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Connecting TYK2 Biology to Psoriasis Pathogenesis

Dr. Turck:

This is *DermConsult* on ReachMD. I'm Dr. Charles Turck, and joining me to discuss what TYK2 biology is teaching us about psoriasis is Dr. Steven Feldman, Professor of Dermatology at Wake Forest University School of Medicine in Winston-Salem.

Dr. Feldman, welcome to the program.

Dr. Feldman:

Dr. Turck, it's a great pleasure to be with you today.

Dr. Turck:

Well, let's start with the bigger picture, Dr. Feldman. How has our understanding of the immune pathways driving psoriasis evolved in recent years?

Dr. Feldman:

I remember, going back to when I started taking care of psoriasis patients, learning about pathogenesis and studies going back to the 1960s when people were measuring how fast the skin cells were growing. They thought, "Oh, psoriasis must be like cancer because it's an overgrowth of skin cells." And then with work, a lot of it done at the University of Michigan, where they looked at immune function and how cyclosporine stopped psoriasis, we became aware that this is an immune disease.

And then they started looking at the pathways. Every time there was a new pathway scientifically, like adenylate cyclase, cyclic AMP, G proteins, or prostaglandins, they would look at their biopsies of psoriasis, and they would find that these pathways were abnormal, and they would say, "Oh, this is what's causing psoriasis." Those kinds of association studies don't really tell you a whole lot.

I remember when I was getting my PhD, I attended a biochemistry lecture at Duke, and a guy gave a talk, and he was talking about these associations and claiming causality. The top biochemist at Duke at the time, Irwin Fridovich, who identified superoxide dismutase, very gently said, "If you really want to know if something is causative, you have to use a specific inhibitor." And now we've done that. So we have specific inhibitors of tumor necrosis factor, interleukin-23, IL-17, and TYK2, and those specific inhibitors of those cytokines make psoriasis disappear. So we know without question that those cytokines are directly involved in psoriasis.

And then there's a second tool that we have, which is reverse genetics. So if you take the population, find the people who have psoriasis and the people who don't, compare their genes, and you find certain genes are linked to having psoriasis, you, again, can know what's causative. In the case of psoriasis, each of the two subunits of interleukin-23, the gene for the interleukin-23 receptor, and the gene for TYK2 are all genetically linked to having psoriasis.

Dr. Turck:

Now, where does TYK2 fit into that picture, particularly when it comes to IL-23, IL-12, and type I interferon signaling?

Dr. Feldman:

One of the things I learned in derm path is that if you take a biopsy of psoriasis and compare it to a biopsy of a superficial fungal infection, they look identical. You can't tell them apart. The only way to tell them apart is to stain for fungus. If you find fungus, you call it fungus. If you don't find fungus, you say it's psoriasis. You can't tell the two apart clinically or histologically because I believe it's the same immune pathway. And what is that immune pathway? It's that interleukin-23, TYK2, IL-17 axis.

Dr. Turck:

Now, you started to touch on this before, but genetic and translational research has also helped clarify TYK2's role in immune-mediated

disease. What have those findings added to our understanding of TYK2's relevance in psoriasis?

Dr. Feldman:

I love utilizing genetic defects for understanding what I should expect a new drug to do. When I heard somebody was developing a TYK2 inhibitor for psoriasis, first thing I did was say, "Well, what happens when genetically, you don't have TYK2?" And if you have complete loss of TYK2, you have a pretty severe immunodeficiency, which doesn't sound so good. You're susceptible to mycobacteria, and you're susceptible to viral infections. Why? Well, probably because TYK2 is important not only for mediating the interleukin-23 signaling in that psoriasis pathway, but it's also important for mediating certain interferons—type I interferons alpha and beta—and so you're susceptible to mycobacteria and viral infections. But if you have a genetic partial loss of TYK2, you don't have that immunodeficiency. Instead, you're protected against developing immune diseases. And so by making sure you don't have a lot of interferon, you're probably less likely to develop lupus.

So again, I think these genetic conditions may be informative to a degree. I wouldn't count on them because complete absence is different from pharmacological blockade that may not inhibit the thing entirely. Also, when you are born without something and your immune system is in development and doesn't have it, it may be very different from having a normal immune system develop and then blocking it later in life. So ultimately, we have to rely on clinical trials for safety and efficacy data.

Dr. Turck:

For those just tuning in, you're listening to *DermConsult* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Steven Feldman about where TYK2 fits into psoriasis biology.

So Dr. Feldman, how should clinicians think about TYK2 within the broader JAK family, and what distinguishes the signaling pathways mediated by TYK2 from those associated with JAK1, JAK2, and JAK3?

