Inflammopharmacology (2025) 33:5909–5932
https://doi.org/10.1007/s10787-025-01975-9

Inflammopharmacology

REVIEW

Interleukin-10 family cytokines: key regulators and novel therapeutic targets for respiratory diseases

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Received: 30 July 2025 / Accepted: 11 September 2025 / Published online: 28 September 2025

Abstract

Respiratory disorders such as asthma, chronic obstructive pulmonary disease (COPD), acute respiratory distress syndrome (ARDS), pulmonary fibrosis, and infectious conditions including COVID-19 and tuberculosis continue to rank among the foremost causes of illness and death worldwide. Although vaccines, antimicrobial treatments, and anti-inflammatory agents have improved disease management, their overall impact remains limited because of the intricate regulation of immune responses at epithelial surfaces. Within this context, the interleukin-10 (IL-10) cytokine family (comprising IL-10, IL-19, IL-20, IL-22, IL-24, and IL-26) has been identified as a key immunological axis in the respiratory tract. These cytokines possess structural homology and predominantly transmit signals through heterodimeric class II receptors via the JAK–STAT cascade. However, their functions are far from uniform: IL-10 primarily exerts suppressive effects on inflammation, whereas IL-19, IL-20, IL-24, and IL-26 are commonly associated with tissue injury, chronic inflammation, and airway remodeling. IL-22 occupies an intermediate role, promoting epithelial regeneration under certain conditions but aggravating inflammation or tumorigenesis in others. This article reviews recent findings on the IL-10 family in a range of respiratory diseases, emphasizing their context-dependent activity, value as potential biomarkers, and relevance as therapeutic targets. A clearer

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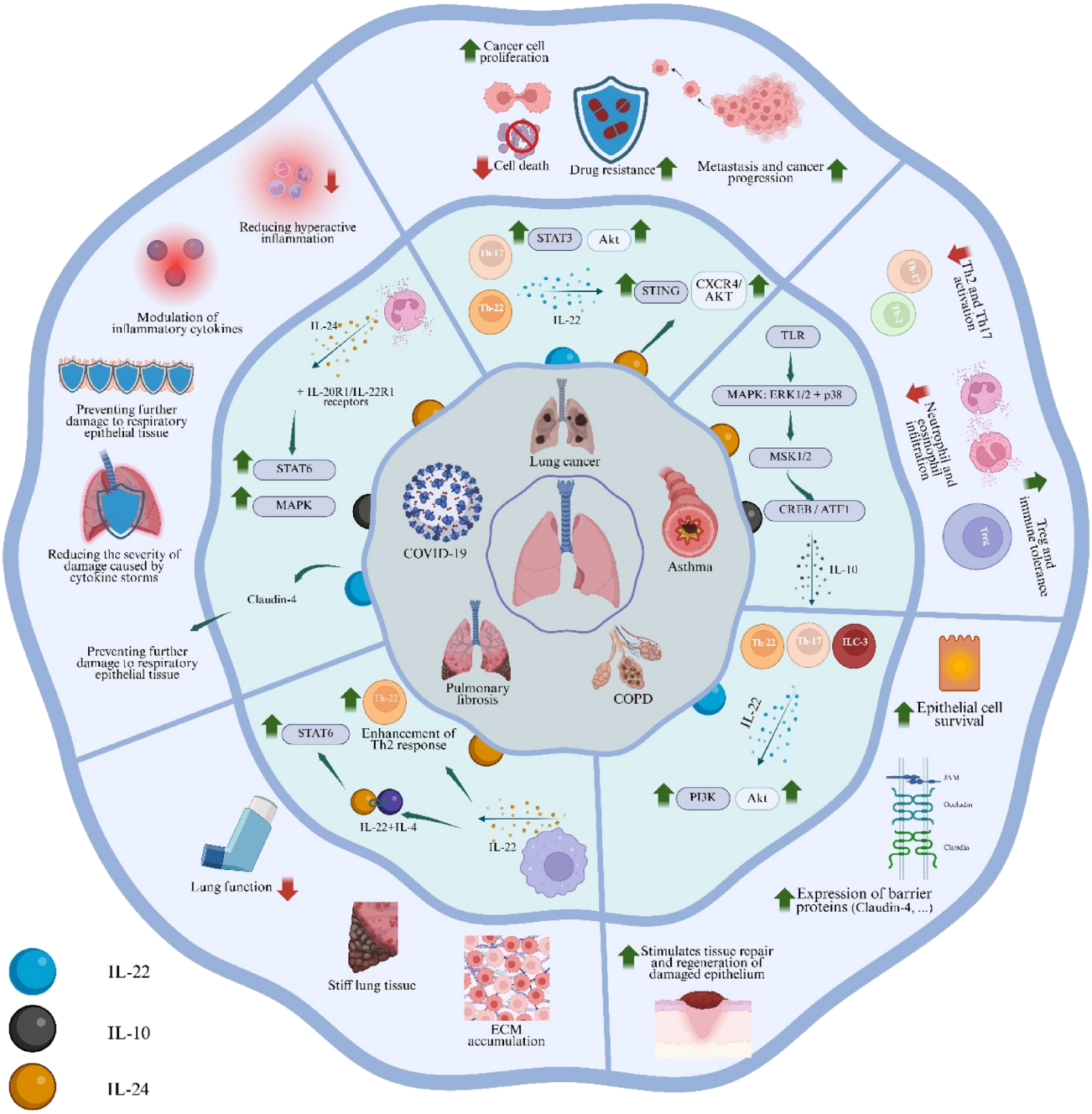
understanding of how protective versus pathogenic signals are balanced within this cytokine network is essential for designing targeted interventions that preserve host defense while restoring airway integrity.

Graphical abstract



Keywords IL-10 family · IL-19 · IL-20 · IL-22 · IL-24 · IL-26 · Respiratory diseases · Asthma · COPD · ARDS/COVID-19 · Pulmonary infections · Pulmonary fibrosis · Cystic fibrosis · Epithelial barrier · JAK–STAT · Therapeutic targets

Introduction

Respiratory illnesses continue to be the most common cause of mortality in developing countries. Globally, chronic respiratory conditions rank as the third highest contributor to death, accounting for approximately 4 million fatalities yearly (Agusti et al. 2022; Chen et al. 2023). Given that infectious variants can frequently be controlled with vaccines or drugs, the World Health Organization (WHO) has responded by formulating strategies aimed at reducing non-communicable respiratory diseases such as asthma and COPD (Das 2022; Yu et al. 2024). Primary risk factors for these diseases are occupational exposures, environmental toxins, and tobacco smoke (active and passive) (Tiotiu et al. 2021; Balan et al. 2023). Since most respiratory ailments are preventable, cost-effective public health measures such as educational campaigns, surveillance, and awareness programs must be employed to reduce their global burden. Identification of high-risk populations and monitoring risk factor trends can help policymakers to take prudent steps to avert preventable disability and untimely deaths (Agusti et al. 2022; Momtazmanesh et al. 2023).

