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Understanding the Role of the Complement Pathways in IgAN

Announcer:
You're listening to *Clinician's Roundtable* on ReachMD, and this episode is sponsored by Novartis Pharmaceuticals Corporation. Here's your host, Dr. Charles Turck.

Dr. Turck:
Welcome to *Clinician's Roundtable* on ReachMD. I'm Dr. Charles Turck, and joining me to discuss the role of complement pathways in IgA nephropathy is Dr. Carl Walther. Dr. Walther is a nephrology specialist and Associate Professor of Medicine at Baylor College of Medicine in Houston. Dr. Walther, thanks for being here today.

Dr. Walther:
Glad to be here, Dr. Turck.

Dr. Turck:
So if we start with some background, Dr. Walther, would you tell us how the complement system works in healthy individuals?

Dr. Walther:
Sure. Well, the complement system is really a critical part of our innate immune system. This innate immune system is basically constantly working to keep us safe from extrinsic pathogens and from our own damaged cells or tissues that could have the potential to harm our healthy cells and tissues. So the complement system really does this by identifying and marking things in our bloodstream and our tissues that shouldn't be there, and these could be extrinsic things like bacteria that are somewhere where they shouldn't be, like in the bloodstream, or our own cells that have been damaged by some processes, and that could be spilling material that's potentially harmful to our body. So really, the complement system, by identifying and marking these harmful things, it causes our body's other cells to ingest and then digest and dispose safely of bacteria or damaged cells. The complement system can even kill harmful pathogens itself by causing lysis through the membrane attack complex.

Dr. Turck:
And which are the complement pathways relevant to IgA nephropathy?

Dr. Walther:
So to concentrate on the two pathways that we think are quite important in IgA nephropathy, the alternative pathway is really one of the oldest, most basic parts of our immune system. It doesn't require antibody or any prior exposure to a microbe or stimulus to effectively destroy it, so to have this rapid onset of action, the alternative pathway is always self-activated a little bit. It's always running in a feedback cycle. The good thing about the alternative complement pathway, and also one of the reasons that it can be harmful and dysregulated, is it is so good at rapidly amplifying itself through a positive feedback loop. So this can be good if it's fighting off a bacterial infection or something because it's rapidly generating these substances to really ramp up the immune system to bring a lot of the body's innate and adaptive immune system to bear on the problem. And also, it could engage the membrane attack complexes, which can kill pathogens. So that's one of the benefits. One of the bad things about this is if it's dysregulated, it has the potential to do a lot of harm to healthy tissues, and we think that this is an important part of what is happening in IgA nephropathy and why so many patients with IgA nephropathy do have significant kidney damage and end up even progressing to kidney failure sometimes.

The other pathway that seems to be important in IgA nephropathy is the lectin pathway. It looks like this pathway is probably only active in a subset of people with IgA nephropathy. But in that subset, it appears to be quite harmful. The lectin pathway is similar to the classical pathway in that it's activated by external signals, so these are complexes and proteins called pattern recognition molecules.

These molecules are able to bind to sugar residues on things like bacteria and other pathogen surfaces and really recognize, hey, this should not be here, and get a pathway going. We think that pathway is active in some people with IgA nephropathy based on some histological findings of these pattern recognition molecules kind of co-locating with IgA deposits and with some complement components in kidney biopsies of people with IgA nephropathy.

Dr. Turck:
Now if we zero in on the alternative pathway, would you tell us about the molecular mechanisms that lead to its dysregulation?

Dr. Walther:
There are several different ways that this pathway can be dysregulated. This pathway is very complex, very evolutionarily ancient, so there are a lot of parts that if things are a little bit out of whack, it could really disbalance this pathway and lead to damage of healthy tissues. One example of this is with the C3 glomerulopathies. With this group of kidney diseases, the only abnormality really is alternative complement pathway activation. And this can occur due to complement factor H and complement factor I loss of function. Those are 2 important regulators that help to prevent excessive alternative pathway activation. If those regulators aren't functioning perfectly, that can really instigate this alternative complement pathway damage. And in nephrology, there's a classic autoantibody that we call C3 nephritic factor that can actually stabilize the C3 convertase that's part of an important feedback loop in the alternative complement pathway, and by stabilizing this, it kind of keeps that positive feedback loop going at an excessive level, and that could cause kidney damage.

Dr. Turck:
Now as a quick follow-up to that, how does that dysregulation impact disease progression in patients with IgA nephropathy?

Dr. Walther:
There's a lot of interesting research recently that's shown that this local complement activation within the glomerulus seems to really be the driving force for glomerular damage in IgA nephropathy. Some of the evidence we can look at is even clinical, when we do kidney biopsies on patients who are ultimately found to have IgA nephropathy. Usually there'll be C3 deposits, along with those IgA deposits, and the severity of the C3 deposition can actually correlate with prognosis of more severe C3 deposition. These patients seem to have a worse prognosis; this is one measurement of alternative complement pathway activation.

We also see evidence that lectin pathway activation is ongoing because you can actually see C4d deposit in the glomeruli along with lectin pathway components such as mannose-binding lectin, but you don't see the C1q that you expect to see with C4 if you have classical pathway activation, so that's again telling us that that pathway is active in some patients. And so it's the activation of these complement pathways that really seems to be an important mediator for how these IgA deposits really cause damage to the glomerulus and damage to these mesangial cells. When these complement pathways are activated, they release substances that call a lot of inflammatory cells into the glomerulus, and in addition to that, it may be leading to formation of membrane attack complexes that can actually potentially damage mesangial cells. So with recent years and with more research, it's really looking more and more like this complement is really mediating the damage in IgA nephropathy.

Dr. Turck:
For those just tuning in, you're listening to *Clinician's Roundtable* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Carl Walther about the dysregulation of the complement system in IgA nephropathy.

So, Dr. Walther, given everything we've discussed, how might this knowledge of complement pathways optimize our approach to treating IgA nephropathy?

Dr. Walther:
Yeah, I think it's exciting, and there are definitely therapeutic opportunities on the horizon to target the complement pathway, and specifically the alternative complement pathway or the terminal attack complex in treating IgA nephropathy. There have been a lot of medications developed in recent years targeting different aspects of the complement system. A lot of those have been approved in different disease processes. We don't have any proven therapies right now targeting the complement system for IgA nephropathy. Currently, our proven therapies for IgA nephropathy are corticosteroid-based. Either systemic steroids or this delayed-release budesonide formation that is the one FDA-approved treatment for IgA nephropathy. So I think while this information about the complement pathway probably doesn't affect treatment decisions for a patient being seen today, it certainly is exciting and we can see that in the near future, it seems quite likely that we're going to have specific ways to target this disease process and to really get better outcomes for these people.

Dr. Turck:
And before we close, Dr. Walther, are there any final thoughts you'd like to leave with us?

Dr. Walther:
Yeah, I think overall this is a really exciting time to be treating glomerular diseases, including IgA nephropathy. Important advances are coming every year and we have so many more therapeutic options now than we did recently. The kind of way we treat glomerular disease is really shifting from a non-targeted shotgun approach, if you will, of using high doses of glucocorticoids and other kinds of nonspecific immunomodulation agents to really targeted therapy. So I think we're already seeing improved therapies, and there's a lot more coming.

Dr. Turck:
Well those final thoughts bring us to the end of today's program. I want to thank my guest, Dr. Carl Walther, for joining me to examine the role of the complement system in IgA nephropathy. Dr. Walther, it was a pleasure having you on the program.

Dr. Walther:
Thank you. It was a pleasure being here.

Announcer:
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