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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Understanding the Role of TSLP in Severe Asthma

Announcer Intro:
You're listening to ReachMD.

This medical industry feature, titled "Understanding the Role of TSLP in Severe Asthma" is sponsored by Amgen & AstraZeneca. This program is intended for physicians.

Here's your host, Dr. Matt Birnholz.

Dr. Birnholz:
This is ReachMD, and I'm Dr. Matt Birnholz. Joining me to discuss the role of TSLP in severe asthma is Dr. Jonathan Corren, an Associate Clinical Professor of Medicine and Pediatrics at the David Geffen School of Medicine at UCLA in Los Angeles.

Dr. Corren, welcome to the program.

Dr. Corren:
Thanks, very much, for having me.

Dr. Birnholz:
Great to have you with us.

So, to begin, why don't we review some of the most pressing challenges for patients with severe asthma, despite ongoing advances in treatment.

Dr. Corren:
Sure. So, asthma is a chronic disease of airway inflammation that is estimated to affect more than 25 million people in the United States.[1–3]

Asthma, overall, has a very significant impact on productivity with some people estimating 8.7 million lost workdays per year and 5.2 million lost school days per year in the United States.[4]

And our patients with severe and uncontrolled asthma who have frequent exacerbations represent nearly 40% of all asthma-related direct cost;[5] these patients have a higher frequency of emergency room visits or hospitalizations due to severe asthma attacks.[5,6]

Airway inflammation and narrowing are the major drivers of asthma symptoms, including cough, chest tightness, shortness of breath and wheezing.[1-3]

But it is important to remember that the inflammatory processes that drive asthma are heterogeneous between patients. While many have type 2 or T2 disease, [7] a sizable group have non-T2 disease.[8]As a result, numerous cell types, mediators, and immune pathways determine inflammatory pathways in asthma.

In addition, inflammation in asthma is also heterogeneous and dynamic *within* patients,[7]whocan have concurrent or overlapping inflammatory pathways and their dominant inflammatory pathway can change over time.[7–10]

The heterogeneity of asthma inflammation makes treating the disease complex. Many patients fail to achieve control with high-dose inhaled corticosteroids and additional controllers, which can results in continued exacerbations that are treated with repeated bursts of systemic corticosteroids.[5]

Dr. Birnholz:
So, thinking about underlying inflammatory pathways in asthma, how does the airway epithelium factor into the asthma pathophysiology, as we currently understand it?

Dr. Corren:
So, I think it's important to recognize that the airway epithelium is the first point of contact for environmental exposures. And the epithelium plays a foundational role in subsequent asthma inflammation.[11]

It can act as a physical barrier, but it's also able to sense the environment around us.[11,12] The airway epithelium also plays several active roles, including mediating immunity in both innate and adaptive responses,[12] inducing inflammation through the production of epithelial cytokines and alarmins,[11,12] and structural changes through airway remodeling and smooth muscle changes.[11,13,14]

In severe asthma specifically, the airway epithelium is significantly altered through several different mechanisms:

- The first is goblet cell hyperplasia and increased mucus production, which can contribute to airway blockage;[11,15]
- Second, epithelial tight-junction number and integrity do decrease, causing tissue damage, and allowing external insults to penetrate deeper through the airway wall;[15,16]
- Third, an increased matrix deposition in the epithelial layer causes thickening of the epithelium, which then leads to airway narrowing;[11,15,17]
- And finally, sub-epithelial inflammation and fibrosis may lead to fixed airway obstruction.[15,17]

But if we step back a little bit, there are several environmental exposures that trigger airway inflammation at the epithelium.[18–21]

Pathogens including respiratory viruses and bacteria.[18,19]

Aeroallergens include dust mites, cockroaches, animal dander, molds, and pollen.[20]

And air pollutants include smoke, dust, chemical pollution, and particulate matter.[21]

All of these may trigger airway inflammation, which starts first at the epithelium.

Dr. Birnholz:
I'd like to dive deeper into the molecular contributors responsible for driving this inflammation triggered at the epithelium, Dr. Corren. What do we need to know, here?

