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## Psoriasis Pathophysiology Insights: What Clinicians Need to Know

### Announcer:

This is ReachMD, and you're listening to Psoriasis: What's Beneath the Surface, sponsored by Lilly.

### Dr. Birnholz:

About 125 million people worldwide are diagnosed with psoriasis, a common inflammatory skin condition resulting in scaly patches; but despite its global prevalence, the pathogenesis of psoriasis is complex and multifactorial, eluding many in the healthcare community.

This is ReachMD, and I'm Dr. Matt Birnholz. Joining me is Dr. Jerry Bagel, Director of the Psoriasis Treatment Center of Central New Jersey and Clinical Associate Professor of Dermatology at Mount Sinai School of Medicine. Today we'll be taking a deep dive into the pathophysiology of psoriasis and what we need to know.

So, to start, Dr. Bagel, the pathogenesis of this disease is not yet completely understood, so can you just tell us what do we know at this time?

### Dr. Bagel:

Well, I think we know a lot more than we did 10 years ago, or even 5 years ago. What we've known for a long time is that the epidermis proliferates too quickly in psoriasis, and what we understand now is

that this is an immunologic-mediated disease. But just because it's immunologic-mediated, I think the epidermis is also part of the immune function of our body. The epidermis functions as part of the immune system. So, what we have is an upregulation of the immune system, an upregulation of the immune system whereby T-cells are producing molecules that are making the epidermis grow too quickly. So we know that the dendritic cells produce interleukin-23 that induce the differentiation and proliferation of T helper 17 cells, and T helper 17 cells produce IL-17 and IL-22. And IL-17, interleukin 17, induces the keratinocytes to produce antimicrobial peptides on the surface of their membranes and thereby induces the keratinocytes to produce other IL-17C that perpetuates the T helper 17 cells, producing more IL-22, which then induces the proliferation of these T-cells.

This is all part of the adaptive immune system; all the while, initially, you also have the induction of the innate immune system, because one of the first things you see in psoriasis under the microscope histologically are numerous collections of neutrophils, pustules of Kogoj and Munro microabscesses in the upper epidermis that are full of neutrophils of IL-17, and they are also inducing the proliferation. So we know IL-17 and IL-22 are really involved downstream in the pathogenesis of psoriasis.

Dr. Birnholz:

And to that point, are there any gaps in our molecular understandings at this point, areas that we just don't know whether that goes to the level of triggering events or even at the molecular level areas that are just not elucidated yet?

Dr. Bagel:

What clearly is inducing the dendritic cells to start producing IL-12 and IL-23? I mean, we know that strep molecules may. We know that certain medications like lithium, systemic steroids, antimalarial agents can exacerbate psoriasis, and we know that koebnerization, friction on skin, can exacerbate psoriasis, but what molecules are actually being produced that are binding toll receptors on the dendritic cells, and how does that make a dendritic cell produce IL-12 and IL-23, and also, even more specifically, how do genes get activated in psoriasis? Why do they get activated at certain points in time and not at other points in time? And what are the major genes? And why do some medications work in some people and not work in other people? These are all questions that are unanswered.

Dr. Birnholz:

So let me then come back to the general question of trying to identify the crucial characteristics of this disease that, from your vantage point, we should be keeping top of mind for our patients, such as what's triggering these manifestations. How do you look at that?

Dr. Bagel:

Well, one of the worst times I ever saw for psoriasis is about 4 months after Hurricane or Super Storm

Sandy here in New Jersey when people were coming in with the most severe forms of psoriasis I had seen, and I think a lot of it is because they were living in shelters, they were living in hotels, they were out of work, they were totally stressed out, and I think when that happens, stress is clearly an exacerbating factor for psoriasis. Now, how do you cope with stress is a whole other issue, but we know that's a factor. In addition, I tell people when I see them for the first time, and it's adolescents or young adults when they get psoriasis, like things they need to notice is that if they get strep infections, they should get that treated aggressively. I'd let them know that if they are traveling overseas, if they are going to get on antimalarial agents, they should be really careful, that that could be... Maybe they want to go on doxycycline instead of an antimalarial agent as a prophylaxis against malaria. I warn them that if they get poison ivy, they shouldn't go on systemic steroids because that could exacerbate their disease. I warn them about beta blockers, which may be an exacerbating factor for psoriasis. I also tell them to actually try to lose weight and avoid alcohol as much possible and to eat more of a Mediterranean diet. These are all things I tell people when I see them, either initially or during the course of my treatment period.

Dr. Birnholz:

And are there specific patient populations who are at greater risk for developing severe psoriasis? It sounds like you ran through some of the key populations, some of the key concerns you have with patients who are on certain medications or about to travel. What other populations do you speak to?

Dr. Bagel:

Demographically, there is more psoriasis as you move north and south of the equator and less psoriasis as you move towards the equator. The inverse is true for atopic dermatitis. I think we see psoriasis associated with obesity. I don't think that psoriasis causes the obesity. I think it's part of the systemic disease. We know that with psoriasis there's an increased frequency of metabolic syndrome, diabetes, anxiety, depression, hypertension, arthritis. Twenty-five percent of people with psoriasis have psoriatic arthritis. And I don't think necessarily you can say that a certain subgroup has more severe psoriasis. I think you can say a certain subgroup might be more difficult to treat.

Dr. Birnholz:

Dr. Bagel, my last question to you then is whether there are any developments, either on the research or education end, that are on the horizon for helping to lead to a better understanding of this disease? What can you tell us?

Dr. Bagel:

Well, I clearly think that we've gone from 15 years ago when we didn't understand the roles of specific interleukins, and now we're getting to the point where some oral medications with JAK kinase and TIK

2 inhibitors are actually being able to inhibit the transcription of certain proteins of proinflammatory molecules, and that's at the gene level. So, as we're able to understand which genes are more likely to produce proinflammatory molecules and inhibit them, then we could understand the pharmacogenetics of who might respond best to which medication.

Dr. Birnholz:

Excellent. Well, Dr. Bagel, I very much want to thank you for taking us through both these known and as yet undiscovered territories behind the development of psoriasis. It was great speaking with you.

Dr. Bagel:

Thank you very much. I appreciate it.

Dr. Birnholz:

I'm Dr. Matt Birnholz. Thank you for listening.

Announcer:

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