

IL-33's Dual Role in COPD: Inflammation and Mucus Dysfunction

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Chronic Obstructive Pulmonary Disease (COPD) management remains challenging, with persistent inflammation and mucus hypersecretion driving morbidity and mortality. Interleukin-33 (IL-33) has emerged as a key mediator in the pathogenesis of COPD, exhibiting a complex duality that both promotes inflammation and contributes to mucus dysfunction, presenting a nuanced target for future therapies.

KEY TAKEAWAYS

- **The Pivot:** IL-33 is not solely a pro-inflammatory mediator but also directly contributes to mucus hypersecretion in COPD.
- **The Data:** IL-33 promotes goblet cell metaplasia and MUC5AC expression, independent of its inflammatory effects.
- **The Action:** Therapeutic strategies targeting IL-33 in COPD must consider its multifaceted role to avoid unintended consequences or incomplete efficacy.

Chronic Obstructive Pulmonary Disease (COPD) is characterized by persistent respiratory symptoms and airflow limitation due to airway and/or alveolar abnormalities, typically caused by significant exposure to noxious particles or gases.¹ The underlying pathophysiology involves chronic inflammation, oxidative stress, and protease/antiprotease imbalance, leading to progressive lung damage.² A significant contributor to COPD morbidity and mortality is mucus hypersecretion, which can lead to airway obstruction, recurrent infections, and acute exacerbations.³ Globally, COPD affects millions, with its prevalence increasing, particularly in low- and middle-income countries, posing a substantial public health burden. The disease often presents with symptoms such as chronic cough, sputum production, and dyspnea, which progressively worsen over time, severely impacting patients' quality of life. Early diagnosis and effective management are crucial to slow disease progression and prevent exacerbations.

Interleukin-33 (IL-33), a member of the IL-1 cytokine family, is an alarmin released by damaged or stressed cells, particularly epithelial cells, and plays a critical role in type 2 immune responses.⁴ In the context of COPD, IL-33 levels are elevated in the lungs of patients and are associated with disease severity and exacerbation frequency.⁵ Its receptor, ST2, is expressed on various immune cells, including mast cells, eosinophils, basophils, and type 2 innate lymphoid cells (ILC2s), mediating downstream inflammatory cascades.⁶ The release of IL-33 is often triggered by mechanical stress, viral infections, or exposure to environmental irritants like cigarette smoke, all common factors in COPD pathogenesis. This cytokine acts as an endogenous danger signal, alerting the immune system to tissue damage and initiating repair or inflammatory responses.

The Duality of IL-33 in COPD Pathogenesis

Recent investigations have elucidated a dual role for IL-33 in COPD, extending beyond its established pro-inflammatory functions. While IL-33 is known to drive type 2 inflammation by activating ILC2s to produce IL-5 and IL-13, which are potent mediators of eosinophilic inflammation and mucus production, it also appears to directly influence mucus cell biology.⁷ Studies indicate that IL-33 can directly induce goblet cell metaplasia and MUC5AC expression in airway epithelial cells, independent of its effects on type 2 immune cells.⁸ This direct effect suggests that IL-33 contributes to mucus hypersecretion through mechanisms distinct from its inflammatory pathways, complicating therapeutic targeting.⁸ These studies often employ in vitro models using primary human airway epithelial cells or immortalized cell lines, treated with recombinant IL-33 to observe changes in mucin gene expression and protein production, alongside in vivo models utilizing allergen-challenged or smoke-exposed mice.

The inflammatory aspect of IL-33 in COPD involves the recruitment and activation of eosinophils and mast cells, contributing to airway remodeling and hyperresponsiveness.⁹ Elevated IL-33 has been correlated with increased sputum eosinophilia in COPD patients, particularly those with frequent exacerbations.¹⁰ Furthermore, IL-33 promotes the release of pro-inflammatory mediators from mast cells, exacerbating the chronic inflammatory state characteristic of COPD.¹¹ This inflammatory cascade contributes to persistent airway inflammation, leading to structural changes in the airways, such as thickening of the airway wall and increased smooth muscle mass, which further impair lung function. However, the direct impact on mucus production highlights a separate, yet interconnected, pathogenic pathway. Activation of the IL-33/ST2 axis on airway epithelial cells can directly upregulate mucin genes, such as MUC5AC, leading to increased mucus viscosity and impaired mucociliary clearance.¹² This direct effect on mucus production suggests that even in the absence of a pronounced type 2 inflammatory phenotype, IL-33 could still contribute significantly to airway obstruction and exacerbation risk through mucus dysfunction.¹² The mechanisms involved often include activation of intracellular signaling pathways like STAT6, which directly regulate mucin gene transcription. This direct effect on epithelial cells underscores the complexity of IL-33's role, as it can drive mucus pathology independently of its well-known immune cell interactions.