Dr. Corren:
The key molecular contributors to epithelial-associated inflammation are the epithelial cytokines also known as alarmins. These alarmins may be rapidly released after epithelial damage or immune cell activation,[12,22]but they may also be released in response to a wide range of environmental exposures.[11]

These epithelial cytokines or alarmins activate both innate and adaptive responses in overlapping, but distinct, ways.[12] Each of the alarmins to be discussed is a potent activator of type 2 innate lymphoid cells, with varying effects on Th2 cells.[12]

I'd like to focus on three epithelial cytokines that drive downstream responses in asthma. These include interleukin 33 or IL-33, IL-25, and thymic stromal lymphopoietin, known as TSLP.

So IL-33 is mainly produced by epithelial and endothelial cells.[12]It has several cellular targets,[12] augmentation of Th2 responses.[12]

But IL-25, on the other hand, is mainly produced by the epithelial tuft cells (or brush cells).[12] It has fewer cellular targets, compared with IL-33.[12] IL-25, along with IL-4, may augment Th2 responses.[12]

Now moving on to TSLP, this cytokine is primarily produced by epithelial cells.[12] TSLP also has many cellular targets;[12] it drives Th2 responses indirectly through dendritic cells and T cells.[12]

Dr. Birnholz:
So, with that in mind, I'd like to focus on TSLP. Now, what can you tell us about this epithelial cytokine and its role in asthma pathophysiology?

Dr. Corren:

Dr. Birnholz, interestingly, human TSLP was first described as early as 2001, [23] but now a lot more of the recent research has demonstrated the important role that TSLP plays in asthma inflammation.[24,25]

Once released from the epithelium, TSLP drives multiple inflammatory pathways, including downstream innate and adaptive immune responses.[26–29]

Variants at TSLP gene locus have been associated with asthma, with airway hyperresponsiveness,[30] and other non-respiratory T2-associated diseases.[31,32]

And as I've already alluded to, both allergic and non-allergic triggers, such as allergens, viruses, bacteria and pollutants, can induce TSLP release.[33]

While epithelial cells are the major source of TSLP,[11] other sources of TSLP include mast cells, dendritic cells, fibroblasts, and airway smooth muscle cells.[11,12,27,34,35]

Dr. Birnholz:
For those just joining us, this is ReachMD, and I'm Dr. Matt Birnholz. Today I'm speaking with Dr. Jonathan Corren about insights of the asthma inflammatory cascade with a focus on the role of TSLP.

So, Dr. Corren, mechanistically speaking, how does TSLP act across the spectrum of asthma inflammation?

Dr. Corren:
Yeah, that's a very important question. TSLP can drive T2 and non-T2 inflammatory pathways.[37] These include the allergic and eosinophilic pathways that would account for traditional T2 inflammation, but may also include non-T2 pathways and pathways that cause airway structural changes.

Focusing first on the allergic pathway, TSLP is involved in the maturation of naïve T cells to allergen-specific Th2 cells.[29] These cells release cytokines such as IL-4 and IL-13 that are involved in the production of IgE from B cells. Allergen binding to IgE bound to mast cells results in mast cell activation and the release of mediators of inflammation such as histamine and leukotrienes.[38]

For the eosinophilic pathways, not only does TSLP foster Th2 cell cytokine release, but also activates innate lymphoid cell type 2, or ILC-2 cells, which also release cytokines such as IL-5 and IL-13. IL-5 is involved in eosinophil maturation, survival, and activation.[37] These cytokines also have direct effects on the epithelium, on airway inflammation, and smooth muscle function.

TSLP can also drive structural cell effects through direct effects on airway smooth muscle, by activating mast cells which then further affect smooth muscle cells, and direct effects on fibroblasts leading to increased collagen production.[11,37,39]

There are other effects such as the release of eotaxin, IL-6, and IL-8, all of which may have direct effects on smooth muscle and these structures underlying the smooth muscle.[11]

These TSLP-driven effects on airway smooth muscle may be particularly important in understanding the non-T2 effects of TSLP in.

Dr. Birnholz:
So, given all these mechanistic understandings, why don't you help us understand what is known about the association of TSLP with the clinical features of asthma?

Dr. Corren:
TSLP has been found to be associated with many of the key clinical features of asthma, including asthma severity, asthma exacerbation risk, reduced lung function, potential airway remodeling, and reduced steroid response. Along with this, an exaggerated T2 response to viral infections.

Dr. Birnholz:
And all of those features are so important to the pathogenesis and development of asthma.

So, in our remaining time, I'd very much like to explore some of these clinical features in turn, try to get a better sense of TSLP's impact. Can you just walk us through that?