Dr. Feldman:

So you have interleukin 23, the cytokine binding to its receptor on the cells, and the interleukin 23 receptor. That receptor couples to members of the JAK family—two members, TYK2 and JAK2. Activation of those activates STATs, which go down to the nucleus and turn on interleukin-17 gene expression, so interleukin-17 is produced.

By blocking JAKs, we have new targets for inhibiting these immune signaling pathways. Now, we have very targeted immune inhibitors, and the JAK family as a whole is a little less specific. For example, I said that interleukin 23 signals through TYK2 and JAK2. So in theory, you could inhibit JAK2 and make psoriasis better; you can do that. But JAK2 also mediates numerous other signals, including blood cell production, red cell production, white cell production, and platelet production. You don't want to inhibit JAK2.

The nice thing about TYK2 is it mediates a signal for a narrower group of cytokines. It mediates signals for interleukin 23, interleukin 12, and some of our interferon. So if you block it, you're going to block the IL-23 pathway, which seems to be pretty much totally safe to do. But you're also going to block some interferon. That's limiting in some ways because you would like to have interferon around to prevent viruses from forming. And what we see with the TYK2 inhibitor that's already on the market is that you have a tiny little signal that seems like a somewhat increased risk of developing zoster. I like to tell patients, "Get a zoster vaccine when you start this drug."

But in theory, some of our patients probably have their psoriasis because they have the gene that overproduces TYK2, because remember, the TYK2 gene is genetically linked to psoriasis. And for those patients, we're actually getting to the heart of the problem.

Dr. Turck:

Now, as research continues to evolve, what questions about TYK2 and its role in psoriasis biology remain unanswered?

Dr. Feldman:

I'd really love to know which of my patients have psoriasis because they have too much TYK2. I have a feeling that it could be patients who have psoriasis and lupus or psoriasis and dermatomyositis. They're overproducing the TYK2 pathway, which would create too much interleukin-23 signaling, causing psoriasis, and it would create too much interferon signaling, which might be the cause of lupus or dermatomyositis in some people.

Another issue would be why the TYK2 inhibitors we have now aren't quite as effective as our most effective biologics. And I think the immunologists might be looking at the pathways that are blocked, and immune pathways are so complicated that you could develop a story to explain anything you find.

I'm not sure the research questions need to be about the biology as much as about the adherence to treatment because one of the nice things about these TYK2 inhibitors is that they're oral agents, so a lot of patients prefer oral drugs. These small-molecule drugs get into the cell, where they can inhibit TYK2, which is an intracellular protein. But getting people to take a pill is different than getting people to

rub slop on their skin and different than getting them to take an injection. And so a lot of our research might be that they take enough pills to make them happy, but they're not taking enough pills to get the same level of efficacy that they get with an injection treatment once every month or couple months.

Dr. Turck:

Now looking ahead, Dr. Feldman, how could a more precise understanding of TYK2-mediated signaling inform the way we think about targeting inflammatory pathways involved in psoriasis?

Dr. Feldman:

We have this interleukin-23, TYK2, IL-17 pathway, but within that pathway, there may be other proteins involved and other things that could be potential targets. Finding a signaling molecule within the nucleus that's specific for that interleukin-17 gene might be better than something that blocks interferon as well. The reverse genetics has found over 100 different genes that are genetically linked to psoriasis. So there's a lot of other targets there, and how they interact with TYK2 may be helpful.

We may be at the point where we should be focusing on getting people to use their medicines better. So for example, with a TYK2 inhibitor, it's probably going to be delivered in a bottle. The bottle may be a beige color designed to blend into any environment so that you don't notice that it's there. It's made for that. And if you're like me and you get your medicine in a bottle, you would forget many days to take the medicine. And on the days that you took the medicine, you'd forget that you had taken it, and you would take it a second time, or in my case, maybe even a third time. I think it's insane that we send patients medicines in these bottles. When starting patients on a TYK2 oral drug, the first thing I would tell them is, "Get a seven-day pill container." We know this from birth control pills. In the 1960s, birth control pills came in a bottle, and they worked some, but they weren't great. But then, without changing the chemistry much at all, they just changed the packaging telling you what pill to take what day, and they became phenomenally effective. I hope what we see with TYK2 inhibitors is that they start coming in 30-day pill packs telling you what drug to take what day.

Dr. Turck:

Well, with those reflections in mind, I want to thank my guest, Dr. Steven Feldman, for joining me to discuss the role of TYK2 in psoriasis.

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

Dr. Feldman:

My pleasure.

Dr. Turck:

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