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Molecular Mechanisms of COPD

Announcer:
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Dr. Han:
Hello. My name is Dr. Meilan Han, and this is CME on ReachMD. Here with me today is Dr. Surya Bhatt. So let's start our discussion with the biopathology of COPD. Dr. Bhatt, there's been increased attention recently on COPD phenotypes and pathophysiology, in particular the role of type 2 inflammation in COPD. So, why does this matter for practicing clinicians?

Dr. Bhatt:
Yeah, thank you, Dr. Han. I think there has been a huge amount of research done and significant advances made in the understanding of inflammation and inflammatory pathways in COPD, just in the past several years. And we are increasingly recognizing that a substantial proportion of patients with COPD have type 2 inflammation. Now, inflammation in COPD has traditionally been thought of as predominantly neutrophilic, with T1 and T17 pathways being involved, but we now discover that almost 20 to 40% of patients have type 2 inflammation, commonly indicated by elevated blood eosinophil counts.

And there are several studies indicating that this kind of type 2 inflammation is important in terms of predicting exacerbation risk, as well as increasing the risk for other bad outcomes such as FEV1 decline. And type 2 inflammation can be detected either by elevated blood eosinophil counts or elevated fractional exhaled nitric oxide or elevated IgE, all of which have been associated with greater risk of exacerbation in COPD.

In the ECLIPSE study, increasing eosinophil counts going from, say, less than 150 to 150 to 300 and greater than 300 are almost monotonically associated with monotonic increases with exacerbation frequency. And the higher the eosinophil counts and the higher the markers of type 2 inflammation, it appears that there is a greater risk of severe exacerbations.

In one study, genetic signatures of type 2 inflammation were studied, and even in patients without asthma and only COPD, there was a strong association between the presence of these type 2 inflammatory signatures and increased exacerbation frequency.

There are several pathways that have been discovered as to how all these operate in the human lungs. In response to several insults, such as microbes, cigarette smoke, oxidative stress, viruses, and bacteria, certain initial molecules are released, which are called alarmins, which are commonly IL-33, TSLP, and IL-25. And these can stimulate dendritic cells to then stimulate Th-naïve cells to get converted to Th-2 cells, or they can directly stimulate ILC2 cells, or they can stimulate eosinophils, and all of which can then release type 2 inflammatory cytokines, most common of which are IL-5, IL-4, and IL-13. And all of these have significant downstream effects in the form of eosinophil activation in the bone marrow, M2 macrophage polarization from M1 macrophages, B-cell class switching to produce more IgE, airway remodeling, upregulation of other chemokines, and then inflammatory cell trafficking into the tissue; and perhaps very importantly, alterations in the mucus biology, increasing MUC5A production and increased mucus production, and also

increasing smooth muscle cell contractility.

Dr. Han:
Thanks so much for that really excellent explanation. Surya, I know for many of us, maybe this isn't something we thought about since medical school, but it is really important, because estimates adjust roughly 20 to 40% of patients with COPD may demonstrate evidence of type 2 inflammation. And the clinical implications are increased risk for exacerbations, but also differential response to therapies such as inhaled corticosteroids and potentially type 2 inflammation-targeted biologics, where I know the biomarkers are under development, but certainly elevated eosinophil count seems to be a good one right now for identifying patients who have increased type 2 inflammation and can potentially help to guide treatment selection.

So this has been a great bite-sized discussion, but unfortunately, our time is up. So thank you for listening.

Announcer:
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