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New Study Shows EBV-Specific T-Cells Contribute to MS Development

Announcer:
You're listening to *NeuroFrontiers* on ReachMD. On this episode, we'll hear from Dr. J. William Lindsey, professor and Director of the Division of Multiple Sclerosis and Neuroimmunology with McGovern Medical School at UT Health Houston. He'll be discussing his research on EBV-specific T-cells and how they play a key role in the development of multiple sclerosis. Let's hear from him now.

Dr. Lindsey:
So we were looking for the antigen specificity of the T cells that are in the brain. And you can't actually, in most cases, look at the T cells that are in the brain in MS, but we sometimes get spinal fluid for diagnosis, and you can look at the T cells there, which are probably very similar to the ones that are actually in the brain. So our interest was to find out what those cells were specific for, and we used RNA sequencing, which is a relatively new technique, to be able to do that.

So we took cells from the spinal fluid, and we got cells from the blood at the same time. With the cells from the spinal fluid, we saved them all and extracted RNA, and then sequenced the T cell receptors that are there. With the cells in the blood, we did several different things. One is the spinal fluid, we extracted RNA for T cell receptor sequencing. Second is that we stimulated cells with different antigens, which included Epstein-Barr virus as the virus and varicella virus—that's another virus that's been argued to be causative in MS—and then a couple of unrelated antigens or pathogens candida and influenza as negative controls. We also took some of the cells from the initial blood sample and started Epstein-Barr virus-infected cell lines, so that's one of the convenient things about studying Epstein-Barr virus is it infects B cells, and B cell-infected cell lines will grow forever in culture as long as you keep giving them fresh media, so the virus infection circumvents the usual growth regulation in B cells. So we started a virus infected cell line for each of the subjects, and once that was grown out, usually after six to 12 weeks, we would use the virus-infected cells to stimulate frozen T cells, and we would sort out the responding T cells to that. Then we sequenced the T cell receptors from spinal fluid, blood, and from all the different types of antigen-responding cells, and we used the T cell receptor sequences from the antigen-responding cells to assign antigen specificity to the cells that were present in the spinal fluid.

And a couple of major findings. One is that the number of cells in the spinal fluid that were specific for Epstein-Barr-infected cells from the same person—and I'm going to call those LCLs, which stands for lymphoblastoid cell lines, because that's the terminology in the paper—so the number of cells, or T cells, in the spinal fluid that were specific for LCLs was about 13 percent overall. So the cells in the spinal fluid, probably about 60 percent are present in only one copy, so it's just a single cell with that T cell receptor, and then another 20 percent maybe have two copies, and then progressively smaller numbers of cells will have more and more copies. And we think those are more likely to be relevant to causing disease, that those should have likely been either specifically recruited into the spinal fluid or they've been retained there, and they've expanded there, so they're probably seeing an antigen and doing something that keeps them in the spinal fluid.

So if you look at the top one percent, most expanded clones, about 50 percent of those are specific for LCLs, and that's far more than we saw for any of the other antigens. For each of the antigens, there were some cells in the spinal fluid that were specific or that shared T cell receptors, but the LCLs really stood out as being much more common than the others, even more common than the Epstein-Barr virus itself, which I think is an important observation, that it's not the free virus that's the problem; it's the virus-infected cells that are stimulating the autoreactive immune response.

I think there's still a little work to do to demonstrate that the MS people are truly different than other neurologic diseases, but the impression from this first round of data is that LCL-specific T cells are greatly increased in people with MS and that may be one of the defining features of the disease.

Announcer:
That was Dr. J. William Lindsey discussing his recent research on the role of EBV-specific T-cells in the development of multiple sclerosis. To access this and other episodes in our series, visit *NeuroFrontiers* on ReachMD dot com, where you can Be Part of the Knowledge. Thanks for listening.