

Transcript Details

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Exploring Cadherin-6: A Key Driver of Inflammation in Rheumatoid Arthritis

Announcer:

You're listening to *Living Rheum* on ReachMD. On this episode, Dr. Gary Firestein will discuss his research on the role of cadherin-6 in rheumatoid arthritis. He's a Distinguished Professor of Medicine and the Senior Associate Vice Chancellor for Health Sciences at UC San Diego. Let's hear from Dr. Firestein now.

Dr. Firestein:

Rheumatoid arthritis is one of the most common inflammatory forms of arthritis. Treatment has improved dramatically over the last 20 years or so with the advent of biologics and other therapeutics, but even with all of this improvement, there is still a significant percentage of people that have ongoing inflammation or, in some cases, don't respond to any medicines at all.

We have a long history of trying to understand the mechanisms of disease in rheumatoid arthritis because we firmly believe that if you understand those mechanisms, you'll be able to develop therapeutics that target them and improve the lives of our patients. We noted that there was an accumulating literature on a set of molecules called cadherins, which are adhesion molecules that essentially serve as the glue oftentimes for holding cells together within a tissue. And some of the literature that had been developed and some of the more recent discoveries were that one or two individual cadherins might play an important role in how the lining of the joint, called the synovium, is structured and might play a role in a disease like rheumatoid arthritis. One of them, called cadherin-11, actually led to the introduction of a therapeutic that has been tested in clinical trials.

Well, it turns out that there are lots of cadherins, and rather than just trying to go through and testing each one in detail one at a time, we decided to take an unbiased approach because we thought there might be other cadherins that could be important. And that unbiased approach essentially allowed us to look at the entire cadherin family and whether it's expressed, whether it's regulated, and what its functions might be in the lining of the joint. What we discovered was that there were really only one or two cadherins that were abnormally regulated in rheumatoid arthritis cells. One of them was the one that I mentioned previously, which is cadherin-11, but the other was this interesting one called cadherin-6. And that's how we began to study its function, its structure, and how it's regulated in RA.

We obtained samples of the lining of the joint from individuals with rheumatoid arthritis—typically in the course of their standard care—and in this case, it would be someone who has longstanding RA and goes in for a total joint replacement. We then take those samples, and we enzymatically disaggregate them in order to study individual cells rather than the entire clump of tissue. Then, once we have individual cells, we can take them in culture and measure what proteins they're making and what genes are expressed and then use that to try to prioritize what the abnormalities might be in rheumatoid arthritis cells compared with non-rheumatoid arthritis cells.

The standout finding for us was how impressive the difference was in the regulation of cadherin-6 compared to all of the other cadherins. Again, there is a very large number of these genes, and this one was quite different in terms of its potential for being expressed at higher levels. And when that happens, that gives us a clue that maybe it is playing a role in the disease, and so once a spotlight was shined on that particular gene, that then allowed us to, instead of looking at 20 or 30 different genes, focus really on one and characterize it and then determine whether or not that one—in this case, cadherin-6— plays a role in inflammation or the structure of the joint.

And that's exactly what we did with my colleagues, particularly Dr. Camilla Machado and David Boyle in our group. As we studied the function of this particular gene, cadherin-6, one of the things that became clear is that it played a pivotal role in regulating some of the characteristics that distinguish rheumatoid arthritis, and the main ones are things like producing inflammatory mediators, migrating into

and damaging tissue, and so on.

Announcer:

That was Dr. Gary Firestein discussing his research on cadherin-6 in rheumatoid arthritis. To access this and other episodes in our series, visit *Living Rheum* on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening!