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Understanding IL-36 Signaling in GPP and Related Neutrophilic Dermatoses

Announcer:
You're listening to *DermConsult* on ReachMD. This episode is sponsored by LEO Pharma Inc. And now, here's your host, Dr. Charles Turck.

Dr. Turck:
This is *DermConsult* on ReachMD, and I'm Dr. Charles Turck. Today I'm joined by Dr. David Cotter, who's a dermatologist at Las Vegas Dermatology, to discuss our current understanding of IL-36 signaling and neutrophil-driven inflammation in generalized pustular psoriasis and other neutrophilic dermatoses.

Dr. Cotter, welcome to the program.

Dr. Cotter:
Thank you, Dr. Turck. It's a pleasure to be here today.

Dr. Turck:
Well, to set the stage for our conversation today, Dr. Cotter, would you start by explaining the role IL-36 signaling plays in generalized pustular psoriasis and why it's become such a central focus in our understanding of the disease?

Dr. Cotter:
Absolutely. And to set the stage, we have to recognize that IL-36 is a relatively new entrant to our understanding of the cytokine milieu that we're accustomed to in dermatology. And IL-36 is actually a member of the IL-1 superfamily of cytokines, and it's made up of three agonists and one antagonist. What ends up happening when IL-36 binds to its receptor is it activates MAP kinase signaling and NF-kappaB signaling within inflammatory cells and drives production of other inflammatory mediators that typically result in recruitment of neutrophils to the area of activation, which is why overall it's emerged as an important driver of inflammatory activity in generalized pustular psoriasis.

Dr. Turck:
Building on that, what genetic and acquired disruptions in IL-36 signaling are thought to contribute to generalized pustular psoriasis, and how do those abnormalities drive innate immune activation in neutrophil recruitment?

Dr. Cotter:
Thinking about it from a genetic standpoint first, the most common mutation we associate with generalized pustular psoriasis is a mutation in the IL-36 receptor antagonist gene. The reason why that drives generalized pustular psoriasis is because once you activate this pathway, you're not able to turn it off. You have inappropriate activation and perpetuation of the cycle because you're not able to turn it off because the antagonist gene is malfunctioning. Similarly, overexpression of IL-36 receptor agonists can overstimulate the system and also drive phenotypes of generalized pustular psoriasis. Some of the acquired triggers that we see clinically—things as simple as an infection, a medication, and even hormonal changes such as pregnancy—can activate the pathway, even in the absence of genetic mutations. Ultimately, this results in unopposed IL-36 signaling, driving neutrophil attracting chemokine production and neutrophil recruitment to the skin.

Dr. Turck:
Well, once those neutrophils are recruited, what else can you tell us about how their activation drives the clinical manifestations we see in generalized pustular psoriasis, and what sustains that inflammatory activity?

Dr. Cotter:
Thinking about the clinical phenotype of generalized pustular psoriasis, it's one of the most scary diseases a patient in our field will experience. And sometimes it's one of the most scary diseases we'll encounter clinically because you may have a patient present with diffusely erythematous skin studded with small pustules, or they may have entire lakes of pus that are coalescing throughout their entire epidermis. And that's because at a microscopic level, you have a massive accumulation of neutrophils into the epidermis, and that's what's driving pustule formation. It's a series of positive feedback loops between neutrophils and IL-36 signaling that sustain and amplify inflammatory activity. And it can get to the point that there's actually systemic spillover of these inflammatory mediators, and that's what's resulting in the fever and other systemic manifestations we see clinically in some of our patients with severe GPP.

Dr. Turck:
For those just joining us, this is *DermConsult* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. David Cotter about the role of IL-36 dysregulation in neutrophil-driven inflammation in generalized pustular psoriasis and related neutrophilic dermatoses.

So let's explore how the inflammatory mechanisms involved in generalized pustular psoriasis may extend across other conditions.

Dr. Cotter, as our understanding of IL-36 biology continues to evolve, what does the emerging evidence tell us about the role IL-36 signaling may play in other neutrophilic dermatoses like pyoderma gangrenosum?

Dr. Cotter:
Certainly, both diseases are neutrophilic in nature from an underlying pathomechanism. Clinically, they're very distinct, but they're still united by prominent neutrophilic inflammation and activation of innate immune pathways. Emerging evidence is implicating IL-36 signaling in the inflammatory pathways that drive PG. Some evidence supporting that is that IL-36 expression has been observed in PG lesions, suggesting a shared mechanistic basis with GPP. Currently, the evidence is still evolving, but it does point to IL-36 as a broader driver of neutrophilic inflammation that extends beyond just GPP.

Dr. Turck:
Now, despite those shared inflammatory features between the two conditions, what are the key differences in the underlying biology of these conditions, and how might those differences influence clinical presentation and systemic involvement?

Dr. Cotter:
While both diseases feature neutrophil-rich inflammation, we see distinct clinical presentations. In PG, we have neutrophilic ulcers with violaceous borders, undermined edges, and pain out of proportion to what the ulcer looks like to us as the clinician, whereas GPP we've described as diffusely erythematous skin studded with pustules and sometimes lakes of pus.

And what's accounting for these clinical differences, even though they may both function at a central node that involves IL-36 signaling, can be differences in the upstream triggers and the downstream cytokine networks. Differences in the tissue involvement and inflammatory responses may also contribute to the variations in the clinical presentations and systemic manifestations.

Dr. Turck:
Now, given everything we've discussed today, Dr. Cotter, how might our growing understanding of IL-36 biology help inform the future management of these inflammatory diseases, particularly when it comes to potential therapeutic targets?

Dr. Cotter:
I'm a firm believer that as we learn more about the underlying immunopathomechanisms of disease, we can eventually develop appropriate targeted therapies that truly address the root cause of disease. What we're seeing in generalized pustular psoriasis as well as pyoderma gangrenosum is the emergence of targeted specific innate immune pathway therapies. What we're seeing in generalized pustular psoriasis are drugs that are actually approved to treat this disease, and they target the IL-36 receptor itself. Similar drugs are actually in clinical trials to treat pyoderma gangrenosum, which to me is so satisfying, not just as a clinician, but also a guy with a background in molecular cell biology. We understand that IL-36 is a driver of these two similar but distinct neutrophilic dermatoses, and we now have targeted therapies that actually inhibit the abnormal signaling of IL-36. Of course, we need more research, and in fact, ongoing research is occurring, and it's continuing to explore how the mechanistic similarities and differences across neutrophilic dermatoses may influence future treatment strategies.

Dr. Turck:
Well, with those potential impacts in mind, I want to thank my guest, Dr. David Cotter, for joining me to explain how IL-36 dysregulation drives inflammation in neutrophilic dermatoses.

Dr. Cotter, it was great having you on the program.

Dr. Cotter:
Thank you, Dr. Turck. The pleasure was all mine.

Announcer:
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