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The Aryl Hydrocarbon Receptor and Lupus: Diagnostic and Therapeutic Advancements

Dr. Colbert:
Welcome to *Living Rheum* on ReachMD. I'm Dr. Gates Colbert, and today I'm joined by Dr. Deepak Rao to discuss how a receptor called aryl hydrocarbon may hold the key to improved lupus treatments. Dr. Rao is an Associate Professor of Medicine at Harvard Medical School and the Co-Director of the Brigham and Women's Hospital Center for Cellular Profiling. He recently published a study documenting the link between an imbalance in T-cell populations and systemic lupus erythematosus, or SLE. Dr. Rao, welcome to the program.

Dr. Rao:
Thank you so much for having me.

Dr. Colbert:
Dr. Rao, can you start by explaining what SLE is and why it's considered a prototypical autoimmune disease?

Dr. Rao:
Lupus is an autoimmune disease that is characterized by a broad production of autoantibodies, and those antibodies can target a number of different proteins across the body, causing quite a wide range of clinical manifestations. It can cause rashes and joint pains. A feared complication of lupus is when the immune system affects the kidneys, causing a condition of lupus nephritis. I would consider it a prototype of an autoimmune disease because it, at its core, involves this activation of autoreactive T-cells and autoreactive B-cells, production of autoantibodies that then cause a number of these different problems and the inflammatory consequences that follow cause the range of clinical symptoms that we see. But at its center is this activation of the adaptive immune system of T-cells and B-cells that are both recognizing cell proteins and driving this disease.

Dr. Colbert:
Now, what were your findings on the aryl hydrocarbon receptor and its role in SLE progression?

Dr. Rao:
Well, we've been trying to understand the T-cell response that drives disease in lupus, and to do that, we've been collecting samples from patients with lupus and patients without lupus and comparing the extent of T-cell activation and the flavor of the activated T-cell response. As we identify T-cell populations in patients with lupus that are overrepresented—there's too many of those cells that are too active—they have a particular feel to them. Those cells that are expanded in patients with lupus tend to be a specialized population of T-cells that are particularly good at driving a B-cell response, recruiting B-cells, activating B-cells, and inducing their production of autoantibodies. As we went looking for signals that could control the function of B-cells or maybe suppress their accumulation or their differentiation, we identified the aryl hydrocarbon receptor, this one specific protein, one specific receptor as quite a strong negative regulator of this activated T-cell response. So we did this by a CRISPR screen, taking primary human T-cells in vitro, stimulating them to try and induce the generation of B-cell helper T-cells like the ones that we see in patients with lupus, and then one by one disrupting the expression of different genes that we thought could potentially be relevant for controlling this T-cell response. What came out of that was the recognition that if we specifically disrupt the expression of this one protein, the aryl hydrocarbon receptor, it was actually much easier to turn T-cells into these B-cell helper T-cells that we see prominently in patients with lupus, so it suggested that whatever the aryl hydrocarbon receptor was doing was suppressing the accumulation of what we think of as this pathologic T-cell response. The rest of the work from there is trying to understand the specific roles of the aryl hydrocarbon receptor in suppressing the ability of T-cells to turn into these pathologic effector T-cells.

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Dr. Colbert:
And how can the aryl hydrocarbon receptor be leveraged to reduce inflammation and immune dysregulation in SLE patients?

Dr. Rao:
The aryl hydrocarbon receptor is a transcription factor. The neat thing about it is that it's a transcription factor that is turned on by small molecules, specific types of small molecules. So normally, it sits in the cytoplasm of the cell and it's not doing very much, and when it binds the ligand, it moves into the nucleus, and it turns on expression of a set of genes that then are these AHR—aryl hydrocarbon receptor-induced genes. The useful thing about this is that you can control the activity of the aryl hydrocarbon receptor with small molecules, either activators or inhibitors of the receptor. So what we showed in vitro with T-cells either from healthy donors or from patients with lupus is that if you stimulate the aryl hydrocarbon receptor with a small molecule agonist, an activator, we could suppress the function or the differentiation of B-cell helper T-cells that we think are pathogenic in lupus. The extension from there then is if we can find ways to activate the aryl hydrocarbon receptor in vivo in patients, this may be a strategy to suppress this active inflammatory response that we think is central to the disease.

