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From Heterogeneity Comes New Insights: Exploring the Role of T Cells & OX40 Signaling in Atopic Dermatitis

Announcer:
You're listening to ReachMD. This medical industry feature, titled "From Heterogeneity Comes New Insights: Exploring the Role of T Cells and OX40 Signaling in Atopic Dermatitis," is sponsored by Amgen and Kyowa Kirin.

Your host is Dr Charles Turck.

Dr. Turck:
This is ReachMD, and I'm Dr. Charles Turck. Joining me today is Dr. Jonathan Silverberg, who's a professor and Director of Clinical Research and the Director of Patch Testing at George Washington University School of Medicine and Health Sciences. Dr. Silverberg, welcome.

Dr. Silverberg:
Thank you for having me.

Dr. Turck:
To start us off, Dr. Silverberg, can you tell us a little bit about atopic dermatitis and your experience in the clinic managing patients with this disease?

Dr. Silverberg:
Sure. Many patients with atopic dermatitis experience chronic symptoms, intensified by unpredictable flares, which can result in significant clinical burden, that impacts the patient's overall quality of life. In fact, atopic dermatitis is the skin disorder with the highest disease burden. This is particularly true for the patients I see in my clinic with moderate to severe disease, who may experience skin symptoms including redness, dryness, and skin thickening, 5-7 days per week. Itch and skin pain have a significant impact on these patients, with over 40% of them reporting skin pain within the past week, and about a third experiencing itching 5-6 days a week. In many patients, these skin symptoms can result in sleep disturbances or loss of sleep, which further increase the burden of disease. As you can imagine, over the course of the disease, these sorts of symptoms negatively impact multiple aspects of patients' daily lives.

Dr. Turck:
Do your patients experience burden beyond the skin symptoms you described?

Dr. Silverberg:
Unfortunately, yes. The burden of atopic dermatitis can be far-reaching, and I've certainly seen this in my patients. In addition to their clinical symptoms, many patients also experience negative emotional or social impacts of the disease. This is

further substantiated by a systematic review, published by the American Academy of Dermatology in 2022, that showed clinically diagnosed depression and anxiety are associated with atopic dermatitis. Many of my patients also tend to feel embarrassed or self-conscious about their skin, and so they avoid social interactions altogether. Over half of my patients are also limited in their ability to complete common daily activities, even household chores. All in all, you can start to see how the overall burden in atopic dermatitis extends beyond the skin and can significantly impact a patient's overall wellbeing and quality of life.

Dr. Turck:
Hearing a little more about the impact that this disease has on your patients, I can understand why keeping the symptoms of the disease under control would be an important goal for both patients and clinicians. Can you briefly comment on topical and systemic therapies

that are currently used in atopic dermatitis? And based on your experience, what are the remaining challenges regarding management of moderate to severe atopic dermatitis?

Dr. Silverberg:
Sure. So, topical therapies have been a mainstay of atopic dermatitis treatment for decades. While they continue to have a place in the treatment paradigm, especially for patients with mild disease, our understanding of atopic dermatitis pathophysiology and treatment options has evolved over time, providing more options for patients with moderate to severe disease. We now know that the inflammation that drives many of the skin symptoms associated with atopic dermatitis, including lesion development, itch and pain also has an impact outside of the skin. The systemic nature of the underlying inflammation, coupled with the potentially large body surface area involved, are two reasons why patients with moderate to severe disease often have inadequate disease control, despite the standard use of topical therapies. It is recommended that these patients be evaluated for systemic therapy to help better control their disease. Now, current systemic therapies in moderate to severe atopic dermatitis target individual cytokines such as interleukin-4, interleukin-13 or interleukin-31, or broadly inhibit the activity of molecules required for downstream signaling of multiple cytokines. While these therapies have provided significant benefit to patients with moderate to severe atopic dermatitis, some patients still fail to reach, and/or maintain, adequate control of their disease with systemic therapies. This could be due to a lack of efficacy, loss of response, or safety and tolerability issues.

Considering these challenges, additional research is underway, seeking to identify distinct inflammatory pathways, and cell types that contribute to the heterogeneity of atopic dermatitis pathogenesis.

Dr. Turck:
How can what we know about atopic dermatitis pathophysiology inform research into novel inflammatory pathways?

Dr. Silverberg:
That's a great question. When thinking about novel inflammatory pathways, we must also keep in mind what we already know about atopic dermatitis pathophysiology. Atopic dermatitis is a complex and heterogeneous disease. In the clinic, we see atopic dermatitis patients who have skin lesions with different characteristics and variable distribution throughout the body. What we cannot see is that these diverse clinical manifestations are driven by multiple inflammatory pathways that are the underlying cause of these clinical symptoms. T cells appear to play a central role in many of the inflammatory pathways that drive atopic dermatitis pathogenesis. One clear indication of their importance is that T cells are the most abundant infiltrate in atopic dermatitis lesions. This T cell influx and expansion within the skin, as well as the release of various proinflammatory cytokines, drives multiple aspects of atopic dermatitis pathogenesis, including inflammation, flares, epidermal hyperplasia, itch and skin pain.

Dr. Turck:
So, Dr. Silverberg, how does one cell type – the T cell - contribute to so many different activities in atopic dermatitis?

