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Investigating Inflammatory Mediators in Chronic Rhinosinusitis

Announcer:
You're listening to ReachMD, and this is *Deep Breaths: Updates from CHEST*. This is a nonpromotional, non-CME disease state educational podcast brought to you by the American College of CHEST Physicians in collaboration with and paid for by GSK. Here's your host, Dr. Peter Howarth. Dr. Howarth is a Professor of Allergy and Respiratory Medicine, and Honorary Consultant Physician within Medicine at the University of Southampton. He is also the Global Clinical Scientific Lead at GSK.

Dr. Howarth:
Welcome to *Deep Breaths: Updates from CHEST*, on ReachMD. I'm Dr. Peter Howarth. Joining me to provide expert perspectives on emerging roles of key inflammatory mediators in chronic rhinosinusitis with nasal polyps, or CRSWNP for short, is Dr. Katie Buchheit, an Associate Professor of Medicine at Harvard Medical School and an allergy and immunology specialist in Foxboro, Massachusetts and Professor Philippe Gevaert, ENT specialist at the Department of Otorhinolaryngology at Ghent University and the Upper Airway Research Laboratory. Dr. Buchheit and Dr. Gevaert, welcome to the program and thank you for being here today.

Dr. Buchheit:
Thank you so much for having me. I'm excited to have this discussion.

Dr. Gevaert:
Me, as well, I'm very happy to help you with this discussion.

Dr. Howarth:
Perhaps we can dive straight in and think about the role of Type 2 inflammatory mediators. So, Dr. Gevaert, what's known about the presence of Type 2 cytokines, such as IL-4, IL-5 and IL-13 in nasal polyp tissue? And also, about the local tissue presence of other factors such as IgE?

Dr. Gevaert:
Well, Peter, that's very interesting. we started investigating chronic sinusitis with nasal polyps, and we found that IL5 tissue levels were highly increased in nasal polyps, and especially in those patients with comorbid asthma.[7]

It was later on that we could find increase in both IL-4 and IL-13, on the other hand, one other very striking thing we found is that we had high levels of local IgE in nasal polyp tissue. [9,10]

And interestingly, this levels of IgE locally there in nasal polyp tissue, were not related to the presence or absence or positive skin prick tests that you do for routine allergy testing. So, we dived deeper into specificities of those IgE's, and what we found is that we had IgE's that were directed to many epitopes, so you had it to the classical allergens, but also for example, to super-antigens like staphylococcus antigens IgE. [11,12]

Dr. Howarth:
Thank you. And Dr. Buchheit, I know your one area of interest is aspirin-exacerbated respiratory disease. Do we find the same profiles in those patients?

Dr. Buchheit:
Yeah, that is an excellent question. And we've found that patients with AERD have very high tissue IgE levels, and this is, in fact, linked with the severity of their nasal polyposis. [11,12]

Patients with higher tissue IgE levels are more likely to have nasal polyp recurrence very quickly after surgery and we know in our patients with AERD that IL-5, IL- 4 and IL-13 are all very important as well. [11, 13]

Dr. Howarth:
We've appreciated the presence of Type 2 inflammation, and with a range of different cytokines involved. Dr. Gevaert, how do you apply this in your clinical practice?

Dr. Gevaert:
So thank you Peter, for the question. Standardly when we do surgery in our patients, we do an endotyping and a phenotyping of the patient, so we measure in the tissue that we collect during surgery, all the cytokines and mediators.

Now what we found is exactly that in the tissue that IgE levels and especially those with high IL-5 – high eosinophils, high Ig polyclonal Ig – both in tissue and in nasal secretions were those with the most need for revision surgeries. [11, 15]

And that's why, since then, we do endotyping of all our patients so that we try to predict the outcome of their surgery, and also the need, maybe, for better treatments. [15, 16]

Dr. Howarth:
That's very interesting to hear about that, how the relevance of Type 2 inflammation gives worse outcomes and makes the likelihood of polyps recurrence greater. So, perhaps, Dr. Buchheit, how do you see the role of the different components of the Type 2 inflammation contributing to that recurrence of the polyps?

Dr. Buchheit:
Yeah, that's a great question. We know that the nasal polyp is a complex microenvironment and there is actually pretty widespread expression of some receptors for Type 2 cytokines, such as the IL-4 receptor alpha and IL-5 receptor alpha, on multiple potentially relevant cell types. So I think, certainly in the case of IL-4 and IL-13, this signaling influences a variety of immune functions specifically the respiratory epithelium, has effects on mast cells, basophil cells, and eosinophils.[1-3]

In terms of interleukin-5, it's thought of classically as being really important maturation and differentiation factor for eosinophils and we know that eosinophils likely play many roles in the pathogenesis of nasal polyps such as releasing cytotoxic granule proteins extracellular traps containing DNA, Charcot-Leyden crystals which can really propagate the inflammatory environment within the nasal polyps. So, there are many ways, I think, that these Type 2 cytokines can influence nasal polyp pathogenesis leading to more severe disease and recurrence in patients who are very Type 2 high.[12, 17]

Dr. Howarth:
We classically label polyps as being eosinophilic polyps or non-eosinophilic polyps, and the focus is on eosinophils, but you raised an interesting point there, about the potential impact of IL-5 outside of eosinophils.

Dr. Howarth:
Katie, if you can give us some insight about the potential impact of IL-5, and indeed, perhaps IL-4 and IL-13 on different cell populations.