Pro-inflammatory cytokines are thought to be the central players in the pathogenesis of various lung diseases, including ARDS, asthma, cystic fibrosis-associated bronchiectasis, and COPD. These diseases share similar mechanisms characterized by excessive cytokine production of pro-inflammatory cytokines and chronic airway inflammation, which can lead to airway hypersensitivity, structural remodeling, and lung injury (Atamas et al. 2013; Aghasafari et al. 2019; Branchett and Lloyd 2019). Environmental stimuli such as pathogens, toxins, pollutants, irritants, and allergens typically induce airway inflammation. The innate immune receptors recognize the conserved pathogen-associated molecular patterns, activating immune cells, including macrophages, dendritic cells, natural killer (NK) cells, and T cells. In turn, the cells release inflammatory mediators such as chemokines, growth factors, and pro-inflammatory cytokines. Key cytokines, i.e., tumor necrosis factor (TNF) and interleukins (IL), produced in response to infection or tissue damage, are known to play a central role in the pathogenesis of respiratory diseases. Their release initiates a cascade of signaling processes that cause inflammation and impair respiratory tissues, thus resulting in the progression of disorders (Moldoveanu et al. 2008; Robb et al. 2016; Aghasafari et al. 2019; Branchett and Lloyd 2019). Notably, while some cytokines (e.g., IL-1, chemokines, and interferon [IFN]) promote inflammation and worsen disease, others (e.g., IL-4, IL-10, and IL-13) suppress inflammation and enhance tissue repair. This twofold role has put cytokine kinetics in the limelight of biological research and therapeutic innovation (Wang and He 2018).

This review evaluates the biological activities, defensive, and pathogenic mechanisms of the IL-10 family cytokines and their role in respiratory disease, with a focus on their dual functions in respiratory disease and health.

The IL-10 family cytokines: structure, signaling, and function

Structure of IL-10 family

IL-10, which is the founding member of its family cytokines, was first identified as a factor produced by activated CD4+T helper (Th) 2 cells and named cytokine synthesis inhibitory factor (CSIF) (Ouyang et al. 2011). The IL-10 family includes the IL-20 subfamily (IL-19, IL-20, IL-22, IL-24, and IL-26) and interferon (IFN)-λ group (IL-28A, IL-28B, and IL-29). These cytokines are primarily produced by immune cells such as T cells, B cells, natural killer (NK) cells, monocytes, macrophages, and dendritic cells (DCs). Signaling by IL-10 family members is by binding to specific heterodimeric receptors, including IL-20Rα, IL-20Rβ, IL-10Rα, IL-10Rβ, and IL-22Rα, which mediate their biological effects. In the IL-10 receptor family, α chains are the primary ligand high-affinity binding subunits and the β chains have minimal or no direct interaction with ligands. Thus, the α chains not only determine the specificity of which ligands are bound, but also regulate the selectivity of target cells, since they are only expressed in some cell types (Yoon et al. 2010, Wei, Li et al. 2019). Their classification as IL-10 family members is based on structural similarities, shared receptor use, and identical downstream signaling cascades. They share a similar six α-helix (A–F) structure with interdomain loops, forming a left-handed four-helix bundle, a helical cytokine signature feature (Zdanov 2010; Wang et al. 2019; Wei et al. 2022). Class II receptors (IL-10 family cytokine receptors) lack the extracellular Trp-Ser-X-Trp-Ser motif and have varied cysteine residue organizations, defining their unique functional and structural properties (Ouyang et al. 2011; Wei et al. 2019).

Signaling and functions of IL-10 family

Upon secretion by immune cells, IL-10 exerts its effects on target cells by binding to the IL-10Rα and IL-10Rβ receptors, inducing intracellular activation of Janus kinase 1 (JAK1) and tyrosine kinase 2 (TyK2). The latter phosphorylate transcription factors signal transducer and activator of transcription (STAT)1, STAT3, and STAT5, thus stimulating anti-inflammatory and immune-regulatory responses mediated by IL-10 (Ouyang et al. 2011; Druszczyńska et al. 2022; Wei et al. 2022). IL-10 exerts its principal immunosuppressive effect on myeloid cells by suppressing the

expression of pro-inflammatory cytokines and the activity of antigen-presenting cells (APCs) (Yaseen et al. 2020). IL-10 also directly inhibits the memory of Th17 and Th2 cells but induces Foxp3 + regulatory T cell (Treg) survival and activity (Chaudhry et al. 2011; Kamanaka et al. 2011; Coomes et al. 2017). Dysregulation of IL-10 signaling is correlated with inflammatory disease and immunopathology following infection, whereas overproduction or dysregulation of IL-10 may result in chronic infection (Wilson and Brooks 2010; Redford et al. 2011; Oldstone 2015; Zhu et al. 2017). Recent research has characterized several mechanisms by which IL-10 modulates CD8 + T cell function in chronic viral infection. Smith et al. demonstrated that IL-10 activates Mgat5, a glycosyltransferase that increases N-glycan branching on surface glycoproteins. Post-translational modification elevates the antigenic threshold for T cell activation. The newly elucidated IL-10–Mgat5–N-glycan axis was found to suppress not just CD8 + T cells but CD4 + Th17 and Th1 cell functions as well (Smith et al. 2018).

IL-10 production in myeloid cells such as DCs and macrophages is induced primarily through pattern-recognition receptors (PRRs) signaling pathways such as Toll-like receptor (TLR) agonists and pro-inflammatory cytokines. Co-stimulatory receptors such as CD40, Dectin-1, and dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN) can work in conjunction with TLR signaling to control IL-10 production (Gabryšová et al. 2014). IL-10 gene expression in these cells is controlled by a cross-talk network of signaling cascades, including MAP kinases (MAPKs) such as tumor progression locus 2 (TPL2), extracellular signal-regulated kinase (ERKs), and p38; mitogen- and stress-activated kinases (MSK)1/2 kinases; phosphoinositide 3-kinase (PI3K)–protein kinase B (AKT) signaling modules; nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathways; and transcription factors activating transcription factor 1 (ATF1) and cAMP response element-binding protein (CREB) downstream of PRRs (MacKenzie et al. 2014, Danne et al. 2017, Danne and Powrie 2018). Type I IFNs, which are induced in macrophages by lipopolysaccharide (LPS) or *Mycobacterium tuberculosis* infection, enhance IL-10 mRNA induction and stability via STAT1 and ERK1/2 MAPK activation. This keeps IL-10 activity in check to balance cytotoxic inflammatory activity through control of pro-inflammatory cytokine release (Guarda et al. 2011; McNab et al. 2014; Howes et al. 2016). Curiously, TPL-2, a MAPK that transduces ERK1/2 activation and induces TNF and IL-10 production (and is induced by IL-10 itself), suppresses IL-12 and Type I IFN in macrophages. This highlights the intricate feedforward and feedback circuitry governing IL-10 regulation during innate immunity (Kaiser et al. 2009).

