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Why inflammation leads to a leaky blood-brain barrier: MicroRNA-155

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Until now, scientists have not known exactly how inflammation weakens the Blood-Brain Barrier, allowing toxins and other molecules access to the brain. A new research report appearing in the June 2014 issue of *The FASEB Journal* solves this mystery by showing that a molecule, called "microRNA-155," is responsible for cleaving epithelial cells to create microscopic gaps that let material through. Not only does this discovery help explain the molecular underpinnings of diseases like multiple sclerosis, but it also opens an entirely new avenue for developing therapies that can help penetrate the Blood-Brain Barrier to deliver lifesaving drugs.

According to Ignacio A, Romero, Ph.D., "We are beginning to understand the mechanisms by which the barrier between the blood and the brain becomes leaky in inflammatory conditions. Based on these and other findings, drugs that reduce the leakiness of the barrier have the potential to improve symptoms in many neurological conditions." Romero is one of the researchers involved in the work from the Department of Life, Health and Chemical Sciences of the Biomedical Research Network at The Open University in the United Kingdom.

To make this discovery, Romero and colleagues first measured microRNA-155 (miR-155) levels in cultured human cells and compared them to cells under inflammatory conditions. Researchers then measured levels in the blood vessels of inflamed brain areas of patients with multiple sclerosis (MS) and compared them to non-inflamed areas. In both cases, miR-155 was elevated in inflammation. Then, in mice,

normal mice were compared with mice that were genetically altered to lose miR-155. When an inflammatory reaction was induced in these two groups of mice, the mice that could not express miR-155 had a much reduced increase in "leakiness" of the Blood-Brain Barrier than normal mice. Finally, scientists investigated in cultured human cells the mechanism by which miR-155 levels cause leakiness of the barrier and concluded that miR-155 affects the organization of the complex structures that form the tight connections between endothelial cells.

"This study has the potential to be a game-changer in terms of how we treat neurological conditions and how we deliver drugs to the brain," said Gerald Weissmann, M.D., Editor-in-Chief of *The FASEB Journal*. "Since it was first discovered, the Blood-Brain Barrier has always been a touch elusive. Now, after careful analysis, we are learning exactly how our bodies keep our brains safe and that microRNA-155 is a key player."

More information: Miguel Alejandro Lopez-Ramirez, Dongsheng Wu, Gareth Pryce, Julie E. Simpson, Arie Reijerkerk, Josh King-Robson, Oliver Kay, Helga E. de Vries, Mark C. Hirst, Basil Sharrack, David Baker, David Kingsley Male, Gregory J. Michael, and Ignacio Andres Romero. MicroRNA-155 negatively affects blood–brain barrier function during neuroinflammation. *FASEB J.* June 2014 28:2551-2565; DOI: 10.1096/fj.13-248880

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