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Surprising contributor to Rett syndrome identified

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The immune system is designed to protect us from disease. But what if it was malfunctioning? Would it make a disease worse? That appears to be the case with Rett syndrome, a neurodevelopmental disorder, and possibly in other neurological disorders as well, new research from the University of Virginia School of Medicine has found.

UVA's discovery suggests that immune cells bearing a mutation in the Rett gene, MeCP2, cannot perform their normal function and are instead amplifying the disease. By identifying a new role of the immune system in the disorder, through cells known as "macrophages," the UVA team has opened up an exciting new pathway to targeting the disease therapeutically.

Rett syndrome, until recently classified as a severe case of autism-spectrum disorder, affects girls almost exclusively. Children with the disease develop normally at first, but then symptoms begin to appear—children lose their acquired cognitive and motor skills, develop seizures and experience breathing problems. Scientists previously linked the condition with a mutation of the MeCP2 gene within brain cells called neurons. UVA's discovery, however, shows that a lack of that gene in immune cells has disastrous consequences that reach beyond the brain.

"These immune cells may be functioning OK when there is no problem, but the moment there is any sort of problem in any tissue, to respond they need this gene," said Jonathan Kipnis, PhD, of the UVA

Department of Neuroscience and director of UVA's Center for Brain Immunology and Glia. "And without this gene, macrophages not only do not respond properly. They respond abruptly, and they start to produce molecules that are further damaging the tissue. ... Cells which are supposed to maintain tissue are killing that tissue."

The discovery points to the immune system as a promising target for slowing the progression of Rett syndrome. Unlike most brain cells, which are never replaced, the immune system can be easily manipulated or even replaced entirely via a bone-marrow transplant. "I don't think you could cure this disease without fixing the neurons, but fixing neurons is a really tall order," said researcher Jim Cronk, the lead author of a new paper outlining the findings. "So our tact is to look at what else is going on here and what else can we do to help. What's feasible with the tools that are available?"

The researchers identified the role of the immune system after contemplating the scope of the Rett symptoms. "Many organs are suffering from this disease - guts, bones, muscles, heart," Kipnis said. "And we said, wait a second, we see that MeCP2 plays a very important role in microglia. Microglia are brain macrophages [immune cells]. What about other macrophages? Each tissue has its own macrophages - and their No. 1 goal is to ensure homeostasis of tissue. If macrophages are impaired, then every tissue may be suffering."

The work, a close collaboration between the Kipnis lab and the lab of Vladimir Litvak, PhD, of the University of Massachusetts Medical School, has been published online by the journal *Immunity*.

Kipnis hailed Cronk's important contributions to the work, noting that Cronk is a student in UVA's Medical Scientist Training Program.