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APRIL Uncovered: An Upstream Driver in IgAN

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Dr. Zhang:

Hello, everyone. This is a CE on ReachMD, and I'm Dr. Hong Zhang. Here with me today is Dr. Dana Rizk. Today, we are discussing the biological function of APRIL in the pathophysiology of IgA nephropathy.

Dr. Rizk, what can you tell us about APRIL?

Dr. Rizk:
Hi, Hong. It's a pleasure seeing you. So just to remind our audience, IgA nephropathy is considered to be an immune-mediated disease, and the pathogenesis has been summarized into a 4-hit hypothesis. So the first step in the disease pathogenesis is an increase in the serum level of galactose-deficient IgA1 that is then met by autoantibodies; that's considered hit 2. The 2 bind together to form circulating immune complexes, also referred to as hit 3, that end up depositing in the kidneys and causing a cascade of events leading to inflammation and ultimately fibrosis and decline in kidney function. And that's hit 4.

So the galactose-deficient IgA1 is thought to be produced at the mucosal surface. And in the genetically susceptible individuals, something triggers this excessive production of galactose-deficient IgA1. So as you can imagine, B cells play a major role in the immune-mediated disease development, and so it stands to reason that cytokines that affect B cell maturation and differentiation would also likely play a very important role in IgA nephropathy.

So APRIL is one such cytokine that is important for B-cell development, differentiation, and survival. And another cytokine that we're aware of is BAFF, that also plays a very important role. They also play an important role in class switching, so B cells switching from one immunoglobulin production to IgA production. And so they both are involved in the disease pathogenesis.

Dr. Zhang:
Thank you. That's a very good overview of the pathogenesis of IgA nephropathy and the focus on the B cell modification in the pathogenesis.

And the elevation of APRIL levels in an Asian IgA nephropathy patient, driven by genetic risk factors, is supported by GWAS and also the functional variation research. And GWAS have identified risk SNPs in *TNFSF13* that's coding APRIL and *TNRSF13B* that's coding

APRIL receptor TACI. They are far more prevalent in East Asians than Europeans. That's, I think, the genetic background, they're different.

And then the functional study showed that B cells from this patient produce significantly higher level of Gd-IgA1 when stimulated with the APRIL compared to B cells from the healthy control. So that means that's pathogenic functions.

And multiple Asian studies, including Chinese and Koreans, report higher plasma APRIL in IgA nephropathy compared to healthy controls. And the plasma APRIL level shows a positive correlation to Gd-IgA1, proteinuria, and reduced eGFR. And some studies also show that APRIL level could predict progression to ESKD in the cohort of Asian populations.

So I think this evidence supports that genetic-driven APRIL elevation is not just a biomarker, but a co-pathogenic factor in Asian IgA nephropathy, at least in the cohort study.

So, however, I think I should mention, most studies focus on East Asian cohort, the reports. And this is a lack of cross-ethnic validation. I think that is the future research direction.

Dr. Rizk:
Yeah, absolutely. So there is definitely strong biology and genetic data to support targeting APRIL in IgA nephropathy patients and, in particular, in the Asian population.

Dr. Zhang:
Thank you. I think it's now widely accepted that IgA nephropathy occurs through a number of pathogenic hits. As revealed by Dr. Rizk, APRIL represents a variable target for therapy in IgA nephropathy, and it is critical for the initial steps in its pathogenesis.

Thank you. Thank you, Dana, for an excellent discussion. And we thank the audience for joining us today. We hope this information will be helpful in your clinical practice.

Dr. Rizk:
Thank you for having me.

Dr. Zhang:
Thank you.

Announcer:
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