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Cytokines and COPD: The Next Frontier in Biologic Therapy

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) is a heterogeneous respiratory disorder characterized by persistent airway inflammation, progressive airflow limitation, and recurrent exacerbations. Recent advances in immunology have highlighted the role of distinct cytokine-mediated pathways in driving COPD pathogenesis, including Type 2 (T2) inflammation, Th17-associated responses, and neutrophilic immune activation. Targeted biologic therapies, such as anti–IL-5, IL-13, IL-33, IL-22, IL-36, IL-17, TRAIL, and TSLP blockers, are emerging as potential precision medicine strategies aimed at modulating specific inflammatory endotypes. Anti–IL-5 antibodies reduce eosinophil-driven inflammation, whereas IL-13 and IL-33 inhibitors disrupt upstream T2 cytokine signaling. IL-22 and IL-36 blockade targets tissue inflammation and neutrophilic responses, and IL-17A/C inhibition addresses chronic airway neutrophilia and exacerbation risk. TRAIL and TSLP blockers offer novel approaches to limit epithelial damage and upstream T2 immune activation. While clinical trials show promising results in selected patient populations, therapeutic efficacy is closely linked to biomarker-driven patient stratification, and long-term safety remains under investigation. Collectively, these targeted interventions represent a shift toward endotype-specific management in COPD, offering opportunities to improve outcomes for patients with refractory inflammation and frequent exacerbations.-

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1. INTRODUCTION

Cytokines are key players in the immune response and inflammation associated with chronic obstructive pulmonary disease (COPD), a progressive lung condition marked by airflow limitation and persistent respiratory symptoms. In COPD, chronic inflammation causes damage to lung tissue, resulting in airway remodeling, emphysema, and a decline in lung function. Cytokines, a group of small proteins secreted by immune cells, epithelial cells, and other structural cells in the lungs, play a crucial role in mediating the immune and inflammatory responses characteristic of COPD [1,2]. Pro-inflammatory cytokines, particularly interleukins (IL), tumor necrosis factor-alpha (TNF-α), and interferon-gamma (IFN-γ), are elevated in COPD and contribute to the recruitment and activation of immune cells, such as neutrophils, macrophages, and lymphocytes, within the lungs. This inflammatory cascade perpetuates tissue damage and remodeling, with the elevated cytokine levels contributing to a continuous cycle of injury and repair. TNF-α, for example, is upregulated in COPD and promotes further inflammation, leading to increased expression of other cytokines, recruitment of additional immune cells, and greater oxidative stress [3]. Consequently, main therapeutic strategies are focused on IL blockers. This will be discussed in details bellow. IL-1β and IL-6 are also prominent in COPD pathogenesis and are associated with the recruitment and survival of inflammatory cells and the induction of acute-phase responses, including the release of proteins that exacerbate systemic inflammation. In addition, IL-8, a key chemokine in COPD, attracts neutrophils to the lungs, which, upon activation, release proteases and reactive oxygen species that degrade lung tissue, worsen emphysema, and contribute to mucus hypersecretion [4,5]. The Th1 and Th17 immune response pathways are also involved in COPD, with IFN-γ and IL-17 acting as pivotal cytokines that drive inflammation and recruit immune cells in response to pathogens or environmental insults like cigarette smoke. IL-17, in particular, enhances neutrophilic inflammation and stimulates the

production of other pro-inflammatory cytokines, creating a persistent inflammatory state within the lung. Moreover, cytokines contribute to systemic inflammation in COPD, which is linked to comorbid conditions such as cardiovascular disease, muscle wasting, and metabolic syndrome [6,7]. The imbalance of pro- and anti-inflammatory cytokines disrupts normal lung homeostasis, as the reduced levels of anti-inflammatory cytokines like IL-10 are unable to counteract the excessive inflammatory response. Anti-inflammatory pathways are often compromised, with regulatory mechanisms failing to suppress the high cytokine production, perpetuating chronic inflammation. Importantly, the persistence of inflammation, along with oxidative stress, contributes to corticosteroid resistance in COPD patients, reducing the effectiveness of one of the primary anti-inflammatory treatments [8,9]. As a result, cytokines remain a critical target in the search for therapeutic strategies that aim to control inflammation and slow the progression of COPD, with various treatments under investigation, including cytokine-targeted therapies, to achieve more effective management of this debilitating disease.