IL-10 family cytokines in respiratory immune regulation

The IL-10 family cytokines is integral to the regulation of innate immune responses, primarily by modulating inflammation and preserving tissue homeostasis especially at mucosal and epithelial interfaces (Mahapatro et al. 2021). This family is comprised of IL-10, IL-19, IL-20, IL-22, IL-24, and IL-26 all of which exhibit structural similarities, share receptor components, and commonly signal through the JAK-STAT pathway, with STAT3 being the principal mediator (Ni et al. 2022; Lin et al. 2025). Among these, IL-10 stands out as the most extensively studied and functionally central member. It is a powerful anti-inflammatory cytokine predominantly produced by innate immune cells, including monocytes, macrophages, and dendritic cells (Steen et al. 2020). Within the innate immune framework, IL-10 plays a critical role in dampening inflammation by suppressing the production of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β. It also inhibits antigen presentation by downregulating MHC class II and costimulatory molecules, while simultaneously enhancing the viability and regulatory capacity of macrophages. These functions are vital for controlling inflammation and limiting tissue injury during infections or non-infectious inflammatory events (Carta et al. 2021; Al-Qahtani et al. 2024). In contrast, IL-19, IL-20, and IL-24 are more involved in maintaining epithelial integrity and responding to damage at barrier surfaces. These cytokines are produced by a range of cells, including monocytes, keratinocytes, and epithelial cells. Their actions are directed primarily at epithelial tissues, where they help modulate local inflammation, facilitate wound repair, and restore barrier function. Depending on the context, their activity can be protective or contribute to inflammatory diseases such as psoriasis (Feng et al. 2024, Toskas et al. 2024). IL-22 is secreted mainly by innate lymphoid cells (particularly ILC3s), T helper (Th17 cells), and γδ T cells. Its effects are largely confined to epithelial cells in organs such as the skin, gut, and lungs (Wei et al. 2020). IL-22 enhances epithelial defense mechanisms by stimulating regeneration, promoting the production of antimicrobial peptides (such as defensins and RegIIIγ), and strengthening barrier integrity. Notably, IL-22 acts directly on non-immune cells and plays a protective role in mucosal immunity, although dysregulation can lead to pathogenic inflammation (Arshad et al. 2020). IL-26 is a cytokine of the IL-10 family that is predominantly secreted by TH17 lymphocytes and is regulated by IL-1β, IL-23, and RORγt. It signals through a receptor composed of IL-10R2 and IL-20R1, activating STAT1 and STAT3 pathways, and has been implicated in various chronic inflammatory diseases due to its pro-inflammatory effects on epithelial cells, monocytes, natural killer (NK) cells, and fibroblasts (Arshad et al. 2020).

Moreover, the IL-10 family cytokines plays a pivotal role in regulating adaptive immunity by shaping T cell activity, modulating the behavior of antigen-presenting cells (APCs), and promoting immune tolerance. While these cytokines are most recognized for their roles in innate immunity and barrier defense, they also significantly impact adaptive immune functions (Golebski et al. 2021; Bugbee et al. 2023). IL-10, the most thoroughly characterized and functionally central member, acts as a powerful immunosuppressive cytokine. It is produced by various adaptive immune cells, including regulatory T cells (Tregs), Tr1 cells, activated $CD4^+$ and $CD8^+$ T cells, and B cells. IL-10 curbs the antigen-presenting capacity of dendritic cells and macrophages by downregulating costimulatory molecules and limiting antigen presentation, thereby dampening the activation and expansion of naïve T cells (Hilligan and Ronchese 2020; Islam et al. 2021; Song et al. 2021). Furthermore, IL-10 suppresses pro-inflammatory cytokine production such as IL-12 and IFN-γ, thereby inhibiting the differentiation of Th1 and Th17 cells. These effects contribute to the maintenance of immune tolerance and the prevention of autoimmunity (Fang and Zhu 2020). In addition, IL-10 enhances Treg function and expansion, reinforcing peripheral tolerance, especially within mucosal environments (Camacho et al. 2020).

In B cells, IL-10 functions as a survival and differentiation factor. It promotes cell proliferation and can enhance antibody production under specific conditions. IL-10 also encourages the development of regulatory B cells (Bregs), which further suppress immune responses through their own IL-10 production and by limiting inflammatory T cell activity (Facciotti et al. 2020; Michée-Cospolite et al. 2022). Other family members, namely IL-19, IL-20, IL-22, and IL-24, do not directly target adaptive immune cells but influence adaptive immunity by modifying the tissue environment. Through their actions on epithelial and stromal cells, these cytokines alter the local production of chemokines and cytokines, which in turn affects T cell recruitment, activation, and polarization (Wei et al. 2020; Zhong et al. 2022a). For instance, IL-22 produced by Th17 and Th22 cells as well as innate lymphoid cells supports the integrity of mucosal barriers and induces antimicrobial peptides, indirectly shaping the antigenic landscape and inflammatory cues that influence T cell responses (Ahn and Prince 2020; Jiang et al. 2021). IL-26, which is primarily secreted by pro-inflammatory IL-17-producing Th17 cells, plays a multifaceted role in adaptive immunity, particularly in chronic inflammatory conditions. Beyond its direct antimicrobial effects, IL-26 binds extracellular DNA released from damaged cells, enhancing local immune activation and inflammation, which may contribute to a persistent inflammatory loop and influence adaptive immune cell behavior and chronic disease progression (Che et al. 2021b; Jiang et al. 2021).

The IL-10 family cytokines function as a double-edged sword in immune regulation, and its effects are highly context-dependent. A single cytokine may provide protection in one scenario while contributing to pathology in another. IL-10 is classically known for its anti-inflammatory properties and its role in preventing tissue damage. For example, in the gut, IL-10 is essential for suppressing excessive inflammation; mice lacking IL-10 spontaneously develop severe, chronic colitis even under normal microbiota conditions (Ye et al. 2020; Chang et al. 2021). However, in certain settings, IL-10 can be subverted by pathogens to suppress host immunity. In chronic infections such as tuberculosis and Leishmania, elevated IL-10 levels impair protective Th1 responses. *Mycobacterium tuberculosis*, for instance, utilizes IL-10 to dampen macrophage activation and limit Th1-driven immunity, enabling persistent lung infection (Redford et al. 2011; Wong et al. 2020). IL-22 primarily targets non-immune (epithelial) cells, promoting tissue repair and maintaining barrier integrity. Its protective role is evident in the lungs, where it supports recovery from influenza-induced damage by stimulating airway epithelial regeneration (Alcorn 2020). In colitis-associated cancer (CAC), interleukin-22 (IL-22) plays a dual role: while it supports mucosal healing during colitis, chronic elevation of IL-22 contributes to tumorigenesis. This occurs through IL-22-induced upregulation of the oncogenic kinase MASTL in intestinal epithelial cells, a process mediated via the AKT signaling pathway. In addition, IL-22 enhances the association of MASTL with carbonic anhydrase IX (CAIX), which stabilizes MASTL and promotes epithelial cell survival and proliferation mechanisms that facilitate the progression from inflammation to cancer in the context of chronic inflammatory bowel disease (Alcorn 2020; Hirano et al. 2020). IL-24, also known as melanoma differentiation-associated gene 7 (MDA-7), exhibits both antimicrobial and anti-tumor effects. In tuberculosis, administration of recombinant IL-24 significantly improves survival in infected mice by enhancing $CD8^+$ T cell-mediated IFN-γ production, a response facilitated by neutrophils. This boosts the host's ability to control mycobacterial infection (Ma et al. 2011; Raguraman et al. 2025). Nonetheless, IL-24 is also implicated in chronic inflammatory and autoimmune conditions. Elevated levels have been observed in diseases such as psoriasis, rheumatoid arthritis (RA), and inflammatory bowel disease (IBD), where IL-24 contributes to persistent inflammation and tissue damage (Mitamura et al. 2020; Feng et al. 2024). IL-26 stands out among the IL-10 family for its direct antimicrobial activity. Produced mainly by Th17, IL-26 can bind extracellular microbial DNA, forming complexes that directly kill bacteria (Gilliet and Modlin 2024). In the context of hepatitis, tuberculosis, and leprosy, IL-26 plays a vital role in immune defense by exerting both antimicrobial and immunoregulatory effects. Primarily

