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Blocking crucial molecule could help treat multiple sclerosis

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Reporting in *Nature Immunology*, Jefferson neuroscientists have identified a driving force behind autoimmune diseases such as multiple sclerosis (MS), and suggest that blocking this cell-signaling molecule is the first step in developing new treatments to eradicate these diseases.

Researchers led by Abdolmohamad Rostami, M.D., Ph.D., Professor and Chairman of the Department of Neurology at Jefferson Medical College of Thomas Jefferson University, found that GM-CSF, which stands for Granulocyte-macrophage colony-stimulating factor, appears to be the key culprit in the onset of MS, because without it, T helper 17 cells (Th17) cells did not induce the MS-like disease in an experimental animal model.

Th17 cells have been shown to play an important pathogenic role in humans and experimental models of autoim¬mune diseases, but the mechanisms behind this have remained elusive until now.

"There was no connection between GM-CSF and Th17 cells before," said Dr. Rostami. "What we have shown in this paper is that GM-CSF derived from Th17 cells is important in the cell-signaling process that leads to inflammation in the central nervous system."

"Now we know how the Th17 cells work and a better understanding of this mechanism and biology leads to new therapeutics," he adds.

The results suggest that blocking GM-CSF activity may be a successful

therapeutic strategy in MS, one of the most common neurological diseases affecting young adults, and other autoimmune diseases, said Dr. Rostami, who is also the Chair of Neurology at Thomas Jefferson University Hospital.

The paper first appears in an advance online publication of *Nature Immunology* on April 24.

These findings identify the interleukin-23 (IL-23)/ Th17/GM-CSF axis as the major pathway in pathogenesis of autoimmune central nervous system inflammation and likely other autoimmune diseases. IL-23, a known cytokine that causes autoimmune inflammation of the brain, induces production of more GM-CSF in Th17 cells, the researchers explain.

Dr. Rostami, who is also director of the Neuroimmunology Laboratory in the Department of Neurology at JMC, and his colleagues used an animal model of MS called experimental autoimmune encephalomyelitis (EAE) for the investigation, a common model used to study the pathogenesis of the disease. Mice whose Th17 cells cannot produce GM-CSF did not develop neuroinflammation, thus GM-CSF is responsible for disease manifestation in this experimental model. This scenario suggests feed-forward loop of IL-23 and GM-CSF driving the pathogenic encephalitogenic immune response in the brain and spinal cord.

Another recently published paper in Nature Immunology by Dr. Rostami and his team unraveled a mechanism that may help fight MS. The researchers found that a protein known as interkeukin-27 (IL-27) helped block, not induce, the onset of symptoms in animals with an MS-like disease. While increasing levels of GM-CSF may cause the disease, as shown in the current paper, increasing IL-27 concentrations may help quell an over-active immune system, the researchers reported.

"That was the first time that we had direct evidence that by actively giving IL-27 like a drug, we can suppress EAE in mice," Dr. Rostami said.

If similar findings from this current study of GM-CSF are found in human blood samples, this approach could eventually also be shown to be useful in the clinical setting, Dr. Rostami explains.

Whether GM-CSF drives neuroinflammation in MS remains unknown, but the current findings highlight the potential that IL-23 and GM-CSF might serve a similar role in human disease.

"This is the first step towards finding a new treatment," he said. "If we can try to neutralize GM-CSF by different means, for example, by trying to mimic it or trying to block the receptor for GM-CSF, we can hopefully ameliorate the disease."

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