Dr. Buchheit:
I'm happy to talk about that. So we know that the IL-5 receptor is found on many nasal polyp cell types in addition to the eosinophil, so, using single cell RNA sequencing techniques, we identified an IL-5 receptor on nasal polyp mast cells nasal polyp ciliated epithelial cells, as well as antibody-secreting cells – so, B cells and plasma cells in the nasal polyp.[15]

And we have some functional data showing that the IL-5 receptor is functional on the human nasal polyp plasma cells, that stimulating those cells with IL-5 leads to up-regulation of some cell cycle transcripts. So we think it's possible that IL-5 could be leading to nasal plasma cell proliferation. In terms of its impacts on epithelial cells we have found that IL-5 may actually weaken cell adhesions reducing the integrity of the epithelial barrier of the nasal polyp tissue. [1-3]

In terms of IL-4 and IL-13, they also have actions, we think, on the integrity of the epithelial barrier. IL-4 and IL-13 can lead to reduced ciliary function increased mucus production and goblet cell metaplasia and increased chemokine expression from the respiratory epithelium. So we think that the integrity of the respiratory epithelium's impacted on multiple fronts here potentially, by IL-4, IL-5 and IL-13.[19]

Dr. Howarth:
Thank you. And Philippe, you've mentioned about the high levels of local tissue IgE, and how that didn't seem to relate to classical

allergy. Do we have any insight into what might be driving that within the polyp tissue?

Dr. Gevaert:
Well, Peter, that's indeed very interesting, and also the findings of Dr. Buchheit that we have IL-5 receptor on the other cells as well, might, of course, explain the strong relationship between IL-5 levels in the tissue and the IgE in the tissue as well, and because it's the IL-5 that is not only found on eosinophils but on the other cells, but also amplifying the IgE production together with IL-4 and IL-13. [15]

Now the question that remains – what drives this IgE production? We do know that indeed there is a relationship to staphylococcus aureus superantigens that have the potential of driving or amplifying or stimulating B and T cells in a different way than the classical allergy, and maybe therefore might be stimulating this local polyclonal IgE formation. [11,15]

Dr. Howarth:
For those of you who are just tuning in, you're listening to ReachMD. I'm Peter Howarth, and today I'm speaking with Dr. Buchheit and Dr. Gevaert about the role of inflammatory mediators in the progression of chronic rhinosinusitis with nasal polyps. We spoke a bit earlier about how cytokines, such as IL-4, IL-5 and IL-13 or factors such as IgE influence multiple cell types in the nasal epithelium. Katie, what contribution do mast cells, do you think, play to the Type 2 cytokine milieu within the polyp tissue?

Dr. Buchheit:
So, we know that there are many mast cells in nasal polyp tissue, and in terms of the Type 2 mediators of inflammation, many of them can certainly act on mast cells. Specifically, we think a lot about IgE, that it's a polyclonal IgE but that can still certainly stimulate mast cells and basophil cells through Fc receptor leading to degranulation of mast cells, as well as mediator-released and IgE can have a role in terms of mast cell survival and activation as well.[11]

In terms of IL-5, we know that mast cells have IL-5 receptor alpha, and additionally mast cells can actually make IL-5 and release it. [11]

And then, in terms of IL-4 and IL-13, mast cells are influenced by these cytokines as well. Our group has found that there was a potential role for IL-4 and IL-13 in the expansion of mast cells in the nasal polyps where there was really high IL-4 and IL-13 expression in the eosinophils. So, there was a correlation between IL-4 and IL-13 levels, and concentration of mast cells in the polyp tissue. [20]

Dr. Howarth:
So Katie, that's interesting to hear about the mast cells. So, Philippe, do we know anything about the state of mast cell activation within polyp tissue?

Dr. Gevaert:
So it looks like they can be activated, but not in the same degree as in a typical allergic rhinitis patient. So we did nasal challenges in our patients – allergic rhinitis patients, nasal polyp patients – and we see that when we do nasal challenges with grass pollen, with house dust mites or with tree pollen, that they do respond when they are really typically allergic. When you do the same experiment on nasal polyp tissue– you see a sort of a dampened response. So you do see a response, but it's always dampened, and that can, of course, be explained by the fact that you have a polyclonal IgE to thousands of specific epitopes that – then, therefore, if you only stimulate with the grass pollen, you don't have a massive mast cell degranulation.[21]

Dr. Howarth:
And there's obviously multiple cell types involved. Perhaps just to end with, Katie, I can ask you what we know about those eosinophil mast cell interactions, and perhaps you could give a perspective on where you think the major unmet needs are in our understanding, and where the future research might take us.

Dr. Buchheit:
Certainly. So, we know that some important mast cell products, such as inflammatory prostaglandins like PGD2 can be potent chemoattractant for eosinophils[22], so really mast cell activation can propagate eosinophilic inflammation, which we think is likely happening in the nasal polyp tissue. I think that, there is so much more that we really need to understand about what initial insults might be driving the development of nasal polyposis and how we can really harness our knowledge about what is most severely dysregulated in the polyp tissue to come up with additional therapeutics in this area and really be able to help our poor patients who have been suffering for many years, and we are certainly making great strides in this area, but I think that there will be even more to come, and hopefully over time, we'll have lots more to offer our patients with severe nasal polyposis.

Dr. Howarth:
That's a really great way to round out our discussion. It brings us back to the patients, and the science is only important if it helps us move forward as far as the understanding and treatment of patients are concerned. Clearly, it's a complex situation, and there's more

that we need to understand, but it's great that we've been able to move forward, and improve the understanding of the Type 2 biology. So, Katie and Philippe, it was really great speaking with you today. I really enjoyed it, and thank you very much, indeed.

Dr. Buccheit:
Yes, thank you so much for having me. It was a great discussion.

Dr. Gevaert:
I also thank you for having me in the discussion and thank you for listening to our stories.

Dr. Howarth:
Thank you. I am Dr. Peter Howarth, and I thank those that have been listening to this discussion and hope that you've found it of interest, and stimulating for you. Thank you.

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