produced by Th17 cells, IL-26 engages a receptor complex composed of IL-10R2 and IL-20R1, triggering the activation of STAT1 and STAT3 signaling pathways to boost immune activity. Due to its unique cationic nature, IL-26 can bind to bacterial DNA and compromise microbial membranes, thereby aiding in the elimination of pathogens such as *Mycobacterium tuberculosis* and *Mycobacterium leprae*, while simultaneously intensifying local inflammation through the recruitment of neutrophils and induction of inflammatory cytokines (Gowhari Shabgah et al. 2022; Shekhar et al. 2022). However, in MS, IL-26 is elevated in both serum and cerebrospinal fluid and is abundantly expressed by CD4 + T cells within brain lesions; although initially thought to promote inflammation, IL-26 was shown to enhance blood–brain barrier integrity and reduce disease severity in animal models, suggesting a dual role. In psoriasis and Crohn's disease, IL-26 acts as a pro-inflammatory cytokine, stimulating epithelial cells, monocytes, and other immune cells, thereby contributing to chronic inflammation and disease progression (Shekhar et al. 2022; Fries et al. 2023) Following injury, IL-19 expression increases in epidermal stem cells, where it facilitates wound healing by engaging the IL-20 receptor and triggering STAT3 activation. Its expression may be driven by Toll-like receptor signaling in response to inflammation, ultimately supporting processes such as epithelial regeneration, fibroblast stimulation, and new blood vessel formation (Ferrer et al. 2023). However, in psoriasis, IL-19 functions more as an immunoregulatory cytokine than a solely anti-inflammatory one. Despite using the same receptor as IL-20 and IL-24, new research indicates IL-19 might carry out a separate role, potentially involving a distinct receptor. Since T cells are not a source of IL-19, its involvement in psoriasis is likely mediated through indirect effects on other immune cell populations. In addition, IL-19 levels are elevated in asthma and RA synovium, where it can exacerbate inflammation by promoting keratinocyte proliferation and cytokine release (Azuma et al. 2011; Fujimoto et al. 2021).

In summary, the IL-10 family cytokines plays a complex and context-sensitive role in immunity. While many members function to protect tissues and resolve inflammation, the same molecules may contribute to chronic disease and immune dysfunction if overproduced or dysregulated. Their dual nature underscores the need for precise regulation to maintain the balance between effective immune defense and the risk of immunopathology (Chen et al. 2018, Perez et al. 2020, Gowhari Shabgah et al. 2022, Zhong et al. 2022a).

IL-10 family cytokines in specific respiratory diseases

IL-10 family cytokines in asthma

IL-10 plays a crucial role as an anti-inflammatory cytokine by suppressing the activity of various immune cells. In individuals with asthma, IL-10 levels are frequently diminished. Genetic research reveals that patients with asthma particularly those with severe forms often possess alleles associated with lower IL-10 production. Similarly, individuals with asthma exhibit reduced IL-10 levels in their bronchoalveolar lavage fluid compared to healthy individuals (Matsuda et al. 2022; Hendriks 2023). In murine models, the absence of IL-10 results in increased eosinophil accumulation and heightened airway inflammation, while administering external IL-10 alleviates both airway hyperresponsiveness and eosinophilia. This indicates that IL-10 plays a protective role in controlling allergic airway inflammation associated with asthma (Branchett et al. 2020; Matsuda et al. 2022).

IL-19 levels rise in asthma and appear to contribute to lung inflammation. Notably, IL-19 has been linked to higher expression of the SARS-CoV-2 entry receptor ACE2 in the lung tissue of individuals with moderate to severe asthma (Saheb Sharif-Askari et al. 2022a). These increased IL-19 levels have been linked to restricted airflow and structural changes in the airways. Laboratory studies show that IL-19 can drive Th2-type inflammatory responses. Therefore, in contrast to IL-10, IL-19 seems to enhance allergic inflammation, particularly in cases of severe asthma (Saheb Sharif-Askari, Saheb Sharif-Askari et al. 2021). IL-20, a member of the IL-10 family cytokines, appears to influence asthma by promoting inflammation and aiding epithelial repair. Elevated IL-20 levels have been detected in both the airway epithelium and serum of individuals with asthma, with concentrations rising in tandem with disease severity. This cytokine shows a strong positive association with Th2 cytokines such as IL-4, IL-5, and IL-13, suggesting its involvement in enhancing Th2-mediated inflammatory responses. Moreover, evidence from COPD studies indicates that IL-20 contributes to epithelial wound healing, pointing to a dual role in asthma pathogenesis intensifying inflammation while also supporting tissue regeneration (Wu et al. 2014; Barada et al. 2023).

In asthma, IL-22 contributes to inflammatory processes, especially within the neutrophilic subtype that often shows poor response to corticosteroids. Studies using a mouse model of acute neutrophilic asthma demonstrated a marked increase in IL-22 levels, along with IL-17, both of which were linked to elevated expression of the chemokine CCL20. These findings indicate that IL-22 facilitates neutrophil accumulation and inflammation in non-Th2 asthma, pointing

to its possible role in driving more severe and steroid-resistant forms of the disease. However, in asthma complicated by pneumonia, where neutrophilic inflammation dominates, IL-22 did not worsen the condition, highlighting its context-dependent effects (Goulart et al. 2023; Kim et al. 2023). IL-24, also known as MDA-7, is localized at higher levels in the airways of individuals with asthma, particularly in those with severe or neutrophilic forms of the disease. IL-24 expression is upregulated in bronchial epithelial cells of asthma patients as well as in mouse models of asthma. This cytokine was shown to stimulate IL-17A production through activation of the STAT3 and ERK signaling pathways, thereby facilitating the recruitment of neutrophils and contributing to airway inflammation (Feng et al. 2022b). In addition, IL-24 contributes significantly to airway remodeling in asthma by promoting epithelial–mesenchymal transition (EMT), a process associated with chronic structural alterations in the airways. Studies conducted both in vitro and in vivo demonstrated that IL-24 increases the expression of EMT-related markers such as vimentin and α-SMA via the activation of STAT3 and ERK1/2 signaling pathways. Elevated IL-24 levels were detected in the airway epithelium of a chronic asthma model, and this effect was mitigated by either silencing IL-24 or administering IL-37, a cytokine that inhibits EMT signaling (Feng et al. 2022a; Luo et al. 2025). IL-26 is prominently elevated in the airways of individuals with asthma, with its expression rising in tandem with disease severity. Research has shown increased concentrations of IL-26 in the sputum and bronchoalveolar lavage fluid of patients with severe or poorly controlled asthma. These elevated levels are closely linked to greater airway obstruction and heightened neutrophilic inflammation, suggesting a role for IL-26 in driving more severe, neutrophil-associated asthma phenotypes. Moreover, IL-26 has been found to be significantly overexpressed in the sputum of individuals with severe asthma, where it promotes the production of pro-inflammatory cytokines and facilitates the differentiation of Th17 cells, further amplifying airway inflammation and immune dysregulation (Louhaichi et al. 2020; Avramenko et al. 2022). For instance, elevated IL-26 levels in the sputum of patients with uncontrolled asthma have been reported, associating this cytokine

