Transcript Details

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Epigenetic Immune Signatures in Alzheimer's: Implications for Diagnosis and Therapy

Announcer:
You're listening to *NeuroFrontiers* on ReachMD. On this episode, we'll hear from Dr. David Gate, who's an Assistant Professor of Behavioral Neurology and the Director of the Abrams Research Center on Neurogenomics at the Northwestern University Feinberg School of Medicine. He'll be discussing his research on epigenetic alteration to the peripheral immune system in Alzheimer's disease. Here's Dr. Gate now.

Dr. Gate:
So we were interested in answering the question of whether Alzheimer's disease patients had epigenetic changes, perhaps influenced by their environment or prior illnesses, and that these influences on their immune system would be reflected epigenetically. And we used ATAC-Seq as an epigenetic readout to look at changes in chromatin accessibility.

What we found with this technique was rather interesting. When we looked at genes that had both open chromatin regions that were more open in Alzheimer's patients than in controls and also had increased expression of that same gene—so more accessibility on the chromatin level and then more expression as well—and when we looked at these genes and what they did, they were primarily if not exclusively proinflammatory genes.

I think really the key finding for us was that there are signs of epigenetic alteration to the peripheral immune system in Alzheimer's patients. And in fact, when we looked deeper into the genetics of this Alzheimer's cohort that we studied, we were able to stratify them by whether they carried one or two copies of the APOE4 genotype, which is one of the major risk factors for late-onset Alzheimer's disease. And what we found was that these APOE4 carriers within the Alzheimer's patient cohort had more of these epigenetic alterations or open chromatin regions in proinflammatory genes.

And we had also identified a particular receptor on T cells called CXCR3 that had an open chromatin region in its promoter, which was an interesting finding for us because it had been recently shown by Rudy Tanzi at Harvard that this CXCR3 receptor mediates the honing of T cells into cerebral organoids in culture. So our data dovetailed nicely with theirs, and we had shown here in living patients that they had an epigenetic alteration to a T cell receptor that had been shown by another group as mediating their response to brain pathology in Alzheimer's disease.

And so what we've learned here is that you have to be careful in how you stimulate the immune system of Alzheimer's disease patients. And where we're going with our research now is trying to understand whether immune responses might be involved in the detrimental side effects to anti-amyloid antibodies. These are side effects known as amyloid-related imaging abnormalities, where patients often have vascular changes in their brains in response to the amyloid antibodies. And so what we're looking at now is the response of the peripheral and cerebrospinal fluid immune system of patients who are being administered these anti-amyloid antibodies in the clinic.

The next steps to translating this work into clinical applications are for us to determine, if immune responses are involved in the response to these anti-amyloid drugs, can we mitigate those immune responses to improve patient outcomes? And so this is going to require studies of patients who are in, perhaps, the early stages of Alzheimer's disease where we can track their response to these drugs.

Announcer:
That was Dr. David Gate discussing epigenetic immune alterations in patients with Alzheimer's disease. 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!