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Epithelial Cytokines Drive Type 2 Inflammation in Eosinophilic Esophagitis

Announcer:
You're listening to *Innovations in Medicine* on ReachMD.

This program, titled "Epithelial Cytokines Drive Type 2 Inflammation in Eosinophilic Esophagitis," is sponsored by Amgen and AstraZeneca.

Here's your host, Dr Jennifer Caudle.

Dr Caudle:
Welcome to ReachMD. I'm your host, Dr Jennifer Caudle, and today, we'll be talking about eosinophilic esophagitis, or EoE, and our evolving understanding of its pathogenesis. We'll explore the role of epithelial cytokines in driving type 2 inflammation in EoE, and how this biology relates to what clinicians see in practice. And joining me for this conversation are Dr Kathryn Peterson and Dr John Leung. Dr Peterson is a board-certified gastroenterologist and senior associate consultant at the Mayo Clinic in Jacksonville, Florida.

Dr Peterson, thank you so much for being here today.

Dr Peterson:
Thanks for having me.

Dr Caudle:
Of course. And also with us is Dr Leung. He is board-certified in both allergy and immunology and gastroenterology and he serves as the founding physician and CEO of Boston Specialists in Boston, Massachusetts. Dr Leung, we're so glad to have you here as well.

Dr Leung:
It's great to be here.

Dr Caudle:
So, Dr Peterson, let's begin our discussion with the broader clinical perspective. Why should EoE remain top of mind for clinicians today?

Dr Peterson:
One of the main reasons is that we're just simply seeing much more of it in clinical practice. The prevalence of EoE has increased, with more than a five-fold increase in the United States between 2009 and 2022.[1] And the incidence continues to rise, outpacing increased recognition and improvements in diagnostic procedures.[2,3] And EoE is one of the most common causes of dysphagia and food impaction in young adults and children.[4,5]

Managing the disease can also be challenging. First-line therapy includes proton pump inhibitors, swallowed topical steroids, or an elimination diet.[5] However, these approaches can carry a high treatment burden, and inflammation may remain.[5-7] In fact, about two-thirds of patients treated with proton pump inhibitors and one-third of those treated with swallowed topical steroids don't achieve histological remission.[6]

At the same time, diagnosis is often delayed, and there are several reasons for that.[8,9] Patients may present with nonspecific symptoms or adapt the way they eat to manage those symptoms.[5,10] Limited awareness of EoE among healthcare professionals can also lead to

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poor access and fewer referrals to appropriate follow-up care.[11,12] And because EoE is a chronic, progressive disease, those delays matter for our patients.[4,5] Persistent inflammation over time can contribute to remodeling, fibrostenosis, and eventually esophageal strictures, so recognizing the disease early is critical.[13-16]

Dr Caudle:
And if we turn to you now, Dr Leung, we've talked about the growing clinical burden of EoE. But how has our evolving understanding of the biology helped reshape the way we think about this disease?

Dr Leung:
Well, I think one of the biggest advancements has been in our understanding of where the disease process begins. We now recognize that esophageal epithelium and epithelial cell-derived cytokines play important roles in the pathogenesis of EoE.[4,17,18] We also know that EoE is frequently associated with atopic conditions such as asthma, atopic dermatitis, food allergies, and allergic rhinitis. In fact, about 60 to 80 percent of patients with EoE have a history of atopic disease.[5,19]

Later in our conversation, we'll take a closer look at how disruption of the epithelial barrier, together with food antigens, aeroallergens, and other environmental insult triggers the release of epithelial cytokines that drive the downstream type 2 inflammatory response and ultimately contribute to the chronic inflammation and remodeling seen in EoE.[15,16,20-22] But to come back to your question, we now recognize that EoE is initiated by a complex interplay of environmental, immune, and genetic factors that drive the disease process.[16,21-25]

Dr Caudle:
You know, that's really great insight. Coming back to you, Dr Peterson, how are the biologic processes Dr Leung described reflected in the endoscopic and histologic findings we see in EoE?