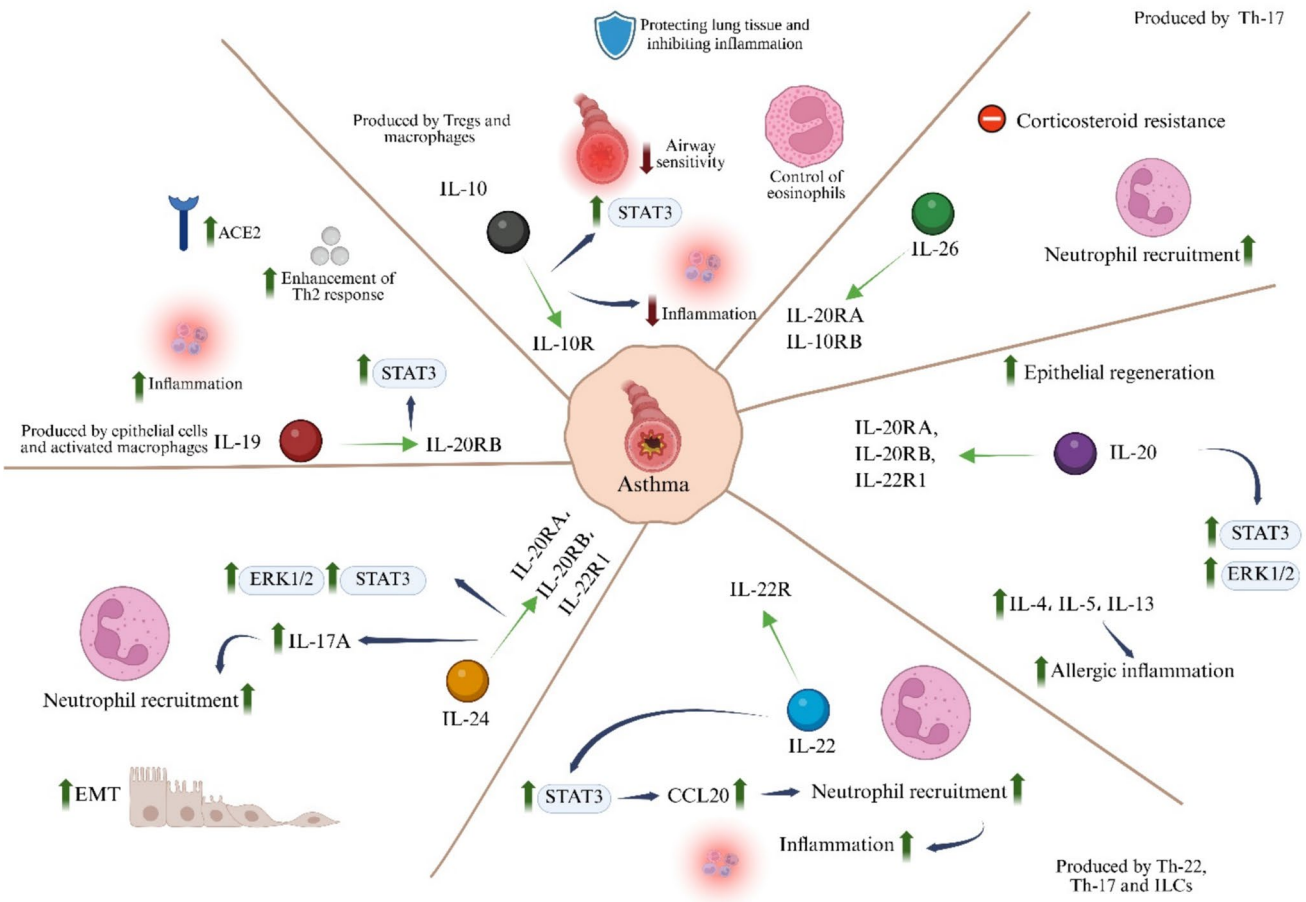


Fig. 1 Contribution of IL-10 family cytokines in asthma and their association with eosinophilic and neutrophilic inflammation. Created with BioRender.com

Table 1 Summary of IL-10 family cytokines in asthma

Cytokine	Immunologic role	Status in asthma	Clinical effect/mechanism	Ref
IL-10	Immunoregulatory cytokine with potent anti-inflammatory effects; inhibits Th2 cell function	Decreased in asthma	Suppresses allergic inflammation, reduces eosinophilia and hyperresponsiveness	(Branchett et al. 2020; Matsuda et al. 2022; Hendriks 2023)
IL-19	Promotes Th2-type inflammation	Increased in moderate to severe asthma	Promotes Th2 cytokine production and airway remodeling; linked with airflow limitation and increased ACE2 expression	(Saheb Sharif-Askari et al. 2021; Saheb Sharif-Askari et al. 2022a)
IL-20	Epithelial repair + pro-inflammatory	Increased in severe asthma	Positively correlates with IL-4, IL-5, and IL-13; supports both epithelial regeneration and chronic inflammation	(Wu et al. 2014; Barada et al. 2023)
IL-22	Epithelial protection, neutrophilic inflammation	Increased in neutrophilic asthma	Induces CCL20 expression, promotes neutrophil infiltration, steroid-resistant inflammation	(Goulart et al. 2023; Kim et al. 2023)
IL-24	Neutrophilic inflammation	Increased in airways of severe asthma	Activates STAT3 and ERK1/2 pathways; induces IL-17A and EMT markers (vimentin, α-SMA); implicated in structural airway changes	(Feng et al. 2022b; Luo et al. 2025)
IL-26	Neutrophilic inflammation	Increased in severe asthma	Stimulates production of pro-inflammatory cytokines and Th17 polarization; associated with airway obstruction and corticosteroid resistance	(Louhaichi et al. 2020; Avramenko et al. 2022; Cardenas et al. 2022a)

with neutrophilic inflammation that tends to be resistant to corticosteroid treatment (Cardenas et al. 2022a) (Fig. 1) (Table 1).