Dr. Colbert:
For those just tuning in, you're listening to *Living Rheum* on ReachMD. I'm Dr. Gates Colbert, and I'm speaking with Dr. Deepak Rao about the aryl hydrocarbon receptor and its relation to systemic lupus erythematosus, or SLE.

So Dr. Rao, we spoke a bit earlier about how the aryl hydrocarbon receptor plays a role in SLE, but now I'd like to ask you about what lies ahead. How could your findings help improve diagnostic tools or treatments for lupus patients?

Dr. Rao:
I think we're really excited about two directions here. One is a direct implication of this work trying to use activators of the aryl hydrocarbon receptor as a new therapeutic strategy to treat lupus or related autoimmune conditions that also feature an activated T-cell/B-cell response. There are already some activators of the aryl hydrocarbon receptor that have made it to clinical use. There's a drug called tapinarof, which is a topical AHR, aryl hydrocarbon receptor activator that's used to treat psoriasis. It has been a challenge to try and identify ways to deliver a medication that can activate the aryl hydrocarbon receptor systemically without causing a lot of toxicities, so this is a topic that we're interested in but one that has a lot of preclinical data now supporting the idea that this could be useful.

The second direction we're interested in is trying to use some of the features here of the abnormal T-cell response that now we can see quite clearly from the kinds of immune profiling studies that we did, and others have done and use those metrics of immune activation as new diagnostic tests or prognostic tests to be able to assess activation of the adaptive immune system in patients with lupus. So we already have some tests to measure immune activity in patients with lupus. We can measure antibodies against double-stranded DNA, we can measure complement levels in the circulation to assess whether there are immune complexes that have been formed and are doing anything, but we really don't have a set of tests to measure whether the relevant T-cell populations are active, the extent of an activated B-cell response. Those are things that we can do in the lab easily, but we just don't do clinically right now, so I'm very interested in the idea that we can develop a couple of simple metrics by flow cytometry or other methods to be able to quantify these active T-cell or B-cell responses that we can see in patients with lupus, that we can tell are influenced by the aryl hydrocarbon receptor, and begin to track those in patients to help us get a better sense about how active the pathologic immune response is in any individual patient as we see them in clinic.

Dr. Colbert:
To expand more on that, what are the next steps in your research?

Dr. Rao:
We're trying to develop now new strategies to generate a medication that can be an aryl hydrocarbon receptor agonist, an activator, that we can deliver selectively to T-cells. There it's a process of drug development, seeing, can you come up with a strategy to do this, can you design a molecule to do it, and then demonstrate that it works initially in vitro and then in animal models and ultimately in patients? And then the second approach we're trying to develop is more accurate measures of immune activation. The process there is to continue with these kinds of studies but in a larger scale, enrolling patients who are interested, having them participate in studies where we can in detail track activity of the immune system based on these metrics, and following them over time to see whether disease activity clinically correlates with these cellular features of immune activity. And then as a next step, can we use these measures to predict treatment response in longitudinal studies as patients are studied in cohorts over time.

Dr. Colbert:
And before we close, Dr. Rao, are there any final takeaways you'd like to share with our audience today?

Dr. Rao:

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I would say that I view this as a really nice example of the power of human immunology studies where we're putting a dedicated effort into studying patients with the disease now using some of the tools of cellular immunology, the sophisticated immune profiling that we do routinely in our research lab, now taking those tools and applying them to patients that we see in clinic, trying to identify features of the disease that we can measure now and understand in a new way. So the study that we reported here is entirely human. It relies on samples from patients with lupus. It relies on analyses of patients as they're treated with drugs like anifrolumab, which blocks the interferon receptor. And I'm really optimistic about these kinds of studies where we're taking the tools of cellular immunology and use it to really understand patients and their experience, especially their experience over time as they're treated with different medications. And we rely on the participation of patients who are interested to work with us on these kinds of studies. So this has been a really satisfying study to execute. We're looking to do more of this kind of work.

Dr. Colbert:
With those final insights in mind, I want to thank my guest, Dr. Deepak Rao, for joining me to discuss the aryl hydrocarbon receptor and its role in lupus, or SLE. Dr. Rao, it was great having you on the program.

Dr. Rao:
Thank you so much for having me.

Dr. Colbert:
For ReachMD, I'm Dr. Gates Colbert. 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.

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