Pathophysiology of COPD

Clinical Features and Disease Forms

COPD is a progressive respiratory condition characterized by persistent airflow limitation, chronic inflammation, and structural changes within the lungs. It primarily manifests in two forms: chronic bronchitis, marked by chronic mucus production and airway inflammation, and emphysema, which involves the irreversible destruction of alveolar walls, resulting in reduced surface area for gas exchange [10].

Risk Factors and Epidemiology

The pathogenesis of COPD is closely associated with long-term exposure to irritants such as cigarette smoke, environmental pollutants, and occupational dusts, which trigger an abnormal inflammatory response in the lungs. Smoking remains the most significant risk factor, with nearly 80% of COPD cases attributed to smoking, although genetic factors like alpha-1 antitrypsin deficiency also contribute to susceptibility. COPD is now recognized as a systemic disease due to its association with systemic inflammation and comorbidities such as cardiovascular disease, diabetes, osteoporosis, and muscle wasting [11].

Inflammatory Mechanisms

Biochemically, the disease is marked by an influx of inflammatory cells—primarily neutrophils, macrophages, and T-lymphocytes—into the lungs, which release a variety of cytokines, chemokines, and proteolytic enzymes. These inflammatory mediators, including interleukin-8 (IL-8), tumor necrosis factor-alpha (TNF-α), and matrix metalloproteinases (MMPs), promote tissue destruction and airway remodeling, leading to increased mucus secretion, airway narrowing, and a decline in lung function [12,13]. Oxidative stress, a key biochemical feature of COPD, arises from both external sources like smoke and internal cellular processes, further damaging lung tissue by modifying proteins, lipids, and DNA. Reactive oxygen species (ROS) generated within the lung overwhelm the body's antioxidant defenses, aggravating inflammation and reducing the efficacy of corticosteroid treatment by altering histone deacetylase (HDAC) activity, which is necessary for anti-inflammatory responses. This oxidative stress also perpetuates a vicious cycle where immune cells release more inflammatory mediators, promoting sustained inflammation and structural changes [14,15].

Systemic Inflammation and Comorbidities

Inflammation in COPD is not limited to the lungs but also spills over into the systemic circulation, contributing to the high prevalence of comorbidities seen in COPD patients. Epidemiologically, COPD is one of the leading causes of morbidity and mortality worldwide and poses a significant public health burden. It is currently the third leading cause of death globally, accounting for over three million deaths annually, with projections indicating an increase in prevalence due to aging populations and continued exposure to risk factors, particularly in low- and middle-income countries [16,17]. COPD predominantly affects older adults, and while it has traditionally been more common among men, the prevalence in women is rising due to increased smoking rates among women and greater exposure to biomass smoke in certain regions. The disease is often underdiagnosed, as symptoms such as chronic cough, sputum production, and shortness of breath develop gradually and may be mistaken for normal aging or other respiratory conditions. Diagnosis typically involves spirometry to measure lung function, specifically the forced expiratory volume in one second (FEV1) to forced vital capacity (FVC) ratio, with a ratio below 0.7 indicating airflow limitation [18,19]. Management of COPD includes smoking cessation, pharmacological interventions like bronchodilators and inhaled corticosteroids, pulmonary rehabilitation, and, in severe cases, oxygen therapy or surgical options such as lung volume reduction. Despite these treatments, COPD remains a progressive disease with no cure, making early detection, lifestyle modification, and interventions to limit exposure to risk factors crucial for managing disease progression. The economic impact of COPD is substantial, including healthcare costs associated with frequent hospitalizations, exacerbations, and loss of productivity, which underline the importance of preventive strategies and research into targeted therapies that address both the pulmonary and systemic components of the disease [20,21].