IL-10 family cytokines in COPD

IL-10 serves as an anti-inflammatory and regulatory cytokine in COPD, helping to control immune responses. However, its production and function are diminished in smokers and individuals with COPD. Research indicates a marked decline in IL-10 producing Bregs in the lungs and bloodstream of these populations, with cigarette smoke extract (CSE) further suppressing IL-10 synthesis and down-regulating essential transcription factors in memory B cells. Clinically, reduced IL-10 levels correlate with poorer lung function, heightened inflammation, and more severe COPD, particularly in cases complicated by pulmonary hypertension (COPD-PH). These findings suggest that IL-10 deficiency plays a key role in disease advancement and could serve as a valuable indicator of COPD severity and associated complications (Jacobs et al. 2022; Yang et al. 2022). IL-19, IL-20, and IL-24 contribute notably to the development and exacerbation of COPD, especially during viral infections and when epithelial repair is disrupted. Their expression is elevated in response to cigarette smoke and viral challenges, which intensifies lung inflammation, damages epithelial cells, and weakens the pulmonary barrier. Studies using mouse models have shown that eliminating the IL-20 receptor subunit (IL-20Rb) alleviates lung injury and inflammation while preserving epithelial integrity during viral flare-ups. These findings highlight the role of IL-19, IL-20, and IL-24 in advancing COPD pathology and support their potential as therapeutic targets for reducing disease exacerbations and enhancing airway repair (Le Roux et al. 2021; Le Roux 2022; Barada et al. 2023).

IL-22 has an extensive role in COPD, acting as both a protective and potentially harmful factor. Studies have shown elevated IL-22 levels and receptor expression in COPD patients, while certain genetic variants that enhance IL-22 expression are linked to a decreased risk of developing the disease, highlighting its protective potential. IL-22 supports lung health by aiding epithelial repair and modulating immune responses. However, in the setting of lung cancer especially in COPD patients IL-22 may facilitate tumor progression by promoting cell survival and inhibiting apoptosis. Thus, IL-22's function in COPD is context-dependent, offering promise for therapeutic repair strategies but raising concerns in oncogenic conditions (Wang et al. 2022c; Petta et al. 2023; Fang et al. 2024). IL-26 contributes significantly to the development of COPD through its pro-inflammatory and immune-regulating activities, particularly among smokers and individuals with chronic airway inflammation. Primarily secreted by T cells in the respiratory tract, elevated IL-26 levels correlate with poorer lung function, heightened neutrophil-driven inflammation, and more severe symptoms. IL-26 promotes neutrophil accumulation, facilitates the transport of extracellular DNA from damaged cells, and sustains inflammation via a reinforcing cycle. In addition, it has direct antimicrobial action by damaging bacterial membranes and exerts complex, dual effects (both activating and suppressing) on epithelial and immune cells. These multifaceted roles position IL-26 as a potential biomarker and therapeutic target for COPD stratification and treatment

Table 2 Summary of IL-10 family cytokines in COPD

Cytokine	Immune/biological role	Status in COPD	Clinical effect /Mechanism	Refs
IL-10	Anti-inflammatory, Breg regulator	Lower in smokers and patients	Reduced Breg function, worsens inflammation and lung damage	(Jacobs et al. 2022; Yang et al. 2022)
IL-19	Pro-inflammatory, epithelial injury	Upregulated after smoke exposure and infections	Undermines epithelial barrier, induces viral-induced exacerbations	(Le Roux et al. 2021; Le Roux 2022; Barada et al. 2023)
IL-20	Dual role: injury and repair	Upregulated during viral flares	Promotes epithelial cell death and inflammation; IL-20Rb knockout reduces injury	(Le Roux et al. 2021; Le Roux 2022; Barada et al. 2023)
IL-22	Protective or pathogenic	Upregulated in COPD	Supports epithelial repair, but may promote tumor growth in COPD-lung cancer overlap	(Wang et al. 2022c; Petta et al. 2023; Fang et al. 2024)
IL-24	Enhances inflammation and tissue damage	Upregulated in respiratory epithelium	Promotes inflammation, barrier dysfunction	(Le Roux et al. 2021; Le Roux 2022; Barada et al. 2023)
IL-26	Pro-inflammatory, neutrophilic	Overexpressed in severe COPD	Drives neutrophil recruitment, NET formation, antimicrobial & immunoregulatory effects, DNA release	(Bartziokas et al. 2022; Cardenas et al. 2022a; Arebro et al. 2025)

(Bartziokas et al. 2022; Cardenas et al. 2022a; Arebro et al. 2025) (Table 2).

IL-10 family cytokines in COVID-19

IL-10 plays a nuanced role in COVID-19, functioning as both an indicator of disease severity and a regulator of immune responses. Its levels are frequently elevated in infected individuals, especially those with severe or critical forms of the illness, and show a strong positive correlation with inflammatory indicators such as C-reactive protein (CRP). IL-10 concentrations typically increase during the early and intermediate stages of infection, then decrease as patients recover. Although IL-10 is primarily known for its anti-inflammatory properties, its heightened presence in severe cases suggests it may be part of a feedback mechanism aimed at controlling the excessive inflammation seen in cytokine storms. This dual role underscores the potential of IL-10 as a marker for diagnosing disease progression and exploring immune system imbalances in COVID-19 (Han et al. 2020; Lu et al. 2021; Rajamanickam et al. 2023). IL-19, IL-20, IL-22, and IL-24 exert immunoregulatory and potentially protective effects during COVID-19 infection. Elevated levels of these cytokines have been consistently observed in individuals with severe disease compared to those with milder symptoms, indicating their potential role in disease advancement. IL-19 is notably increased in both blood and saliva and has been closely linked to adverse clinical outcomes, including higher risks of mechanical ventilation and mortality. Likewise, IL-20, IL-22, and IL-24 are associated with immune mechanisms that may help limit lung injury; for instance, IL-22 promotes epithelial barrier maintenance, while IL-24 has recognized anti-inflammatory properties. While this rise in cytokine levels may represent a protective, compensatory response to inflammation and tissue damage, their uncontrolled expression could exacerbate immune dysregulation and contribute to the cytokine storm seen in severe COVID-19 cases (Saheb Sharif-Askari 2022b; Rajamanickam et al. 2023).

IL-26 plays a crucial role in the inflammatory and immune response associated with COVID-19, especially in patients with severe or critical illness. Its plasma levels are notably elevated during acute infection and closely linked to high viral loads, heightened neutrophil activity, and indicators of tissue damage, including elevated lactate dehydrogenase. IL-26 facilitates neutrophil recruitment and stimulates the formation of neutrophil extracellular traps (NETs), amplifying inflammatory responses. It also exhibits strong positive associations with pro-inflammatory cytokines such as IL-8 and TNF-α, as well as increased expression of CD47 on neutrophils, which may prevent their clearance and prolong inflammation. Collectively, these findings indicate that IL-26 contributes to both antiviral defense and the pathological hyperinflammatory state seen in severe COVID-19, positioning it as a potential biomarker and target for therapeutic intervention (Cardenas et al. 2022b; Cardenas et al. 2024) (Table 3).

