author Brad E. Hoffman of the University of Florida. "In contrast, most current therapies for autoimmune diseases such as multiple sclerosis are based on general immune suppression, which has various side effects or complications."

Multiple sclerosis is the most common disabling neurological disease in young adults, affecting approximately 2.5 million people worldwide. The symptoms can range from relatively benign to devastating, as communication between the brain and other parts of the body is disrupted. The disorder can cause muscle weakness, numbness, a loss of muscle coordination, and problems with vision, speech, and bladder control. Currently there is no cure, but some conventional treatments can improve symptoms, reduce the number and severity of relapses, and delay the disease's progression.

Although the exact cause of the disease is unknown, it is thought to result from activation of self-reactive effector T cells that attack myelin sheath proteins such as myelin oligodendrocyte glycoprotein (MOG). Normally, regulatory T cells keep such autoimmune responses in check by curbing the self-destructive activity of effector T cells, thereby maintaining immune tolerance. The transfer of regulatory T cells to mice with a multiple sclerosis-like disease can temporarily prevent or reduce neurological symptoms. Moreover, injection of regulatory T cells appears to be safe and effective in patients with other autoimmune disorders such as type 1 diabetes, Crohn's disease, and graft-versus-host disease. However, these immunotherapy approaches are not sufficiently potent or long-lasting.

To overcome this hurdle, Hoffman and his team developed a gene immunotherapy strategy that leverages the unique ability of the liver to induce immune tolerance. The researchers used an adeno-associated virus (AAV) vector, similar to those currently being evaluated in clinical trials, to deliver myelin oligodendrocyte glycoprotein to the liver in a mouse model of multiple sclerosis. A single injection effectively induced immune tolerance, stimulating regulatory T cells that protected the myelin sheath by suppressing self-destructive effector T cells.

This gene immunotherapy approach protected mice from developing clinical signs of multiple sclerosis over a seven-month period, demonstrating stable and robust immune tolerance. Moreover, the treatment reversed symptoms in mice that had already developed mild to moderate neurological deficits, and even restored mobility in mice that had developed more severe symptoms such as hind-leg paralysis.

"Traditional AAV gene therapy has been focused on delivering a transgene that produces a therapeutic protein," Hoffman says. "Here we use the platform purposely to induce specific regulatory cells in order to restore immune tolerance and reverse an autoimmune disease."

While AAV immunotherapy alone did reduce clinical symptoms, it was not sufficient to fully reverse end-stage disease. However, when combined with a short dose of the clinically approved immunosuppressive drug rapamycin, this gene immunotherapy approach induced complete remission in nearly all mice at late stages of the disease, restoring mobility after severe paralysis and protecting mice from symptoms until the end of the experiment approximately 100 days later.

Because myelin oligodendrocyte glycoprotein is only one protein implicated in multiple sclerosis, Hoffman and his team have developed other viral vectors to deliver additional myelin sheath proteins. They are also currently looking to expand the range of autoimmune diseases that could benefit from this methodology.

"Our results are very promising. We have demonstrated that stable immune tolerance can be re-established and that active disease can be stopped and clinical symptoms reversed using our gene immunotherapy, especially during early onset of disease," Hoffman says. "Even though these studies were performed in a less complex mouse model, the data suggest this may be a potential therapy in humans with additional optimization."

More information: *Molecular Therapy*, Keeler et al.: "Gene Therapy Induced Antigen-Specific Tregs Inhibits Neuro-inflammation and Reverses Disease in a Mouse Model of Multiple Sclerosis" www.cell.com/molecular-therapy … 1525-0016(17)30413-6 , DOI: 10.1016/j.ymthe.2017.09.001

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