Transcript Details

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Improving Diagnosis of Castleman Disease: The Key Role of Stromal Cells

Announcer
You're listening to *Project Oncology* on ReachMD. On this episode, Dr. Joshua Brandstadter will discuss his research on Castleman disease, or CD, which he presented at the 2024 American Society of Hematology Annual Meeting. Dr. Brandstadter is an Instructor of Medicine in the Division of Hematology and Oncology at the University of Pennsylvania and serves as the Director of Clinical Research for the Center for Cytokine Storm Treatment & Laboratory. Let's hear from Dr. Brandstadter about his findings now.

Dr. Brandstadter:
Castleman disease affects the body in a number of different ways. It's a polyclonal lymphoproliferative disorder. Patients have big lymph nodes like lymphoma patients, but the cells are not copies of each other. When it's present in one location, we call that unicentric disease, and patients primarily suffer from the lymph node pushing on things nearby. When it's present all over, called multicentric Castleman, a systemic inflammatory syndrome can develop that can light the body on fire. In its most severe form, patients can present dramatically with rapidly worsening blood counts, organ function, and swelling. They might have life threateningly low blood pressure and require intensive care.

The two biggest challenges patients with this disease face are one, achieving a prompt and correct diagnosis, and two, treating the roughly half of patients that do not respond to siltuximab, the IL-6 pathway-blocking antibody that is the only FDA-approved therapy for idiopathic multicentric Castleman disease. My research tackles this first problem about diagnosis. Many patients can be diagnosed incorrectly with Castleman. It's rare. It's seen infrequently by hematopathologists, and it's tricky for the diagnosis for pathologists to make based on the lymph node biopsy. Some of the diagnostic criteria can be seen in other diseases, and some of these features can be seen to different extents in different parts of the lymph node. I'm trying to find a way to make their job easier so we can more quickly arrive at the correct diagnosis and start treatment before the worst consequences of the disease.

So nonimmune cells, fibroblasts and endothelial cells, so-called stromal cells, were long thought to be simply structural, the dividing walls between the different parts of the lymph node, but this isn't true. They secrete all sorts of immune signals to immune cells. So even though the stromal cells make up less than 5 percent of the total cellularity of the lymph node, they have an outsized effect on controlling the immune response, like air traffic controllers.

There's been a lot of work in mice showing how these cells influence the immune response to infection or cause autoimmunity or cause graft-versus-host disease, a severe immune consequence of bone marrow transplantation. No one has directly shown a role for these cells in human disease, but in polyclonal lymphoproliferative disorders, like Castleman disease, we can analyze the immune cells to death and only find broad, nonspecific changes of the increased inflammation response characteristic disease. In Castleman disease, these nonimmune cells look abnormal under the microscope. It's part of how the pathologists make the diagnosis. So, therefore, I thought it was worthwhile to explore roles that these cells might play in causing the disease.

The challenge that we've experienced in trying to understand how lymph node stromal cells may play a role in human disease has been the inability to effectively get these cells that are stuck to extracellular matrix and collagen into solution. These cells do not come out into solution when you simply mechanically digest lymph nodes in a more traditional fashion when lymph nodes are processed for flow cytometry in a conventional gross pathology laboratory. To extract these cells, you require carefully calibrated enzymatic digestion protocol. I help adapt protocols that have been initially developed in mice to human tissue and then which allowed me to get these cells into suspension and show, using single-cell RNA sequencing, exactly how these cells are different in Castleman disease compared to otherwise inflamed lymph nodes that didn't have Castleman disease. This method then allowed me to find very specific changes in the

Castleman disease lymph node that were not seen in otherwise inflamed lymph nodes that can be used more broadly by pathologists to develop immunohistochemical stains that will help us to identify calcium and make a more specific and clear diagnosis of Castleman disease and not just generalized inflammation.

My findings have shown ways that stromal cells can be used to help us to more easily diagnose Castleman disease. That's still correlative work. We need now to take the next step in showing that these cells can actually functionally cause Castleman disease, and to do that I've taken a PDGFR beta mutation that was discovered in a subset of patients with unicentric Castleman disease, and I've made a mouse that can conditionally express this mutation in the stromal cells to actively show whether this mutation in stromal cells alone is sufficient to cause a Castleman-like condition. And that's work that's currently ongoing in my lab.

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That was Dr. Joshua Brandstadter talking about his research on Castleman disease, which he presented at the 2024 American Society of Hematology Annual Meeting. To access this and other episodes in our series, visit *Project Oncology* on ReachMD dot com, where you can Be Part of the Knowledge. Thanks for listening!