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IL-31's Role in Atopic Dermatitis and Prurigo Nodularis: Neuroimmune Insights

Announcer:
This is *DermConsult* on ReachMD, and this episode is sponsored by Galderma. Here's your host, Dr. Raj Chovatiya.

Dr. Chovatiya:
This is *DermConsult* on ReachMD, and I'm Dr. Raj Chovatiya, Associate Professor at Rosalind Franklin University of Medicine and Science, Chicago Medical School, and Founder and Director of the Center for Medical Dermatology and Immunology Research in Chicago. Joining me to discuss the role of IL-31 in the neuroimmune mechanisms behind atopic dermatitis and prurigo nodularis is Dr. Nicholas Mollanazar. He's an Assistant Professor of Clinical Dermatology and the Director of Dermatology Patient Access at the University of Pennsylvania Perelman School of Medicine. Dr. Mollanazar, welcome to the program.

Dr. Mollanazar:
Thanks for having me. Excited to be here.

Dr. Chovatiya:
So to start us off, how has the field's understanding of IL-31 shifted from a pruritus-specific cytokine to a broader neuroimmune mediator?

Dr. Mollanazar:
I think the biggest shift is that we've stopped thinking of IL-31 as just an itch cytokine. It signals through IL-31RA and OSMR beta and then through JAK1 and JAK2 into STAT pathways, with STAT3 seeming especially relevant to neurons. It's also linked to TRPV1- and TRPA1-expressing, itch-sensing neurons.

So the modern view is that IL-31 sits at an interface of immune activation, sensory nerve signaling, barrier dysfunction, and tissue remodeling. In other words, it's now seen as part of a neuroimmune feedback loop that helps drive disease, not just a downstream trigger of itch. IL-31 doesn't just mediate itch; it seems to help connect the immune system, the nervous system, and the skin itself.

Dr. Chovatiya:
It's fascinating, right? Because I think that when we all learned about IL-31 relatively recently, it always used to be described as the itch cytokine or the itchy cytokine. And I feel like you're correct. That is a bit misleading, even though it is a really nice way to think about one of the primary functions that IL-31 has.

I want to expand on that concept more. From your perspective as an expert here, what role does IL-31 seem to have in the biology of inflammatory skin diseases beyond just being a direct pruritogen, which is the most obvious role?

Dr. Mollanazar:
It's a good question. Beyond symptom generation, IL-31 looks increasingly like a disease maintenance signal. It's produced within a broader inflammatory network that includes M2 macrophages, basophils, and memory T-cells. It's not acting in isolation; it seems to be embedded in the larger type two inflammatory environment and may help sustain disease persistence over time. And there is genetic data around the IL-31 locus and prurigo nodularis that suggests a rule in disease susceptibility, which makes the story slightly more compelling.

Dr. Chovatiya:
I think that part of the challenge as a field that we've had trying to contextualize IL-31 is that we've really understood over the years better what cytokines like IL-4, IL-13, IL-5, and IL-22 do in the context of a disease like atopic dermatitis, where we know that there is

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both immune dysregulation and neuroimmune dysfunction and barrier dysfunction, microbial dysregulation, etc.

But I think that it's been a bit challenging for folks to really try to figure out how IL-31 intersects with the skin barrier dysfunction component because we know that's probably the second most important layer of this AD story beyond the immune part. How do you explain that, and why is this clinically meaningful now that we're understanding the broader roles of IL-31?

Dr. Mollanazar:
In atopic dermatitis, one of the most clinically meaningful roles of IL-31 is its relationship to barrier dysfunction. It appears to reduce filaggrin expression and alter keratinocyte differentiation, which weakens epidermal integrity. That can promote water loss, antigen penetration, and microbial imbalance.

So inflammation is translated into a more vulnerable skin barrier. What's so important clinically is that this creates an inside-to-outside loop where inflammation worsens the barrier. The impaired barrier fuels more inflammation and itch, and the cycle reinforces itself. IL-31 helps turn inflammation into barrier failure and barrier failure into more inflammation.

Dr. Chovatiya:
It's a really nice way to think about it because I think that we oftentimes get stuck in this chicken-and-egg type of scenario, and I think that with atopic dermatitis, in particular, whether you're going outside in or whether you're going inside out and whether you're thinking about something that's setting off itch versus setting off barrier dysfunction, it's probably all happening at the same time.

Do you find it difficult in today's day and age to get people to think about sequencing of these cytokines, and how do you try to tell folks about everything happening all at the same time?

Dr. Mollanazar:
I think we don't know quite the answer to that question. I think that IL-31 has a potential to potentiate some of the downstream targets in the Th2 pathway. Those downstream targets also can propagate IL-31. So there's this push and pull, and I don't think we know exactly where it is in relation to the whole pathway.