Dr. Silverberg:
Well, there are actually many different types of T cells, each with a specific set of functions that drive inflammation. Included in this mix are both effector and memory T cells, which contribute to acute and chronic inflammation respectively. T helper 2 cells are one type of effector T cell, and play a key role in atopic dermatitis pathogenesis, and are best known for their release of the proinflammatory cytokines interleukins 4 and 13. However, it's important to appreciate that the T helper 2 cells also release other cytokines, such as interleukin-5 and interleukin-31, that exert their own effects on the inflammatory response. And while pathogenic T helper 2 cells are dominant in atopic dermatitis, other pathogenic T cell subsets and their associated cytokines may also contribute to disease pathophysiology. The relative contribution of each T cell-mediated inflammatory pathway may evolve over the course of the disease, or may even vary by age and ethnicity, and this drives the complex variations of disease presentation in atopic dermatitis. As I mentioned, memory T cells represent another cell type with an important role in atopic dermatitis. They are long-lived, poised for reactivation, can contribute to inflammation even in the absence of visible lesions, and can drive disease persistence and chronic symptoms.

Taken together, this idea of a T cell inflammatory network in atopic dermatitis highlights the unique role of T cells upstream of the individual cytokines that they produce.

Dr. Turck:
And these T cells that you described as critical to the atopic dermatitis disease process, what exactly makes them pathogenic?

Dr. Silverberg:
In order to address this question, let's first think about T cell activation in a normal immune response. To form a productive response, T cells need to expand, survive and mature into robust, effector T cells in response to an infectious threat, such as a bacteria or virus.

After the threat is cleared, the effector T cells contract, and a small subset develops into long-lived memory T cells that can quickly

become reactivated if the bacteria or virus is reintroduced. All of these activities require a specific and well-orchestrated set of signals to be delivered to the T cells throughout their development. In patients with atopic dermatitis, T cells become pathogenic when they receive signals to expand and mature into effector and memory T cells, in the absence of an infectious threat. One important activation signal for T cells occurs through the OX40 pathway.

OX40 is expressed on the surface of activated effector and memory T cells. These are the cells that are more likely to be pathogenic in atopic dermatitis. The OX40 pathway is activated when OX40 expressed on T cells binds to the OX40 ligand, which is expressed on a number of cell types, including antigen-presenting cells. Activation of the OX40 pathway promotes T cell proliferation, survival, differentiation and migration to the skin, where they release proinflammatory cytokines that contribute to key aspects of atopic dermatitis pathogenesis, including promotion of skin inflammation, itch and skin pain. Importantly, these effects of OX40 signaling are seen across multiple pathogenic T cell subsets, including memory T cells.

Dr. Turck:
So it seems that the OX40 pathway plays a key role in T cell activation and effector function development. What is known about OX40, specifically in patients with atopic dermatitis?

Dr. Silverberg:
Yeah, so there are some interesting data coming out from multiple groups, showing that the OX40 pathway has direct relevance to T cell-driven inflammation in atopic dermatitis. I think one of the strongest indications that the OX40 pathway plays a role in atopic dermatitis is the increase in expression of OX40 on T cells in atopic dermatitis patients, compared to healthy controls. We've also seen the expression of OX40 and OX40 ligand, in cells colocalizing specifically in lesional skin of atopic dermatitis patients, suggesting that this pathway is actively playing a role in the inflammatory process in the skin. In fact, we've also seen that OX40-positive T cells are better able to home to the skin, which may allow these activated pathogenic T cells to drive inflammation directly in the skin.

Dr. Turck:
Now we've talked a lot about the role of OX40 signaling on multiple effector T cells, Dr. Silverberg, so I'm wondering if OX40 activation also occurs on memory T cells?

Dr. Silverberg:
Absolutely. OX40 signaling plays a key role in promoting both the development and reactivation of memory T cells residing in the skin. These memory T cells develop and persist long after the initial immune response, and can be quickly reactivated, providing the basis for immunologic memory. What is the concept of immunologic memory mean clinically, for patients with atopic dermatitis? Well, there's emerging research that memory T cells in the skin contribute to the chronic and persistent nature of atopic dermatitis. For example, for many patients, atopic dermatitis lesions may recur in the same body location. This may be due in part to memory T cells residing in the skin at these specific locations. The severity and persistence of disease symptoms may also be influenced by the long-lived potential of these memory T cells. In a nutshell, in order to understand and appreciate atopic dermatitis as a chronic disease, we need to also understand and appreciate the key role of memory T cells in disease pathogenesis.

Dr. Turck:
And before we close, Dr. Silverberg, are there any final thoughts on our rapidly evolving understanding of atopic dermatitis pathophysiology and implications for future research that you'd like to leave with our audience today?

Dr. Silverberg:
When seeing patients in the clinic, it's important to keep in mind that atopic dermatitis is more than a disease of the skin. It's a complex and heterogeneous inflammatory disease, mediated by multiple T cell-driven inflammatory pathways, leading to chronic and persistent symptoms and significant burden. Some of our patients, particularly those with moderate to severe disease, may require systemic therapy in addition to topical treatment, to adequately control their symptoms. Moreover, for some patients, treatment with currently available systemic therapies may still not be sufficient to reach the treatment goals.

In the future, focusing on pathogenic T cells directly, rather than individual T cell cytokines or downstream pathways, could provide new insights into our understanding of the pathogenesis of atopic dermatitis.

Dr. Turck:
Well, with those final thoughts in mind, I would like to thank my guest, Dr. Jonathan Silverberg, for sharing his insights on the heterogeneity of atopic dermatitis, and the importance of OX40 signaling in disease pathogenesis. Dr. Silverberg, it was a pleasure having you on the program.

Dr. Silverberg:
Thank you very much.

Announcer:
This program was sponsored by Amgen and Kyowa Kirin. If you missed any part of this discussion, visit ReachMD dot com slash industry feature. This is ReachMD. Be Part of the Knowledge.