IL-10 family cytokines in pulmonary infections

IL-10 serves a multifaceted regulatory function during pulmonary infections by modulating immune responses to prevent excessive inflammation while still aiming to control pathogens. In cases of acute bacterial pneumonia, such as those caused by *Pseudomonas aeruginosa* or *Streptococcus pneumoniae*, IL-10 helps reduce lung tissue damage by downregulating inflammatory mediators such as IL-6 and TNF-α and modulating the activity of neutrophils and macrophages. Interestingly, neutrophils particularly a distinct subpopulation emerge as major producers of IL-10 during pneumococcal infections. Experimental models using IL-10 knockout mice demonstrate that the absence of this cytokine leads to increased bacterial loads, exacerbated inflammation, and more severe lung injury, underscoring its protective capacity. However, IL-10's ability to suppress immune activation can also hinder pathogen clearance, contributing to persistent infections, as seen in conditions such as pneumonia and tuberculosis. Therefore, while IL-10 is critical for preventing immune-mediated lung damage, it also poses a risk by potentially compromising antimicrobial defense, making its role a double-edged sword in respiratory infections (Belo et al. 2021; González et al. 2021; Niu et al. 2024). IL-19, IL-20, and IL-24, part of the IL-20 subfamily within the IL-10 family cytokines, serve as key immunoregulators in pulmonary infections. During early stages of bacterial pneumonia, especially infections caused by *Streptococcus pneumoniae*, their expression in lung tissue rises sharply, typically peaking around 24 h post-infection. These cytokines help control inflammation potentially safeguarding lung tissue but this anti-inflammatory action may come at the cost of reduced bacterial clearance, as demonstrated by enhanced recovery following IL-20 receptor inhibition. Studies in fish, such as the swamp eel, reveal that IL-20-like (IL-20L) genes share strong evolutionary and functional ties with mammalian IL-19, IL-20, and IL-24, suggesting a conserved role in immune modulation. While their involvement in chronic lung infections such as tuberculosis remains unclear, IL-24 has been shown to dampen Th17-mediated inflammation by inhibiting NF-κB signaling, indicating a wider role in regulating immune responses during infection (Madouri et al. 2018; Xu et al. 2022; Zhang et al. 2022a).

IL-22 has an important role in pulmonary infections by reinforcing the epithelial barrier, aiding in tissue regeneration, and dampening inflammation; IL-22 helps defend the lungs during bacterial and viral infections such as influenza. Secreted mainly by Th22 cells, IL-22 enhances the

Table 3 Summary of IL-10 family cytokines in COVID-19

Cytokine	Immune/biological role	Status in severe COVID-19	Association with clinical markers	Potential role/clinical implication	Refs
IL-10	Anti-inflammatory, immune regulation	Increased	Positive correlation with CRP	Dual role as immune regulator and marker of cytokine storm severity, regulator of cytokine storm	(Han et al. 2020; Lu et al. 2021; Rajamanickam et al. 2023)
IL-19	Immunoregulatory, potentially anti-inflammatory	Increased in blood and saliva	Linked to mechanical ventilation and mortality	Unfavorable prognostic indicator; potential therapeutic target	(Saheb Sharif-Askari et al. 2022b; Rajamanickam et al. 2023)
IL-20	Immune modulation, tissue protection	Increased	–	Potential protective role in lung injury	(Saheb Sharif-Askari et al. 2022b; Rajamanickam et al. 2023)
IL-22	Maintains epithelial barrier integrity	Increased	–	Supports epithelial defense and reduces lung tissue damage	(Saheb Sharif-Askari et al. 2022b; Rajamanickam et al. 2023)
IL-24	Anti-inflammatory properties	Increased	–	Potential regulator of excessive inflammation; may help restore immune balance	(Saheb Sharif-Askari et al. 2022b; Rajamanickam et al. 2023)
IL-26	Promotes inflammation, neutrophil recruitment	Increased	Correlates with viral load, LDH, IL-8, TNF-α, CD47	Drives NET formation and hyperinflammation; promising biomarker and therapeutic target	(Cardenas et al. 2022b; Cardenas et al. 2024)

expression of tight junction proteins like claudin-4, which reduces lung permeability and tissue damage, despite having little impact on microbial load. Its function is tightly controlled by IL-22 binding protein (IL-22BP), which is typically suppressed during infection to permit IL-22 activity. Nevertheless, IL-22 can also drive inflammation under certain conditions for instance, in hepatitis B and *Helicobacter pylori* infections, where excessive IL-22 signaling leads to increased immune cell infiltration and the release of pro-inflammatory cytokines, worsening disease outcomes. This context-dependent behavior underscores IL-22's therapeutic promise in acute lung injury, while also cautioning against its potential to exacerbate chronic or unregulated immune responses (Alcorn 2020; Hebert et al. 2020; Zhang et al. 2023). IL-26 serves diverse functions during pulmonary infections, especially in the context of bacterial pneumonia. In response to bacterial stimuli, IL-26 is secreted by lung epithelial cells, macrophages, neutrophils, and T cells, with its concentration markedly elevated in airway fluids of affected individuals and closely linked to neutrophil levels. It exerts antimicrobial effects both directly by inhibiting bacterial proliferation and indirectly by binding bacterial DNA to boost immune recognition. In addition, IL-26 influences the innate immune system by limiting the release of harmful enzymes such as neutrophil elastase and myeloperoxidase, while enhancing cytokine expression, including IL-23 and IL-10. Importantly, neutralizing IL-26 results in increased growth of *Klebsiella pneumoniae* in macrophages, underscoring its role in host defense (Che et al. 2021a).

IL-10 family cytokines in pulmonary fibrosis

IL-10 exhibits a multifaceted but largely protective function in pulmonary fibrosis. Mainly secreted by alveolar macrophages, IL-10 is recognized for its anti-inflammatory and anti-fibrotic effects. In bleomycin-induced pulmonary fibrosis models, IL-10 inhibits the expression of fibrogenic cytokines such as TGF-β1 and sustains IFN-γ levels, thereby limiting inflammatory responses, cellular infiltration, and extracellular matrix deposition. Experimental therapies using IL-10, delivered via plasmids or hydrogels, have demonstrated both preventive and therapeutic potential against fibrosis. However, its efficacy is closely tied to the timing and site of expression while transient overexpression dampens inflammation, sustained elevation can unintentionally worsen fibrosis by promoting immune cell accumulation and fibrocyte activation (Steen et al. 2020; She et al. 2021; Li et al. 2024). IL-19 contributes to the progression of pulmonary fibrosis by enhancing fibroblast activation and promoting the production of extracellular matrix components. Studies in both idiopathic pulmonary fibrosis (IPF) patients and mouse models have shown elevated IL-19 expression in fibrotic lung tissues. IL-19 facilitates fibroblast proliferation and their transformation into myofibroblasts marked by α-smooth muscle actin expression. These effects are driven by the activation of key signaling pathways, including TGF-β/Smad and NF-κB, resulting in increased deposition of collagen and fibronectin. Notably, administration of IL-19 exacerbates bleomycin-induced fibrosis, whereas blocking IL-19 mitigates fibroblast activation, underscoring its potential as a therapeutic target in pulmonary fibrosis (Wang et al. 2022b, ; Bao et al. 2023; Nishiyama et al. 2024). IL-22 serves as a protective, anti-fibrotic cytokine in pulmonary fibrosis by opposing TGF-β-driven fibrotic processes and limiting excessive collagen accumulation. Clinical observations corroborate that IL-22 levels are reduced in patients with IPF, with lower expression linked to greater impairment in lung function. In bleomycin-induced murine models, absence of IL-22 leads to intensified inflammation and fibrosis, whereas intranasal delivery of recombinant IL-22 mitigates these effects by suppressing TGF-β1, its receptor, and downstream Smad2/3 signaling. IL-22 also curbs fibroblast activation and dampens IL-17A-mediated pathways, thereby reducing extracellular matrix buildup (Gu et al. 2021; Qu et al. 2022; Zhang et al. 2022b). IL-24 contributes to the progression of pulmonary fibrosis by reinforcing Th2-mediated immune activity and facilitating macrophage polarization. Studies have shown that IL-24 levels are elevated in both IPF patients and fibrotic animal models. Although IL-24 does not independently trigger M2 macrophage activation, it works in concert with IL-4 to enhance STAT6 signaling, thereby promoting M2 macrophage polarization which is an important mechanism in extracellular matrix (ECM) buildup and fibrosis. Importantly, mice lacking IL-24 demonstrate milder lung damage, reduced TGF-β1 expression, fewer M2 macrophages, and less collagen deposition following bleomycin treatment, underscoring IL-24's pro-fibrotic influence through its modulation of immune responses and amplification of fibrotic pathways (Sziksz et al. 2015; Rao et al. 2021; He et al. 2024a).