Cytokines in COPD

T2 Inflammation and Biologic Therapy

T2 inflammation is a pathway characterized by the activation of certain immune cells, including type 2 helper T cells (Th2 cells), innate lymphoid cells type 2 (ILC2), and eosinophils, which produce cytokines like interleukin-4 (IL-4), interleukin-5 (IL-5), and interleukin-13 (IL-13). While T2 inflammation is more commonly associated with asthma, recent findings suggest that a subset of COPD patients, particularly those with a higher eosinophilic component, may also experience exacerbations driven by T2 cytokines [22,23]. These insights have opened up the potential for biologic therapies, particularly monoclonal antibodies that target IL-4, IL-5, IL-13, or their receptors, as well as IgE, to modify the immune responses implicated in T2 inflammation. The underlying mechanism of T2-targeting biologics centers on their ability to neutralize or block the signaling pathways of T2 cytokines, thereby reducing inflammation, mucus production, and airway hyperresponsiveness. For instance, IL-5 plays a central role in the survival, activation, and recruitment of eosinophils, which are inflammatory cells implicated in airway damage, mucus overproduction, and exacerbations [24,25]. Biologics targeting IL-5, such as mepolizumab and benralizumab, act by either neutralizing IL-5 or depleting eosinophils directly, which has been shown to reduce exacerbation rates in patients with elevated eosinophil counts. Similarly, therapies targeting IL-4 and IL-13, such as dupilumab, interfere with the signaling that leads to T2 inflammation, thereby impacting mucus hypersecretion and remodeling of the airways, which are key features in COPD. Clinical trials have indicated that biologics targeting these T2 pathways may offer particular benefits for patients with eosinophilic COPD, especially those who experience frequent exacerbations and show elevated blood eosinophil counts [26,27]. However, the use of these therapies in COPD has clinical considerations and limitations. Unlike asthma, COPD is primarily a neutrophilic-driven disease, and the majority of COPD patients do not exhibit a T2 inflammatory profile, which restricts the use of T2-targeted biologics to a subset of patients with confirmed T2 biomarkers. Identifying appropriate candidates for these treatments involves measuring blood eosinophil levels as a biomarker to predict the likelihood of a beneficial response, as patients with higher eosinophil counts tend to experience a greater reduction in exacerbation rates when treated with T2-targeting biologics [28,29]. Safety and efficacy are also critical considerations, as COPD patients often have multiple comorbidities, and long-term effects of biologics in this population require further investigation. For example, while reducing eosinophils can decrease exacerbations, overly suppressing eosinophils may impair immune defense against infections, which is a significant concern in COPD. Additionally, biologics are generally administered via injection and are expensive, making cost and patient compliance important factors in their clinical application. Current guidelines suggest reserving T2-targeted biologics for COPD patients with frequent exacerbations despite optimized inhaler therapy and confirmed eosinophilic inflammation [30,31]. Overall, while biologics targeting T2 cytokines hold promise for a specific subset of COPD patients, more research is needed to refine patient selection criteria, understand the long-term effects, and develop comprehensive treatment strategies that account for the diverse inflammatory pathways involved in COPD. The development of biomarkers beyond eosinophil counts may eventually improve the precision of biologic therapies, allowing for more personalized treatment approaches that could improve outcomes and quality of life in COPD patients with T2-driven disease components [32].

Anti–IL-5 Antibodies

Anti-IL-5 directed antibodies in COPD are emerging as potential therapeutic options for a subset of COPD patients with elevated eosinophilic inflammation. Interleukin-5 (IL-5) is a cytokine that plays a central role in the growth, activation, recruitment, and survival of eosinophils, which are inflammatory cells implicated in various respiratory diseases. In the context of COPD, eosinophilic inflammation is associated with a specific endotype of the disease, where elevated levels of eosinophils contribute to increased mucus production, airway hyperreactivity, and a higher frequency of exacerbations [33,34]. By neutralizing IL-5 or inhibiting its signaling pathways, anti-IL-5 antibodies aim to reduce eosinophil activity and presence, thereby mitigating some of the inflammatory responses associated with COPD exacerbations. The two primary anti-IL-5 monoclonal antibodies currently under investigation for COPD are mepolizumab and benralizumab. Mepolizumab is a humanized monoclonal antibody that binds directly to IL-5, preventing it from interacting with its receptor on eosinophils, which ultimately limits eosinophil activation and reduces eosinophil counts in both blood and lung tissue [35,36]. In clinical trials, mepolizumab has demonstrated an ability to decrease the rate of exacerbations in COPD patients with high eosinophil counts, indicating that it may be particularly effective for patients with an eosinophilic phenotype of COPD who do not respond adequately to standard treatments. Benralizumab, on the other hand, is a monoclonal antibody that targets the IL-5 receptor alpha on eosinophils and other IL-5 receptor-bearing cells, promoting eosinophil apoptosis through antibody-dependent cell-mediated cytotoxicity (ADCC) [37,38]. This action rapidly depletes eosinophils, which has been shown to significantly reduce exacerbations and improve health outcomes in COPD patients with elevated eosinophilic inflammation. Clinical trials of anti-IL-5 therapies in COPD reveal mixed but promising results. Studies have demonstrated that anti-IL-5 therapies can reduce exacerbation rates in COPD patients with high baseline eosinophil levels, though the efficacy appears to be less pronounced in patients with low or normal eosinophil counts. This has led to a focus on identifying COPD patients with a “T2-high” inflammatory profile—characterized by elevated eosinophil levels—as these patients tend to derive the most benefit from IL-5 targeted therapies [39]. The choice of anti-IL-5 treatment and its effectiveness in COPD is highly dependent on patient selection, and biomarkers such as blood eosinophil counts are increasingly used to identify candidates who are likely to respond. Higher eosinophil counts are