Dr Peterson:
Well, on endoscopy, we're looking for characteristic findings, including edema, rings, exudates, furrows, and strictures, which are captured by the EoE Endoscopic Reference Score, or EREFS.[5,15] As the disease progresses, those inflammatory findings can evolve into structural remodeling, with more prominent rings, esophageal narrowing, and, ultimately, strictures in some patients.[5]

Histologically, eosinophil-predominant inflammation remains a defining feature of EoE, but we may also see eosinophilic abscesses, basal zone hyperplasia, and fibrosis within the lamina propria. And over time, the disease can progress from an inflammatory phenotype to a fibrostenotic phenotype, reflecting the cumulative effects of chronic inflammation.[4]

Collectively, these findings have shifted our attention to the esophageal mucosa, and, in particular, the epithelial barrier, where many of the earliest events in EoE pathogenesis occur.[15,20]

Dr Caudle:
Dr Peterson, let's talk about that a little bit more. Can you explain how disruption of the esophageal epithelial barrier contributes to EoE pathogenesis?

Dr Peterson:
Absolutely. Under normal conditions, the esophageal epithelium serves as more than a physical barrier. It orchestrates homeostatic and pathogenic immune responses.[20] Intercellular junctional complexes, such as tight junctions, help maintain barrier integrity by controlling paracellular transport. In a healthy esophagus, the basal zone occupies less than 15 percent of the total epithelial thickness.[16,20]

In EoE, however, that epithelial barrier becomes disrupted.[16,20] And we see a loss of key structural proteins that enhance the epithelial barrier in the esophagus, such as E-cadherin, claudins, and desmoglein-1. There's also an imbalance between increased protease expression, including calpain 14, and decreased expression of the protease inhibitor SPINK7.[15,26,27] Together, these changes weaken tight junctions, resulting in apical junction complex defects and dilated intercellular spaces that facilitate allergen penetration and immune activation.[15,16,20,26,27]

Histologically, that's when we may see basal zone hyperplasia, as I mentioned earlier, where the basal layer occupies more than 15 percent of the epithelial thickness, along with subepithelial fibrosis and smooth muscle hypertrophy.[16,20,28,29]

Dr Caudle:
For those of you who are just tuning in, you're listening to *Innovations in Medicine* on ReachMD. I'm your host, Dr Jennifer Caudle, joined by Dr Kathryn Peterson and Dr John Leung. We've been discussing how epithelial barrier dysfunction initiates the disease

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process in eosinophilic esophagitis.

Dr Caudle:
Now, Dr Leung, earlier you introduced the role of epithelial cytokines in EoE pathogenesis. Can you expand on how disruption of the epithelial barrier leads to the downstream type 2 inflammatory response?

Dr Leung:
Of course. The esophageal epithelium is increasingly recognized for its active role in initiating the immune response in EoE.[15,16,20-22]

Once the epithelial barrier is disrupted, food antigens, aeroallergens, and other environmental insults can interact more readily with the esophageal epithelium.[15,20] Upon allergen exposure, epithelial cells release cytokines, including thymic stromal lymphopoietin, or TSLP, IL-33, and IL-25. These cytokines serve as some of the earliest signals that trigger a type 2 inflammatory response, with the TSLP playing an important upstream role in driving downstream inflammation.[15,20,21]

These epithelial cytokines activate type 2 innate lymphoid cells and T helper type 2 cells. In turn, these cells produce the type 2 cytokines IL-4, -5, and -13, which promote eosinophil and mast cell recruitment and activation. Ultimately, this amplifies the inflammatory cascade and further impairs epithelial barrier function.[15,20,21] And over time, this chronic type 2 inflammation can contribute to fibrosis and remodeling, including strictures.[15,16]

Dr Caudle:
You know, that was an excellent overview, Dr Leung. Building on that discussion, Dr Peterson, what have findings from esophageal biopsies revealed about the role of epithelial cytokines in EoE?

