Unique Genetic Marker Discovery May Help Predict Multiple Sclerosis Relapse

Sep. 27, 2012 — Scientists may be one step closer to predicting the uncertain course of relapsing-remitting multiple sclerosis (MS), a disease that can lay dormant for months or years, thanks to the discovery of a unique genetic marker. The marker, detailed by researchers in the August edition of The Journal of Immunology, is the first of its kind to be directly linked to MS.

The study, supported by funding from both the National Institutes of Health (NIH) and the Ohio State Center for Clinical and Translational Science (CCTS) was conducted by a team of scientists with The Ohio State University using blood samples from patients with MS, as well as mouse models. Researchers uncovered the molecule miR-29, while working to identify a biomarker in the blood that could indicate if a patient had an ongoing inflammatory response, such as MS.

"Our research was inspired by the knowledge gap that existed between microRNA and MS, as well as the unpredictable nature of MS," said Kristen Smith, Ph.D., principal investigator, who received a "mentorship grant" to conduct the study alongside senior scientists at The Ohio State University Wexner Medical Center. "By identifying a unique marker associated with MS, we hope to inspire a relatively noninvasive test that could identify and predict the course of the disease, helping clinicians tailor therapies to disease progression."

miR-29 is one member of a group of microRNAs (miRNAs) which are known as critical regulators of the immune system. miRNAs are a relatively new discovery, with nearly 1,400 having been identified to date. In addition to regulating the immune system, miRNAs also regulate gene expression. Previous research has shown miR-29 is responsible for regulating Th1 cells, a type of white blood cell that provides protective immune responses against infection. Uncontrolled, these cells can produce excessive inflammation, leading to tissue damage and autoimmune diseases, such as MS.

Despite the known relationship between miRNAs and the immune response, research regarding the connection between miRNAs found in Th1 cells and autoimmune disorders driven by these uncontrolled white blood cells had not been conducted until now.

"Since we knew miRNAs play an important role in creating and controlling inflammation in the body, we believed it was also likely miRNAs played a role in the inflammation process that underlies MS," said Smith. "What we found was important to the understanding of the disease- the profile of expression or activity of miRNAs did change in MS patients as compared to healthy adults."

What researchers discovered was a negative feedback loop. Specifically, Smith utilized genetic knockout mice to prevent miR-29 from functioning, resulting in unrestrained production of T-bet and interferon gamma (IFN-y). T-bet, a transcription factor, controls the expression of IFN-y, a molecule produced as part of the immune response that is often linked to autoimmune disease when uncontrolled. miR-29b, whose expression is elevated in T cells of patients with MS, regulates T-bet and IFN-y, while at the same time, IFN-y enhances miR-29b expression, creating a novel regulatory feedback loop. Based on these findings, as well as an
understanding of miR-29b levels in patients with MS, researchers concluded the feedback loop is dysregulated in MS patients, likely contributing to the chronic inflammation that underlies MS.

This research team also found miR-29b is increased in the infection fighting memory CD4+ T or T helper cells of MS patients, which may cause chronic Th1 inflammation. However, miR-29b levels decrease significantly once these T cells are activated in MS patients, additionally supporting the theory that a dysregulated feedback loop exists. Based on their findings, these researchers concluded miR-29 serves as a novel regulator of Th1 differentiation, or the specialization of cells, adding to the understanding of T cells' regulatory mechanisms that maintain a balance between protective immunity and autoimmunity.

Researchers involved in the study say they hope their findings will inspire additional research that can help measure the presence of miR-29 across cycles of relapse and remission making it possible to utilize the marker as a predictor of disease.

"We know the earlier we intervene with effective therapy the greater the impact we can have on the course and pace of MS," said Caroline Whitacre, Ph.D., head of the laboratory and vice president for research at Ohio State. "By creating a diagnostic tool that can predict relapse, MS patients' number one complaint, we can potentially change the way clinicians approach therapeutics and treat these patients."

MS is a chronic, autoimmune disease affecting nearly 400,000 Americans. The disease impacts the central nervous system and typically presents in one of four courses, including relapsing-remitting, primary-progressive, secondary-progressive and progressive-relapsing. More than 85 percent of newly diagnosed patients are found to be in the relapsing-remitting stage. Symptoms of MS vary based on the amount of nerve damage caused by the disease and can include numbness, temporary vision loss, dizziness and fatigue. Current treatment options help to slow the course of the disease, but do not offer a cure.

Journal Reference:

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K. M. Smith, M. Guerau-de-Arellano, S. Costinean, J. L. Williams, A. Bottoni, G. Mavrikis Cox, A. R. Satoskar, C. M. Croce, M. K. Racke, A. E. Lovett-Racke, C. C. Whitacre. **miR-29ab1 Deficiency Identifies a Negative Feedback Loop Controlling Th1 Bias That Is Dysregulated in Multiple Sclerosis.** *The Journal of Immunology,* 2012; 189 (4): 1567 DOI: [10.4049/jimmunol.1103171](http://10.4049/jimmunol.1103171)

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