correlated with a more significant reduction in exacerbation frequency when using anti-IL-5 therapy, supporting the idea of a precision medicine approach in COPD management. Nevertheless, there are several clinical considerations and potential limitations associated with anti-IL-5 therapy in COPD. COPD is primarily characterized by neutrophilic, rather than eosinophilic, inflammation, and only a subset of patients displays elevated eosinophil levels, restricting the application of anti-IL-5 therapies to this particular endotype [40]. Additionally, because COPD patients often have comorbid conditions, there is a concern about potential adverse effects associated with long-term use of biologics, particularly regarding the risk of infection due to immunomodulation. While anti-IL-5 antibodies have shown a generally favorable safety profile, long-term studies are necessary to better understand any risks associated with prolonged eosinophil depletion, as eosinophils play a role in immune defense, particularly in protecting against parasitic infections and in maintaining tissue homeostasis. Cost and patient compliance also play important roles in the clinical decision-making process, as biologics like mepolizumab and benralizumab are typically administered via subcutaneous injection and represent a significant expense [41]. Current guidelines suggest that anti-IL-5 therapies should be considered in COPD patients with frequent exacerbations, elevated eosinophil counts, and an insufficient response to optimized inhaled therapies, including inhaled corticosteroids and long-acting bronchodilators. Future directions in research may help refine patient selection criteria further, and there is ongoing investigation into additional biomarkers that could enhance the precision of anti-IL-5 therapy use [42,43]. Additionally, combination approaches that target both eosinophilic and neutrophilic inflammation may eventually improve the efficacy of biologics in COPD, providing a more comprehensive approach to managing the complex inflammatory landscape of the disease. Overall, anti-IL-5 directed antibodies represent a promising therapeutic option for a specific subset of COPD patients, offering the potential for a more tailored approach to treatment that addresses the eosinophilic component of the disease [44,45].

IL-13 and IL-33 blockers

Interleukin-13 (IL-13) and Interleukin-33 (IL-33) blockers are targeted biologic therapies designed to interfere with key cytokines involved in Type 2 (T2) inflammatory pathways, which are central to various respiratory and allergic conditions. IL-13 is a cytokine produced primarily by T helper 2 (Th2) cells, type 2 innate lymphoid cells (ILC2), and mast cells, and it plays a significant role in airway inflammation, mucus production, airway hyperresponsiveness, and tissue remodeling, all of which are common in conditions such as asthma and a subset of COPD with T2-driven inflammation [46,47]. By binding to the IL-13 receptor, IL-13 activates signaling pathways that lead to the recruitment and activation of other inflammatory cells, contributing to ongoing inflammation and the development of fibrotic changes in airway tissue. Inhibitors targeting IL-13, such as dupilumab, which also blocks IL-4 signaling by inhibiting the shared IL-4 receptor alpha subunit, aim to disrupt this pathway, thereby reducing inflammation and improving symptoms in patients with conditions like asthma and, potentially, T2-high COPD [48,49]. By blocking IL-13 signaling, these therapies can reduce mucus secretion, improve airflow limitation, and lessen exacerbation frequency in select patients who have biomarkers indicating elevated IL-13 activity. Clinical trials for IL-13 blockers have shown improvements in lung function, symptom scores, and quality of life, particularly in patients with elevated levels of biomarkers like blood eosinophils and fractional exhaled nitric oxide (FeNO), which suggest a higher likelihood of a T2-driven disease phenotype [50,51].