Dr Peterson:
That's a great question. The biopsy data support epithelial cytokine involvement in EoE.[17,18,30] Compared with healthy controls, esophageal biopsies from patients with active EoE demonstrated significantly higher expression of TSLP, IL-33, and IL-25, reinforcing the role of esophageal epithelium in the disease process.[18]

In a separate biopsy study, patients with EoE were also found to have increased numbers of TSLP-responsive CD4-positive T cells compared with patients without EoE. And what's more, these TSLP-responsive T cells produced higher levels of IL-4 and IL-13 than those that were non-responsive to TSLP. The study also showed that TSLP induced expression of the TSLP receptor, supporting a feed-forward loop that helps sustain type 2 inflammation.[31]

So in line with the cytokine expression data, immunohistochemistry provided additional insight by showing where these cytokines localized within the esophageal tissue. Healthy esophageal tissue demonstrated little TSLP expression within the epithelium, whereas biopsies from patients with active EoE showed prominent TSLP expression, primarily within the suprabasal epithelial layer.[30]

Similarly, IL-33 expression in healthy tissue was largely confined to cells within the lamina propria, including endothelial cells. But in contrast, biopsies from patients with active EoE demonstrated a substantial increase in IL-33 expression within the epithelium, particularly in a subpopulation of basal cells within the interpapillary basal layer.[17]

Dr Caudle:
And Dr Leung, beyond what we see in patient biopsies, what have genetic studies taught us about the role of epithelial cytokines in EoE?

Dr Leung:
Genetic studies provide another important line of evidence supporting the role of epithelial cytokines in EoE. Polymorphisms in both the *TSLP* and *TSLP* receptor genes have been identified in patients with EoE.[32-34] And in a genome-wide association study, researchers identified a risk locus for EoE susceptibility that contains the *TSLP* gene.[32,33]

We also know that genetic factors extend beyond *TSLP*. As Dr Peterson mentioned earlier, increased expression of calpain 14 contributes to epithelial barrier dysfunction by weakening tight junctions and facilitating allergen penetration and immune activation.[16,27,35]

Taken together, these findings reinforce that both epithelial barrier dysfunction and cytokine signaling pathways are fundamental to EoE pathogenesis.[4,17,18]

Dr Caudle:
You know, we've covered a lot of ground today and as we close, what's one thing you hope clinicians think differently about after

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today's discussion? Dr Leung, let's start with you.

Dr Leung:
I hope my colleagues come away thinking about EoE as a disease that begins well before eosinophilic inflammation becomes apparent on biopsy.[15,16,20-22] The esophageal epithelium responds to food antigen, aeroallergen, and other environmental insult by releasing epithelial cytokines, including TSLP, IL-33, and IL-25, that initiate the downstream type 2 inflammatory response.[15,20,21] The growing body of biopsy and genetic evidence reinforce the importance of understanding these upstream pathways in EoE pathogenesis.[17,18,30,32-34]

Dr Caudle:
And Dr Peterson, what would you add?

Dr Peterson:
From a clinical perspective, I hope clinicians come away recognizing how the biology we discussed today connects directly to the natural history of EoE. Epithelial barrier dysfunction and the release of epithelial cytokines, like TSLP, are key drivers of type 2 inflammation within the esophageal mucosa.[15,20,21] That inflammation contributes to the symptoms and tissue changes we see in our patients and, when it persists over time, can lead to remodeling, fibrosis, and fibrostenotic complications, including esophageal strictures.[15,16]

So the endoscopic and histologic findings we evaluate in EoE are downstream manifestations of a disease process that actually begins at the epithelial level.[4,5,15,16,20-22] Understanding these upstream mechanisms gives us a more complete picture of EoE pathogenesis and reinforces the importance of recognizing and evaluating the disease early.

Dr Caudle:
Well thank you both. Those were excellent perspectives and a great way to bring our discussion full circle. And with that, I'd like to thank my guests, Dr Kathryn Peterson and Dr John Leung for helping us better understand how epithelial barrier dysfunction leads to the release of epithelial cytokines and drives type 2 inflammation in EoE.

Dr Peterson and Dr Leung, it was great speaking with you both today.

Dr Peterson:
Thank you for having me.

Dr Leung:
Thank you.

Announcer:
This program was sponsored by Amgen and AstraZeneca. If you missed any part of this discussion, visit *Innovations in Medicine* on ReachMD.com, where you can Be Part of the Knowledge.

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