Dr. Corren:
I'd be happy to.

Firstly, increased airway TSLP expression is correlated with increased asthma severity.[41,42]

There were two separate studies that found that TSLP expression was significantly higher in the airways of patients with asthma, compared with healthy controls, with p-values less than 0.05[41,42]

Similarly, TSLP concentrations have been shown to correlate with disease severity; this result was also significant, with p-value of less than 0.05.[42]

Correspondingly, TSLP concentration is inversely correlated with FEV1. So, as TSLP concentration increased, lung function decreased.[41]

Touching upon the role of TSLP in structural changes, we have evidence that TSLP may drive airway remodeling.[39,44]

When comparing histopathological images from patients with asthma versus healthy controls, we can see broad structural changes, and increased TSLP expression in asthmatic lung tissue.

In the non-asthmatic lung,[36] normal bronchiole lined by pseudostratified ciliated epithelium, as well as the surround interstitium. And there is no significant TSLP expression observed at the epithelium.

However, in the asthmatic lung,[36] we can see epithelial cell hyperplasia in the bronchiole, basement membrane thickening, smooth muscle cell hyperplasia, fibrosis, and mild to moderate peribronchiolar inflammation. Even more interestingly, we observed expression of TSLP in the bronchiolar epithelial cells, and stromal cells.

In other studies, TSLP has been found to potentially contribute to airway remodeling via increases in collagen production by fibroblasts, and proliferation of airway smooth muscle.[39]

In terms of treatment response, TSLP may drive reductions in corticosteroid responses.[45]

In a trial from Liu and colleagues, ILC2s from the bronchoalveolar lavage fluid of patients with asthma exposed to TSLP were found to be resistant to steroids.[45]In this study, resistance to steroids was defined as a lack of inhibition of T2 cytokine expression by ILC2s.

Additionally, the reduced effect of dexamethasone was correlated with higher airway TSLP expression.[45] Corticosteroid resistance was significantly correlated with higher bronchoalveolar fluid and blood eosinophil levels, as well as lower FEV_1.[45]

Given this relationship between viral infections, airway inflammation, and asthma, it's important to see the response of TSLP after viral infection.

In a trial of pediatric patients, after respiratory syncytial virus, or RSV infection, bronchial epithelial cells of children with asthma produced higher levels of TSLP than epithelial cells of healthy children.[46]

In adult trials, bronchial epithelial cells produce significantly more TSLP when exposed to rhinovirus or double stranded RNA, which acted as a viral RNA analog.[47,48]

This increased TSLP drives an exaggerated T2 response to viral infections, and may explain how viruses have the ability to drive exacerbations in patients with asthma.[46–48]

Dr. Birnholz:
Well Dr. Corren, clearly, we've covered a lot of important information today. But, before we close, are there any key points that you want to impart or reiterate for our audience?

Dr. Corren:
I think there are some important findings.

As I mentioned before, the airway epithelium is the first point of contact for environmental exposures, and therefore plays an important role in asthma pathophysiology.[11]

Several epithelial cytokines or alarmins are involved, and they can be rapidly released after epithelial damage or immune cell activation.[12,22] But more importantly for asthma, they may also be released in response to a wide range of environmental exposures.[11]

Three key epithelial cytokines drive downstream responses in asthma: IL-33, IL-25, and TSLP.[12]

TSLP acts across the spectrum of asthma inflammation[37] and acts for several T2 and non-T2 inflammatory pathways.

TSLP can drive allergic inflammation, eosinophilic inflammation, potentially neutrophilic inflammation, and even structural changes of the

airway, mediated by mast cells.

And TSLP levels are correlated with clinically meaningful features including asthma severity,[41,42] exacerbation risk,[43] reduced lung function,[41] potential airway remodeling[39,44] and reduced steroid response.[45] And along with these, an exaggerated T2 response to viral infections.[46-48]

Dr. Birnholz:
Well, these are great insights coming into the end of our program, today. And I very much want to thank my guest, Dr. Jonathan Corren for guiding us through this pursuit to understand the role of TSLP in severe asthma. Dr. Corren, it was fantastic speaking with you, today. Thanks, so much.

Dr. Corren:
Thank you, and it was my pleasure.

Announcer Outro:
This program was sponsored by Amgen & AstraZeneca. If you missed any part of this discussion, visit reachmd.com/industryfeature. This is ReachMD. Be Part of the Knowledge.

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