IL-33 is an upstream cytokine that functions as an “alarmin,” released in response to cellular damage or stress, and plays a pivotal role in activating type 2 inflammatory responses. Unlike IL-13, which operates downstream in the inflammatory cascade, IL-33 acts at an earlier stage by binding to its receptor, ST2, on various immune cells, including ILC2s, mast cells, eosinophils, and Th2 cells [52,53]. This binding triggers the release of other T2 cytokines, such as IL-4, IL-5, and IL-13, creating a cascade that intensifies and sustains inflammation, eosinophil recruitment, and other immune responses characteristic of allergic and respiratory diseases. The IL-33 pathway is particularly implicated in the initiation of inflammatory responses in the lungs, where it is involved in promoting mucus production, airway remodeling, and heightened sensitivity to allergens. IL-33 blockers, which are antibodies that prevent IL-33 from interacting with ST2, aim to halt the T2 inflammatory cascade at its origin, potentially providing a broader anti-inflammatory effect than therapies targeting downstream cytokines alone [54,55]. By blocking IL-33, these therapies may prevent the activation of multiple T2 inflammatory pathways, offering the potential to reduce both the initiation and amplification of inflammation in allergic and respiratory conditions. Early clinical studies on IL-33 blockers, such as those evaluating the drug itepekimab, have shown promising results in reducing exacerbations and improving lung function in patients with asthma and COPD who display T2 inflammation markers, although more research is needed to confirm these benefits across a broader population [56,57].

While IL-13 and IL-33 blockers target different points in the inflammatory pathway, both types of biologics are designed for patients with evidence of T2-driven inflammation, and their use is guided by biomarkers like eosinophil counts and FeNO levels, which help identify patients most likely to benefit from T2-targeted therapies. Safety and efficacy profiles for IL-13 and IL-33 blockers suggest they are generally well-tolerated, with the most common adverse effects being injection site reactions and, occasionally, increased susceptibility to infections due to immune modulation [58,59]. Additionally, their cost and the need for injection-based administration pose challenges for patient compliance, and long-term studies are still required to assess the impacts of sustained cytokine inhibition on immune defense, particularly in patients with respiratory conditions that may be prone to recurrent infections. These blockers represent a precision medicine

approach, aiming to provide better control over T2 inflammation and to offer relief in patients who do not respond adequately to standard inhaled corticosteroids or bronchodilators. Both IL-13 and IL-33 blockers have the potential to not only manage symptoms but also reduce the frequency of exacerbations and slow disease progression in conditions where T2 inflammation is a major contributor, although further research and clinical trials will continue to clarify their role, efficacy, and optimal use cases across different respiratory and allergic disease populations [60,61].

IL-22, IL-36

Interleukin-22 (IL-22) is a cytokine produced by immune cells like Th17 cells, ILC3, and other immune cells within the lung in response to infection, smoking, and environmental pollutants—key factors in COPD pathogenesis. While IL-22 has a dual role in lung disease, where it can be both protective and pro-inflammatory, its involvement in COPD is associated with the promotion of tissue inflammation, airway remodeling, and fibrosis in the chronic phases of the disease. IL-22 acts through the IL-22 receptor, predominantly expressed on epithelial cells, where it triggers signaling pathways that lead to the production of antimicrobial peptides, mucus, and inflammatory mediators that can amplify local inflammation [62,63]. In COPD, excessive or prolonged IL-22 signaling has been implicated in maintaining chronic inflammatory states, particularly through the activation of pathways that worsen epithelial damage, promote goblet cell hyperplasia, and increase mucus production. Blockers targeting IL-22 aim to reduce this excessive inflammatory signaling by inhibiting its binding to the IL-22 receptor, thereby potentially limiting inflammatory damage and mucus overproduction in COPD patients with IL-22-driven pathology [64].