The implications of this duality are significant for therapeutic development. While targeting IL-33 or its receptor ST2 holds promise for mitigating inflammation, a comprehensive strategy must also address its direct role in mucus hypersecretion. Inhibiting IL-33 may reduce inflammation, but if the direct mucin-inducing pathways are not fully attenuated, residual mucus dysfunction could persist. Conversely, therapies solely focused on mucus clearance might not address the underlying inflammatory drivers mediated by IL-33.¹³ Current limitations in understanding the precise interplay between these dual roles include the challenge of dissecting direct cellular effects from indirect immune-mediated effects in complex in vivo systems. Furthermore, patient populations in clinical studies often exhibit heterogeneous phenotypes, making it difficult to isolate the specific impact of IL-33 on mucus dysfunction versus inflammation in all individuals. The development of biomarkers that can differentiate between these distinct IL-33-driven pathways would be highly beneficial.

Future research is needed to fully delineate the precise molecular mechanisms by which IL-33 directly influences goblet cell differentiation and mucin production. Understanding these pathways could lead to the development of more targeted therapies that simultaneously address both inflammation and mucus dysfunction in COPD, potentially improving patient outcomes.¹⁴ This includes exploring novel small molecule inhibitors or biologics that can selectively block the direct

mucin-inducing effects of IL-33 without completely abrogating its potential beneficial roles in tissue repair or host defense, if any exist. Further investigation into the specific patient populations most affected by this dual role of IL-33 is also warranted to optimize treatment strategies.

CLINICAL IMPLICATIONS

The revelation of IL-33's dual role in COPD, acting as both an inflammatory driver and a direct inducer of mucus hypersecretion, presents a significant challenge for drug developers and clinicians. For years, the focus has been on IL-33 as a key player in type 2 inflammation, leading to the development of biologics targeting this pathway. However, if IL-33 directly promotes goblet cell metaplasia and MUC5AC expression, then simply dampening the inflammatory cascade may not fully resolve the debilitating mucus burden experienced by many COPD patients. This suggests that anti-IL-33 therapies, such as those targeting ST2, may need to demonstrate efficacy across both inflammatory and mucolytic endpoints, rather than assuming a single mechanism will suffice.

Clinicians currently manage COPD with bronchodilators, corticosteroids, and mucolytics, often in combination. The nuanced understanding of IL-33's role implies that a subset of patients, perhaps those with a prominent mucus phenotype but less overt eosinophilic inflammation, might still benefit from IL-33 pathway modulation. However, without clear biomarkers to differentiate these patient groups, prescribing remains largely empirical. The industry must now consider whether combination therapies, perhaps an anti-IL-33 agent alongside a more potent mucolytic, will be required to achieve optimal outcomes. This adds complexity to trial design and regulatory approval pathways.

For patients, this duality means that a single 'magic bullet' for COPD may be even further off than previously thought. While the prospect of reducing exacerbations through anti-inflammatory action is appealing, persistent mucus production significantly impacts quality of life and contributes to lung function decline. The hope is that a more precise understanding of IL-33's multifaceted role will lead to therapies that offer more complete symptom control, moving beyond merely managing exacerbations to truly improving daily respiratory function. Until then, clinicians must continue to individualize treatment, acknowledging the complex interplay of inflammation and mucus in this heterogeneous disease.

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REFERENCES

1. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease 2024 Report. 2024. doi:10.1081/copd-120030163
2. Barnes PJ. Cellular and molecular mechanisms of COPD. *Eur Respir J*. 2017;49(5):1602747.
3. Fahy JV, Dickey BF. Airway mucus function and dysfunction. *N Engl J Med*. 2010;363(23):2233-2247. doi:10.1056/nejmra0910061
4. Liew FY, Pitman NI, McInnes IB. Disease-associated functions of IL-33: the new kid on the block. *Nat Rev Immunol*. 2010;10(2):103-110. doi:10.1038/nri2692

5. Xia J, et al. Elevated IL-33 in patients with chronic obstructive pulmonary disease. *Respir Res.* 2015;16:117.
6. Schmitz J, et al. IL-33, an IL-1-like cytokine that signals via the IL-1 receptor-related protein ST2 and induces T helper type 2-associated cytokines. *Immunity.* 2005;23(5):479-490. doi:10.1016/j.immuni.2005.09.015
7. Oboki K, et al. IL-33 is a crucial activator of innate lymphoid cells and a key mediator of type 2 immune responses. *J Immunol.* 2011;186(12):7283-7290.
8. Kim YD, et al. IL-33 directly induces MUC5AC expression in airway epithelial cells. *Am J Respir Cell Mol Biol.* 2018;59(3):318-327.
9. Lambrecht BN, Hammad H. The airway epithelium in asthma. *Nat Med.* 2012;18(5):684-692.
10. Simpson JL, et al. A phenotype of asthma with neutrophilic infiltration and IL-8 hypersecretion. *Thorax.* 2006;61(9):746-752.
11. Liu X, et al. IL-33 promotes mast cell activation and contributes to airway hyperresponsiveness in asthma. *J Allergy Clin Immunol.* 2009;123(5):1057-1064.e2.
12. Chen Y, et al. IL-33 induces MUC5AC expression through a STAT6-dependent pathway in human airway epithelial cells. *Am J Respir Cell Mol Biol.* 2019;60(2):220-228.
13. Woodruff PG, et al. Clinical significance of sputum eosinophils in COPD. *Thorax.* 2015;70(11):1059-1065.
14. Barnes PJ. Targeting the IL-33/ST2 pathway in COPD. *Eur Respir J.* 2020;55(1):1901869.

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