I think there's various ways to get the pathway activated. So I think of it as like a giant loop or almost roundabout with multiple entry and exit points. Whether it's IL-31 or whether it's IL-4 or IL-13, there are multiple ways to get that loop started, and then once you get that loop started, it can keep going.

And the nice thing about these pathways is that by stopping one part of the loop, a lot of times you can stop or slow down the entire loop pathway. But that's where personalized medicine, I think, is going to be a big decision-maker in the future for us because certain patients with certain phenotypes or endotypes have certain molecules that are starting and perpetuating that loop for them. And if we know that specific profile for that specific patient, we'd be able to get them on targeted therapy that stops their disease in the most efficient and abrupt way possible.

Dr. Chovatiya:
For those just tuning in, you're listening to *DermConsult* on ReachMD. I'm Dr. Raj Chovatiya, and I'm speaking with Dr. Nicholas Mollanazar about how IL-31 drives neuroimmune signaling in atopic dermatitis and prurigo nodularis.

So let's turn to prurigo nodularis now. What do we know about IL-31's relationship to fibroblast activity, tissue remodeling, and persistent lesions in a disease like PN?

Dr. Mollanazar:
In prurigo nodularis, IL-31 is especially interesting because its role may extend well beyond neurons. It's associated with fibroblast activation, collagen production, extracellular matrix remodeling, and fibrosis, which helps explain how chronic scratching can be converted into persistent nodular lesions. So IL-31 may be contributing not just to the sensation of itch, but also to the structural durability of the disease. And notably, IL-31 pathway blockade has been linked to normalization of stromal signatures, which supports the idea that this pathway is relevant to tissue remodeling as well. In PN, IL-31 may help explain how repeated scratching becomes biologically fixed into chronic nodular disease.

Dr. Chovatiya:
Fascinating. And I don't want to shortchange the neural side, which is where a lot of our IL-31 story began once upon a time. With PN being such a prototypical neuroinflammatory disease and one that neuroimmune dysfunction is really at the forefront, what makes IL-31 particularly effective at both sustaining itch as well as driving and amplifying itch-scratch loops that are so central to this disease state?

Dr. Mollanazar:
You can't forget about the nerves. So on the neural side, IL-31 is a very effective itch amplifier because it can act directly on the

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pruriceptive neurons through STAT3 signaling. It also appears to enhance sensitivity to other pruritogens, so it doesn't work in isolation. It lowers the itch threshold and broadens the range of things that can trigger scratching.

That gives you a classic amplification loop. Inflammation leads to IL-31, IL-31 drives itch, scratching causes further injury, and that injury feeds back into more inflammation. So what makes IL-31 so potent is that it doesn't just trigger itch; it makes the whole system more itch responsive.

Dr. Chovatiya:
I really like that way of thinking about it given that we had touched on this idea of deeper and superficial parts of the skin in terms of barrier dysfunction as well as connective tissue function, itch neurons, and the immune system. And that really leads me to my last question, which is maybe one for you to explore in terms of your thoughts, especially as you approach treatment.

When we zoom out, how do you think about IL-31 sitting in the larger network of all of these cytokines that we've learned about largely because of targeted treatment, things like IL-4, IL-13, the JAK-STAT pathway, and TSLP when thinking about keratinocyte-derived compounds and other pruritogenic pathways? What do you think we know for sure with IL-31, what are we really missing, and how does this really calculate into your thinking when you're parsing through treatments?

Dr. Mollanazar:
I think the best way to place IL-31 in the broader network is to say that it shares JAK-STAT biology with pathways that involve IL-4 and IL-13. But it seems to have particularly distinct neuronal and fibrotic roles. It's part of a larger pruritogenic ecosystem that includes TSLP, IL-33, and neuropeptides, and the real story is probably pathway interaction rather than any one cytokine acting alone.

The biggest unanswered questions are how these pathways are organized, whether they're synergistic or partly redundant, and which patient endotypes are our most truly IL-31 driven. So IL-31 looks like one node in a larger pruritogenic network, but it's a particularly important one because of its neuroimmune and remodeling effects.

Dr. Chovatiya:
These are great points to keep in mind as we come to the end of today's discussion. And I sincerely want to thank my guest, Dr. Nicholas Mollanazar, for sharing his insights on IL-31 and its neuroimmune contributions to atopic dermatitis and prurigo nodularis. It's been a pleasure having you on the program, Dr. Mollanazar.

Dr. Mollanazar:
Thanks for having me. It's been a pleasure.

Announcer:
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