IL-36, part of the IL-1 cytokine family, has also gained attention in COPD research due to its role in modulating innate immune responses and promoting pro-inflammatory signaling within the lungs. IL-36 cytokines, which include IL-36α, IL-36β, and IL-36γ, bind to the IL-36 receptor, activating downstream pathways such as nuclear factor-kappa B (NF-κB) and mitogen-activated protein kinase (MAPK) signaling, which lead to the release of a range of inflammatory mediators, including chemokines and cytokines that recruit neutrophils and other immune cells [65,66]. Neutrophilic inflammation is a hallmark of COPD, and elevated IL-36 expression has been observed in lung tissue of COPD patients, particularly in response to smoking and infection. By promoting a strong neutrophilic response, IL-36 contributes to persistent inflammation, mucus hypersecretion, and tissue degradation in the lungs. Targeting IL-36 with specific blockers or antibodies could potentially reduce neutrophilic inflammation and the accompanying airway damage, offering a novel approach for managing COPD patients, particularly those with a high degree of neutrophilic infiltration [67,68]. Blocking IL-36 could also limit the feedback loop of inflammation seen in COPD, as IL-36 has been shown to induce the production of other pro-inflammatory cytokines like IL-6 and IL-8, which are elevated in COPD and contribute to chronic lung inflammation and tissue destruction [69,70].

IL-22 and IL-36 blockers are therapeutic strategies currently being explored for COPD due to their role in modulating the inflammatory pathways associated with lung tissue damage and disease progression. Both IL-22 and IL-36 blockers thus represent targeted approaches within COPD management that aim to reduce inflammation and tissue damage, although each focus on different immune pathways that contribute to COPD's complex pathology [71]. While IL-22 blockers are thought to be beneficial in limiting epithelial-driven inflammation and mucus production, IL-36 blockers may be more relevant for controlling neutrophilic inflammation and addressing the heightened innate immune response that characterizes more severe forms of COPD. The use of these blockers in COPD, however, is still in early experimental stages, with ongoing research needed to determine optimal patient selection, given COPD's heterogeneity and the varying contributions of Th17 and neutrophilic inflammation among patients. Potential clinical considerations for these blockers include ensuring they do not excessively inhibit immune responses, as IL-22 has protective roles in mucosal immunity and tissue repair, and inhibiting it could theoretically impair defenses against lung infections [72]. Similarly, while blocking IL-36 may reduce neutrophil-driven damage, it must be balanced to avoid compromising necessary inflammatory responses that protect against pathogens. Current studies are working to clarify the therapeutic balance and long-term safety of IL-22 and IL-36 blockade in COPD, as well as to identify specific biomarkers that could predict which patients may benefit most from these treatments. As knowledge of COPD's molecular underpinnings grows, IL-22 and IL-36 blockers may offer tailored therapeutic options for patients with specific inflammatory profiles, especially those with high levels of Th17 or neutrophilic activity, potentially improving outcomes where standard treatments, such as corticosteroids, have limited efficacy [73,74].

IL-17A and C in COPD and AECOPD

IL-17A is a cytokine primarily produced by Th17 cells, γδ T cells, and innate lymphoid cells, while IL-17C is produced mainly by epithelial cells in response to microbial products and tissue stress. Both cytokines are essential mediators of immune responses in the lungs and are particularly relevant in COPD due to their contribution to chronic inflammation, airway remodeling, and exacerbation episodes. In COPD, IL-17A acts as a potent promoter of neutrophilic inflammation, stimulating epithelial cells, fibroblasts, and airway smooth muscle cells to produce cytokines and chemokines, such as IL-8 and granulocyte colony-stimulating factor (G-CSF), which recruit and activate neutrophils [75,76]. Neutrophils release proteases, reactive oxygen species, and other inflammatory mediators that contribute to lung tissue damage, mucus hypersecretion, and decreased lung function. IL-17A signaling also enhances the survival and activation of neutrophils,

which contributes to persistent inflammation, airway obstruction, and increased risk of exacerbations. IL-17A's role in promoting both chronic and acute inflammatory responses is particularly important in COPD because neutrophilic inflammation is less responsive to corticosteroids, making IL-17A a target of interest for novel therapeutic approaches that could address the neutrophil-driven aspects of COPD. IL-17A is implicated in the upregulation of mucus production, driven by increased expression of mucin genes, which worsens airflow limitation and contributes to the persistent cough and sputum production common in COPD [77,78].

