Transcript Details
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Inflammatory Gateways: Exploring the Role of the Choroid Plexus in Post-TBI Care

Announcer:
You're listening to *NeuroFrontiers* on ReachMD. On this episode, Dr. Prajwal Ciryam will discuss his research on the choroid plexus response to traumatic brain injury. Dr. Ciryam is an Assistant Professor of Neurology at the University of Maryland School of Medicine, and he presented this research at the 2025 American Academy of Neurology Annual Meeting. Let's hear from him now.

Dr. Ciryam:
The reason that we looked at the choroid plexus actually goes back a little. When I was a neurocritical care fellow working in the ICU in New York, we'd get cerebrospinal fluid samples on lots of patients who had had brain hemorrhages and acute brain injuries, and there's this massive inflammatory response that happens early that we really have no treatment for and that we only sort of understand. That inspired me to start trying to understand brain inflammation after these injuries and particularly what happens in the cerebrospinal fluid. And when I decided to do that, it became almost a fait accompli that I would have to think about the choroid plexus. It's what makes the cerebrospinal fluid, but it also serves as this gateway for the body to send cells and inflammatory molecules into the CSF and brain.

We have a model of traumatic brain injury in mice where we induce a contusion on one side of the mouse's brain, and at three hours, six hours, or 24 hours after the injury, we euthanized mice and then dissected out their teeny, tiny choroid plexuses and ground them up, got the messenger RNA out of them, and sequenced that. So then we got expression levels for 16,000 or so genes at three hours, six hours, or 24 hours after injury, and also in animals that had a sham injury where we did a surgery but we didn't hit their brain. And what we found, which was surprising to us, is that especially early after the injury, in those first three or six hours, the response is dominated by these genes that make proteins that are attractants for neutrophils. Neutrophils are the first responders to injury, and what it looks like is that the tissue is just making a ton of these transcripts that make proteins that say, "Hey, neutrophils, come here." And so we think that the first phase of the response is this attraction of neutrophils that totally dominates the work that the choroid plexus is doing in those hours after injury. And then, by 24 hours, a bunch of genes that make enzymes that chew up the matrix start to come in, and so we think that there may be a path that is being made for these cells to then work their way through the choroid plexus.

When we think about the timing of treatments for acute brain injuries, it's all about being as fast as we can. We know this from stroke treatment where time is brain, and early treatment makes a huge difference. I think that's possible in traumatic brain injury as well. We have not been successful in acute brain injury in demonstrating that anti-inflammatory medications work. Part of the reason is we often use these broad-based steroids, like dexamethasone, that do a million things. And we know that the immune response is complex and multifaceted. And so what we want to do is not just anti-inflammatory, but it is the way that we try to do everything in the intensive care unit. It is to take control of a system that we try to understand as well as possible and guide it away from damaging behavior towards functional behavior.

What I envision—and we are way off from this, I mean years and years and years in the best case scenario—is one where we are able to profile the inflammatory status of individual patients using the blood and the cerebrospinal fluid—advanced techniques to give us a snapshot of where they are today, understand that response well enough to know where they should be for repair, and then ideally use this information on how cells are getting in through the choroid plexus, but potentially through other sites as well—the meninges, directly across the blood-brain barrier—in order to deliver treatments that push away from the damaging aspects of the immune system and towards the more reparative ones.

Where does this study come in? It's very early, right? This is in a mouse. It's a limited model. It's looking at some very particular sets of gene expression changes. But where we're going from here is building systems to specifically block these two main chemokines—

CXCL1 and CXCL2. These are the most upregulated genes. So our next step is to ask, if you block those, does that change the inflammatory state of the CSF in the brain in the model?

We are engineering systems to essentially knock out or delete components of these genes in the choroid plexus, specifically in mice, and we're going to be asking over the course of the next year or two whether doing that has an effect on the inflammatory response in the brain and the choroid plexus, or are the cells no longer coming in? Is this the system that matters, and what is the consequence on that for the mouse's function and behavior after getting the traumatic brain injury? So that will help us understand whether this works.

We have been doing single-nuclei RNA sequencing on cerebrospinal fluid from patients after acute brain injuries—brain hemorrhage mostly—but we're starting to do traumatic brain injury, to profile the immune cell population in the central nervous system. We know that we're going to need good diagnostics and biomarkers in order to identify the patients who are going to benefit from treatment, and so we have a two-pronged strategy where, on one hand, we try to get the patients to teach us what's important by looking with deep molecular and cellular techniques and what is happening in their bodies, and then we can validate and test that in the mouse. And my hope is that in the long term, we're able to bring that back to future patients to improve their care.

Announcer:
That was Dr. Prajwal Ciryam talking about the choroid plexus response to traumatic brain injury. To access this and other episodes in our series, visit *NeuroFrontiers* on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening!