Why targeting IL-33 could change how we manage COPD

Written by The Life Science Feed Editorial Team · Published 7 September 2026 · Edited by Mara Voss

Chronic obstructive pulmonary disease (COPD) remains a leading cause of morbidity and mortality worldwide, characterised by persistent respiratory symptoms and airflow limitation. Despite advances in bronchodilator therapies, a significant unmet need persists for treatments that can effectively reduce exacerbation frequency and slow disease progression, particularly in patients with a pronounced inflammatory component.
The immune system's intricate dance in COPD pathogenesis has brought several cytokines into focus, with interleukin-33 (IL-33) emerging as a particularly intriguing, if complex, player. Understanding its trajectory from mechanistic insights to potential therapeutic targets is important for clinicians managing these challenging patients.

KEY TAKEAWAYS

- The Pivot: IL-33 is a key alarmin, driving type 2 inflammation and mucus hypersecretion in COPD.
- The Data: Elevated IL-33 levels correlate with increased exacerbation frequency and disease severity.
- The Action: Targeting IL-33 pathways represents a novel approach to mitigating inflammation and exacerbations in specific COPD phenotypes.

COPD is not a singular disease but a heterogeneous syndrome, often driven by chronic inflammation in the airways and lung parenchyma. This inflammation, primarily triggered by noxious particles and gases like cigarette smoke, leads to irreversible structural changes, including emphysema and small airway fibrosis. The resulting airflow obstruction is progressive, punctuated by acute exacerbations that significantly worsen patient quality of life and accelerate lung function decline. Current standard-of-care treatments, including bronchodilators and inhaled corticosteroids, manage symptoms but do not fully address the underlying inflammatory drivers in all patients.
Interleukin-33, a member of the IL-1 cytokine family, functions as an alarmin, released by stressed or damaged cells. In the context of COPD, epithelial cells, fibroblasts, and smooth muscle cells within the lung can release IL-33 in response to environmental insults. Once released, IL-33 binds to its receptor, ST2, on various immune cells, including mast cells, eosinophils, basophils, and group 2 innate lymphoid cells (ILC2s), initiating a cascade of inflammatory responses. This mechanism is distinct from other inflammatory pathways, making it an attractive target for novel therapies.

The Role of IL-33 in COPD Pathogenesis

The role of IL-33 in COPD is complex, contributing to both the chronic inflammatory state and acute exacerbations. Its primary action involves the promotion of type 2 inflammation, characterised by the release of cytokines such as IL-4, IL-5, and IL-13. These cytokines are well-known drivers of eosinophilic inflammation and mucus hypersecretion, both

prominent features in a subset of COPD patients. The presence of eosinophilia in the airways, even at low levels, has been linked to an increased risk of exacerbations and a poorer prognosis in COPD.

But IL-33's influence extends beyond eosinophils. It also stimulates mast cell activation, leading to the release of histamine and other pro-inflammatory mediators that contribute to bronchoconstriction and airway remodelling. The activation of ILC2s by IL-33 further amplifies type 2 responses, creating a self-perpetuating cycle of inflammation. This intricate relationship between IL-33 and various immune cells shows why IL-33's dual role in COPD is a subject of intense investigation.

IL-33 and Exacerbation Risk

Elevated levels of IL-33 have been observed in the sputum, bronchoalveolar lavage fluid, and serum of patients with COPD, particularly during acute exacerbations. This suggests a direct correlation between IL-33 activity and disease severity. Patients with higher baseline IL-33 levels often experience more frequent and severe exacerbations, indicating that this cytokine could serve as a biomarker for identifying patients who might benefit most from targeted therapies. The link between IL-33 and exacerbations is not merely correlative; mechanistic studies show that IL-33 directly contributes to the inflammatory milieu that precipitates these acute events.

The chronic mucus hypersecretion seen in many COPD patients, often termed chronic bronchitis, is also significantly influenced by IL-33. IL-13, a downstream cytokine of IL-33 signalling, directly promotes goblet cell metaplasia and mucin production. This excessive mucus clogs the airways, impairs mucociliary clearance, and creates a fertile ground for bacterial and viral infections, which are common triggers for exacerbations. Reducing mucus burden is an important, yet often challenging, aspect of COPD management, as discussed in the advances in bronchoscopy training for airway clearance.

Targeting the IL-33 Pathway

Given its central role, the IL-33/ST2 pathway has become a prime target for therapeutic intervention in COPD. Several strategies are under investigation, primarily focusing on blocking IL-33 itself or its receptor, ST2. Monoclonal antibodies designed to neutralise IL-33 or inhibit ST2 signalling aim to dampen the downstream type 2 inflammatory responses and reduce mucus production. The hope is that such targeted approaches could offer a more precise and effective treatment for specific COPD phenotypes, particularly those with evidence of type 2 inflammation or frequent exacerbations.

But the development of these therapies is not without its challenges. The heterogeneity of COPD means that a one-size-all approach is unlikely to succeed. Identifying the specific patient populations most likely to respond to IL-33 inhibition is paramount. Biomarkers, such as blood or sputum eosinophil counts, or even direct measurement of IL-33 levels, could help stratify patients. This precision medicine approach is increasingly important in respiratory diseases, as seen in the discussions around optimising COPD outcomes with triple therapy.

The safety profile of long-term IL-33 inhibition also requires careful consideration. IL-33 has been implicated in tissue repair and host defence against certain pathogens. Broadly blocking this pathway could potentially lead to unintended consequences, such as impaired wound healing or increased susceptibility to infections. Balancing efficacy with safety is a delicate act in drug development, especially for a chronic condition like COPD where patients often have multiple comorbidities. Clinicians often rely on comprehensive resources like the Oxford Handbook of Respiratory Medicine for detailed guidance on managing such complex cases.

Beyond Inflammation: IL-33 and Airway Remodelling

IL-33's impact extends beyond acute inflammation to the chronic structural changes that define COPD. It contributes to airway remodelling, a process involving fibrosis, smooth muscle hypertrophy, and angiogenesis, which further exacerbates airflow limitation. IL-33 can activate fibroblasts, promoting collagen deposition and extracellular matrix remodelling. This fibrotic response contributes to the irreversible nature of COPD and is a significant challenge for therapeutic intervention.

Understanding these broader effects of IL-33 is important for developing therapies that not only reduce exacerbations but also modify the underlying disease progression. The goal is to move beyond symptomatic relief to therapies that can genuinely alter the natural history of COPD. This requires a deep understanding of the molecular pathways involved, a task that continues to evolve with new research. The current focus on IL-33 shows the ongoing effort to unravel the complex mechanisms driving this debilitating disease.

The open-label design of many early-phase studies is an obvious caveat when assessing the true impact of IL-33 inhibitors. While mechanistic data are compelling, robust, placebo-controlled trials are essential to confirm clinical benefits. The challenge lies in demonstrating a meaningful reduction in clinically relevant endpoints, such as exacerbation rates or lung function decline, without introducing unacceptable side effects. The heterogeneity of COPD patient populations also means that a single biomarker or pathway may not be universally applicable, necessitating a more stratified approach to treatment. For example, the role of AAT protein in lung health highlights another distinct pathway.

The next generation of trials will need to precisely define the patient subgroups most likely to benefit from IL-33 inhibition. This will involve careful patient selection based on biomarkers and clinical characteristics, ensuring that these novel therapies are directed to where they can have the greatest impact. The ultimate goal is to integrate these targeted approaches into a comprehensive management strategy for COPD, moving beyond current symptomatic treatments to address the root causes of disease progression and exacerbations.

CLINICAL IMPLICATIONS

The persistent focus on IL-33 in COPD shows a significant gap in current management: the inability to effectively target the underlying inflammatory drivers in all patients. While bronchodilators offer symptomatic relief, they do not halt the relentless progression of airway damage or consistently prevent exacerbations, particularly in those with a pronounced type 2 inflammatory phenotype.

For clinicians, the emergence of IL-33 inhibitors offers a tantalising prospect of precision medicine in COPD. Identifying patients with elevated IL-33 or eosinophilic inflammation could allow for a more tailored therapeutic approach, potentially reducing the burden of exacerbations and improving long-term outcomes. This would represent a significant step beyond the broad-spectrum anti-inflammatory effects of inhaled corticosteroids, which are not universally effective.

But the field must proceed with caution. The pleiotropic nature of IL-33 means that its inhibition could have unforeseen consequences, and the heterogeneity of COPD demands careful patient selection. The challenge will be to integrate these novel agents into existing treatment algorithms, ensuring that their benefits outweigh any potential risks and that they reach the patients who stand to gain the most.

The industry's investment in this pathway reflects a recognition of the substantial unmet need. Success here

> would not only provide a new therapeutic option but also deepen our understanding of COPD's complex pathophysiology, paving the way for further targeted interventions.

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REFERENCES

1. 1. Vázquez-Gandullo E, Hidalgo-Molina A, Montoro-Ballesteros F, Morales-González M, Muñoz-Ramírez I, Arnedillo-Muñoz A. Inspiratory Muscle Training in Patients with Chronic Obstructive Pulmonary Disease (COPD) as Part of a Respiratory Rehabilitation Program Implementation of Mechanical Devices: A Systematic Review. Int J Environ Res Public Health. 2022;19(9). doi:10.3390/ijerph19095564
2. 2. Calverley PMA, Walker PP. Contemporary Concise Review 2022: Chronic obstructive pulmonary disease. Respirology. 2023;28(5):428-436. doi:10.1111/resp.14489
3. 3. Li Y, Tang X, Zhang R, et al. Research progress in early states of chronic obstructive pulmonary disease: a narrative review on PRISm, pre-COPD, young COPD and mild COPD. Expert Rev Respir Med. 2025;19(10):1063-1079. doi:10.1080/17476348.2025.2526775
4. 4. Qian Y, Cai C, Sun M, Lv D, Zhao Y. Analyses of Factors Associated with Acute Exacerbations of Chronic Obstructive Pulmonary Disease: A Review. Int J Chron Obstruct Pulmon Dis. 2023;18:2707-2723. doi:10.2147/COPD.S433183
5. 5. Hattab Y, Alhassan S, Balaan M, Lega M, Singh AC. Chronic Obstructive Pulmonary Disease. Crit Care Nurs Q. 2016;39(2):124-30. doi:10.1097/CNQ.0000000000000105
6. 6. Erhabor GE, Adeniyi B, Arawomo AO, et al. Acute Exacerbation of COPD: Clinical Perspectives and Literature Review. West Afr J Med. 2021;Vol. 38(11):1129-1142. doi:10.55891/wajm.v38i11.25

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