IL-17C, in contrast, is produced by the airway epithelial cells themselves in response to cigarette smoke, pathogens, and other environmental stimuli relevant to COPD pathogenesis. Upon release, IL-17C acts in an autocrine and paracrine manner on epithelial cells, amplifying the production of pro-inflammatory mediators, including IL-6 and IL-8, which further drive neutrophilic infiltration and inflammatory responses within the lung tissue [79,80]. This local production and signaling loop of IL-17C within the epithelium make it a critical player in the initiation and maintenance of airway inflammation in COPD. IL-17C enhances the inflammatory response to respiratory pathogens, a characteristic relevant to AECOPD, where infections are a common trigger for exacerbations. During AECOPD, elevated IL-17C levels in the airways contribute to a heightened immune response, increasing inflammation and exacerbating symptoms such as shortness of breath, sputum production, and cough [81]. IL-17C's actions are particularly problematic in exacerbations because they intensify airway inflammation in response to infections, creating a cycle of inflammation and airway injury that can worsen lung function and accelerate disease progression over time [82,83].

In the context of AECOPD, both IL-17A and IL-17C levels are typically elevated, leading to increased neutrophil recruitment and activation within the airways. This increase in neutrophil activity during exacerbations results in greater release of elastases and other enzymes that degrade the extracellular matrix, leading to further tissue damage, loss of lung elasticity, and worsening airflow limitation. Additionally, the IL-17 pathway contributes to bacterial colonization in the airways, which can create a reservoir for recurrent infections and promote the chronicity of inflammation in COPD [84,85]. This cycle of inflammation and infection perpetuates the progression of COPD, with each exacerbation episode contributing to cumulative declines in lung function. The persistent inflammatory environment driven by IL-17A and IL-17C not only promotes mucus hypersecretion but also enhances tissue remodeling processes that can lead to airway thickening and fibrosis, hallmarks of progressive COPD [86].

Given their roles in COPD and AECOPD, IL-17A and IL-17C are considered therapeutic targets for new treatments aiming to address inflammation that is not responsive to traditional anti-inflammatory therapies like corticosteroids. IL-17 inhibitors, which have shown efficacy in other inflammatory diseases such as psoriasis, are under investigation in COPD as a potential strategy to reduce neutrophilic inflammation and improve disease outcomes, especially in patients who experience frequent exacerbations [87]. However, therapeutic targeting of IL-17 in COPD must be carefully balanced, as IL-17A is also involved in the body's defense against certain pathogens, particularly fungi and extracellular bacteria, which are prevalent in COPD patients due to their compromised lung function. Clinical trials are ongoing to evaluate the safety and efficacy of IL-17 blockade in COPD and AECOPD, aiming to determine the extent to which reducing IL-17-driven inflammation can lead to improvements in lung function, exacerbation rates, and overall quality of life for COPD patients. As understanding of IL-17A and IL-17C in COPD and AECOPD advances, these cytokines represent promising yet complex targets in the quest for more effective and specific treatments that go beyond the limitations of current anti-inflammatory therapies [88].

TRAIL, TSLP blockers

Considering other therapeutic strategies except from IL blockers it's important to pay attention to TRAIL and TSLP. TRAIL and TSLP blockers are emerging therapeutic approaches targeting key cytokines involved in inflammatory and immune responses, particularly in respiratory diseases where they contribute to tissue damage and immune dysregulation. TRAIL, or TNF-related apoptosis-inducing ligand, is a cytokine belonging to the tumor necrosis factor (TNF) superfamily [89]. It is known to bind to death receptors DR4 and DR5, which are expressed on various cell types, including epithelial and immune cells. TRAIL's primary function is to induce apoptosis in target cells, typically as a mechanism to control immune responses and remove damaged or malignant cells. However, in the context of chronic inflammatory diseases like chronic obstructive pulmonary disease (COPD) and certain types of asthma, TRAIL is implicated in promoting apoptosis of lung epithelial cells, contributing to airway damage and structural remodeling. Excessive or dysregulated TRAIL signaling can result in inappropriate cell death within the lung tissue, exacerbating airway destruction and perpetuating chronic inflammation [90,91]. TRAIL blockers, designed as antibodies or small molecule inhibitors, aim to inhibit this apoptotic pathway to preserve epithelial integrity, reduce tissue damage, and potentially slow disease progression in patients with TRAIL-associated respiratory diseases. These blockers are currently under investigation for their potential to halt lung function decline, particularly in conditions where apoptosis-driven tissue loss is prominent. By preventing TRAIL from engaging with its receptors, these inhibitors may help mitigate the loss of airway structural cells, limiting emphysema-like changes and reducing inflammation associated with cellular debris and immune activation [92,93]. Clinical studies are ongoing to assess their effectiveness in patients who experience significant epithelial apoptosis due to TRAIL activity, with a focus on safety and the potential risks of interfering with apoptosis pathways, as TRAIL also plays a role in tumor

surveillance and immune regulation [94].

