Transcript Details

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Understanding iMCD Through RNA Sequencing

Announcer:
You're listening to *Project Oncology* on ReachMD. On this episode, Dr. Michael Gonzalez will discuss his research on idiopathic multicentric Castleman disease, or iMCD, which he presented at the 2024 American Society of Hematology Annual Meeting. Dr. Gonzalez is the Associate Director of Basic and Translational Research at the University of Pennsylvania's Center for Cytokine Storm Treatment and Laboratory. Let's hear from Dr. Gonzalez now.

Dr. Gonzalez:
First, I want to give a brief introduction into Castleman disease more generally. It describes a group of rare disorders that involve enlarged lymph nodes with a similar lymph node appearance under the microscope and a broad range of inflammatory symptoms and laboratory abnormalities. The most common subtype of multicentric Castleman disease where those enlarged lymph nodes occur in multiple compartments around the body is idiopathic multicentric Castleman disease. And as you may have guessed from the name idiopathic, we don't know what causes this particular disease, so the cause is unknown. The motivation for this work is to really understand what's going on at the molecular level in the lymph node tissue of Castleman disease patients.

We used a two-tiered analytical approach, and we used two different methods to measure or quantify gene expression in that lymph node tissue of iMCD patients. One is called bulk RNA sequencing, which is a technique that measures all of the genes being expressed in a given tissue to look at that gene signature in the lymph node tissue of iMCD patients, followed by a more targeted approach that measured gene quantification of about 580 genes that we know are involved in the immune system in an expanded cohort of iMCD patients. What we found was that the gene expression profile of iMCD lymph node tissue was distinct from healthy controls, and the dysregulated genes that we were identifying had functions related to things like increased cell proliferation, dysregulated immune system function and dysregulated cellular signaling.

And in addition to identifying these potential gene pathways that are upregulated in iMCD, we also used several computational approaches to perform what's called cell type deconvolution and drug treatment prediction for iMCD. How we can use cell type deconvolution is we can deconvolute that average gene expression from the bulk RNA sequencing and actually predict how many different cell types and what numbers are in a given tissue. And when we did that, we actually found that iMCD had significantly upregulated monocytes and plasma cells—both cell types that we suspect might have some sort of pathological implication in iMCD.

In addition to getting as much as we possibly can out of the bulk RNA sequencing we used our second approach, which is the targeted gene expression profiling in our expanded cohort, we were able to compare different clinical subtypes of iMCD. And we identified a number of shared gene biomarkers across those iMCD clinical subtypes, but we also identified specific gene targets that are unique to each clinical subtype as well, and we're further exploring those as we speak in the lab.

One gene in particular that was significantly upregulated in all iMCD clinical subtypes was a gene called clusterin, which is a protein that's involved in a number of different cellular processes, including apoptosis and cell death and immune system regulation. And we attempted to validate this finding with another approach known as immunohistochemistry, which is a technique that uses antibodies to detect proteins and tissue samples, and we found that clusterin was indeed significantly upregulated in the lymph node tissue of iMCD patients compared to healthy controls, but unfortunately, it did not differentiate iMCD from either lupus or lymphoma. So clusterin, if it was a home run, would have been a disease differentiator of iMCD compared to other diseases and healthy controls. It did differentiate from healthy controls, but not the disease comparators, so a partial validation.

What we're doing now is we are working with a collaborator that's been able to do additional RNA sequencing on at least 20 other iMCD

lymph node tissue samples and an additional 20 healthy controls, and this will give us increased confidence in our findings and allow us to really further explore the gene expression profiles of the different clinical subtypes of iMCD. And in addition to that, we are working to validate our clusterin findings in a larger cohort of patients using orthogonal techniques to IHC, so in addition to looking at orthogonal techniques to actually quantify clusterin within the lymph node tissue, we're looking at how that clusterin is expressed within a given lymph node tissue and how that compares to disease comparator groups like lymphoma and lupus.

We are also trying to identify other potentially differentiating biomarkers; that's really going to help us distinguish iMCD from other diseases and hopefully increase the speed of iMCD diagnosis, which is difficult to get.

Announcer:
That was Dr. Michael Gonzalez talking about his research on idiopathic multicentric 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.com, where you can Be Part of the Knowledge. Thanks for listening!