TSLP, or thymic stromal lymphopoietin, is an epithelial-derived cytokine primarily released in response to environmental triggers such as allergens, pollutants, and infectious agents. TSLP plays a central role in initiating and propagating type 2 (T2) inflammatory responses by activating dendritic cells, which, in turn, promote the differentiation of T helper 2 (Th2) cells and the release of T2 cytokines such as IL-4, IL-5, and IL-13. TSLP is thus a key upstream driver of allergic and eosinophilic inflammation, making it highly relevant in diseases such as asthma and, to a lesser extent, COPD in patients with T2 inflammation markers [95]. TSLP binds to its receptor complex, composed of the TSLP receptor (TSLPR) and the interleukin-7 receptor alpha chain (IL-7Rα), on immune cells like dendritic cells, basophils, and T cells, leading to the release of cytokines that promote airway inflammation, mucus production, and hyperresponsiveness. Blocking TSLP aims to interrupt this inflammatory cascade at its inception, preventing the downstream release of pro-inflammatory cytokines and the recruitment of eosinophils and other immune cells to the airway tissue [96,97]. TSLP blockers, such as tezepelumab, are monoclonal antibodies that neutralize TSLP, preventing it from binding to its receptor and thereby reducing the type 2 inflammatory response. Clinical trials of TSLP blockers have demonstrated significant reductions in exacerbation rates, improved lung function, and better symptom control in patients with severe asthma, particularly those with elevated biomarkers of T2 inflammation such as blood eosinophils and fractional exhaled nitric oxide (FeNO). These benefits position TSLP blockers as promising options for patients who do not respond adequately to conventional therapies, including inhaled corticosteroids and bronchodilators, which may be less effective in cases with high T2 inflammation [98,99].

Given their distinct mechanisms, both TRAIL and TSLP blockers come with clinical considerations that require careful evaluation. For TRAIL blockers, one concern is the inhibition of apoptosis in contexts beyond the lungs, as TRAIL is involved in immune regulation and tumor suppression; therefore, blocking TRAIL may carry risks related to cancer development or impaired immune defense [100,101]. Similarly, TSLP blockade needs to be precisely targeted to avoid broadly suppressing immune function, as TSLP also plays roles in immune tolerance and mucosal immunity. Furthermore, both types of blockers are expensive biologics requiring injection, which can impact patient compliance and healthcare costs. The use of TRAIL and TSLP blockers is currently tailored to patients with clear biomarker profiles and disease phenotypes that indicate high activity of these cytokines, ensuring that only those likely to benefit receive treatment [102,103]. Future studies and long-term data are essential to determine their optimal use in respiratory disease, establish safety profiles, and explore potential applications in other diseases characterized by apoptosis dysregulation and T2 inflammation. As more is understood about the roles of TRAIL and TSLP in lung disease, these blockers hold promise for adding a targeted and personalized approach to managing chronic and severe inflammatory respiratory conditions.

2. CONCLUSION

COPD is a complex and heterogeneous disease, driven by multiple overlapping inflammatory pathways. Traditional therapies, including bronchodilators and corticosteroids, often fail to fully address underlying immune dysregulation, particularly in patients with eosinophilic or neutrophilic endotypes. Emerging biologic therapies targeting IL-5, IL-13, IL-33, IL-22, IL-36, IL-17, TRAIL, and TSLP offer the potential to modulate key pathogenic mechanisms with greater precision. Evidence to date suggests that the success of these interventions depends on careful patient selection guided by biomarkers such as blood eosinophils, FeNO, and inflammatory cytokine profiles. While many of these therapies remain in early clinical development for COPD, they underscore the promise of a precision medicine approach, aiming to reduce exacerbations, limit tissue damage, and improve quality of life. Future research should focus on refining endotype-based stratification, evaluating long-term safety, and exploring combination strategies to comprehensively address both eosinophilic and neutrophilic inflammation. Ultimately, these targeted therapies have the potential to transform COPD management by providing personalized, mechanism-based treatment options beyond conventional care..

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