IL-10 family cytokines in lung cancer

In lung cancer, IL-10 contributes significantly to creating an immunosuppressive environment that favors tumor growth. This cytokine, produced by tumor cells, regulatory T cells, and various immune components within the tumor microenvironment, inhibits the activity of cytotoxic T cells and NK cells, facilitating tumor immune escape. Elevated IL-10 levels are frequently observed in non-small cell lung cancer (NSCLC), particularly in patients' serum and malignant pleural effusions, and are linked to worse prognosis and decreased survival rates. By reducing the expression of pro-inflammatory cytokines such as IFN-γ and activating STAT3 signaling, IL-10 promotes a Th2-biased, anti-inflammatory immune profile. Moreover, increased IL-10 levels both at

baseline and during treatment with immune checkpoint inhibitors (ICIs) have been associated with a higher incidence of immune-related adverse events (irAEs), including pneumonitis, underscoring IL-10's potential as a biomarker for monitoring both disease progression and immunotherapy-related toxicity in lung cancer (Mirlekar 2022; Wang et al. 2022a; Niu et al. 2024). IL-19 and IL-20, both part of the IL-10 family cytokines, play distinct but increasingly recognized roles in lung cancer progression. IL-20 is commonly altered in NSCLC and may inhibit angiogenesis by suppressing COX-2 and VEGF gene expression, a process influenced by epigenetic mechanisms affecting both the cytokine and its receptors (IL-20RA, IL-20RB, and IL-22R1). In contrast, IL-19 is produced by osteoclasts within the bone metastatic niche and facilitates tumor growth by activating IL-20RB on lung cancer cells, which in turn initiates JAK1/STAT3 signaling and promotes proliferation. High IL-20RB expression correlates with increased metastatic capability and poorer prognosis, suggesting that the IL-19/IL-20RB axis may drive tumor progression in bone and represent a promising target for therapeutic intervention (Baird et al. 2011; Fan et al. 2021; He et al. 2022). IL-22, mainly produced by Th22 cells, has emerged as a significant promoter of tumor progression in lung cancer, especially in NSCLC. Elevated IL-22 levels in NSCLC patients are strongly associated with higher tumor stages and increased metastatic potential. Functionally, IL-22 enhances cancer cell proliferation, facilitates migration, and impairs the effectiveness of chemotherapy and targeted therapies such as cisplatin and gefitinib by inhibiting apoptosis. These tumor-promoting actions are largely driven by the activation of key signaling cascades, including JAK/STAT3, MAPK, and AKT pathways. Notably, IL-22 also plays a role in mediating resistance to EGFR-TKI therapy, indicating its potential as a promising therapeutic target (Yao et al. 2022; Wang et al. 2024, Xu et al. 2024).

IL-24 is recognized as a tumor-suppressive cytokine; it plays diverse roles in lung cancer by contributing to both diagnostics and treatment strategies. In clinical settings, IL-24 levels measured through immunohistochemistry (IHC) serve as valuable prognostic indicators, supporting tumor profiling and guiding therapeutic decisions. Due to the limitations of conventional manual IHC scoring such as variability and subjectivity automated systems like the Darknet-based deep learning model have been introduced to provide more accurate and efficient evaluation of IL-24 expression in lung cancer tissues (He et al. 2024b). At the molecular level, IL-24 suppresses tumor progression by promoting apoptosis and reducing cell proliferation and migration through signaling pathways including p38 MAPK and CXCR4/AKT. In addition, IL-24 stimulates the cGAS–STING pathway, enhancing the innate immune response by upregulating chemokines and cytokines such as CXCL10, CCL5, and IL-6. Notably, mesenchymal stem cells cultured in 3D environments show elevated IL-24 expression, further amplifying these anti-tumor effects. Overall, IL-24 emerges as a promising candidate for both prognostic assessment and immunotherapeutic intervention in lung cancer (Suo et al. 2021; Raguraman et al. 2024). IL-26, mainly secreted by Th17 cells, plays a pro-tumorigenic role in lung cancer, particularly in malignant pleural effusion (MPE). Elevated IL-26 levels in MPE are driven by IL-6 and IL-23 through STAT3-RORγt signaling, promoting Th17 and Th22 cell differentiation and IL-22 production. IL-26 also impairs anti-tumor immunity by reducing granzyme B in cytotoxic T cells. Its expression correlates with poor prognostic markers such as high CEA and NLR, suggesting that IL-26 contributes to tumor progression and may serve as a potential biomarker and therapeutic target in lung cancer-related MPE (Niu et al. 2021; Gowhari Shabgah et al. 2022) (Fig. 2) (Table 4).

IL-10 family cytokines in ARDS

The cytokines IL-10, IL-19, IL-22, and IL-24 are critical regulators of immune responses in ARDS, especially during viral infections such as COVID-19. Among them, IL-10 plays a pivotal role in orchestrating the antiviral THαβ immune pathway. It serves as a strong anti-inflammatory and anti-fibrotic agent, capable of curbing the cytokine storm and reducing lung tissue damage. IL-19 and IL-24 also exhibit anti-inflammatory functions, helping to modulate immune activity and potentially suppress the excessive TH17-driven inflammation commonly associated with ARDS. IL-22, on the other hand, is recognized for its tissue-protective effects, particularly in promoting epithelial repair and regeneration in the lungs. Collectively, these cytokines represent promising therapeutic targets aimed at restoring immune homeostasis and limiting pulmonary injury in ARDS (Taghavi et al. 2021; Shih et al. 2023).

IL-10 family cytokines in cystic fibrosis (CF)

In CF, IL-10 and IL-22 contribute differently to immune regulation. IL-10, known for its anti-inflammatory properties, is found at elevated levels in CF mice even without infection, implying that CFTR dysfunction alone can trigger chronic immune imbalance and inflammation. This increase may represent a feedback response to excessive pro-inflammatory activity. On the other hand, IL-22, essential for maintaining epithelial barrier function and promoting tissue repair, is likely functionally impaired in CF due to the overexpression of its soluble inhibitor, IL-22Ra2. High IL-22Ra2 levels have been observed in both sinus secretions and blood samples from individuals with CF and persist despite CFTR modulator therapy, pointing to ongoing disruption of the

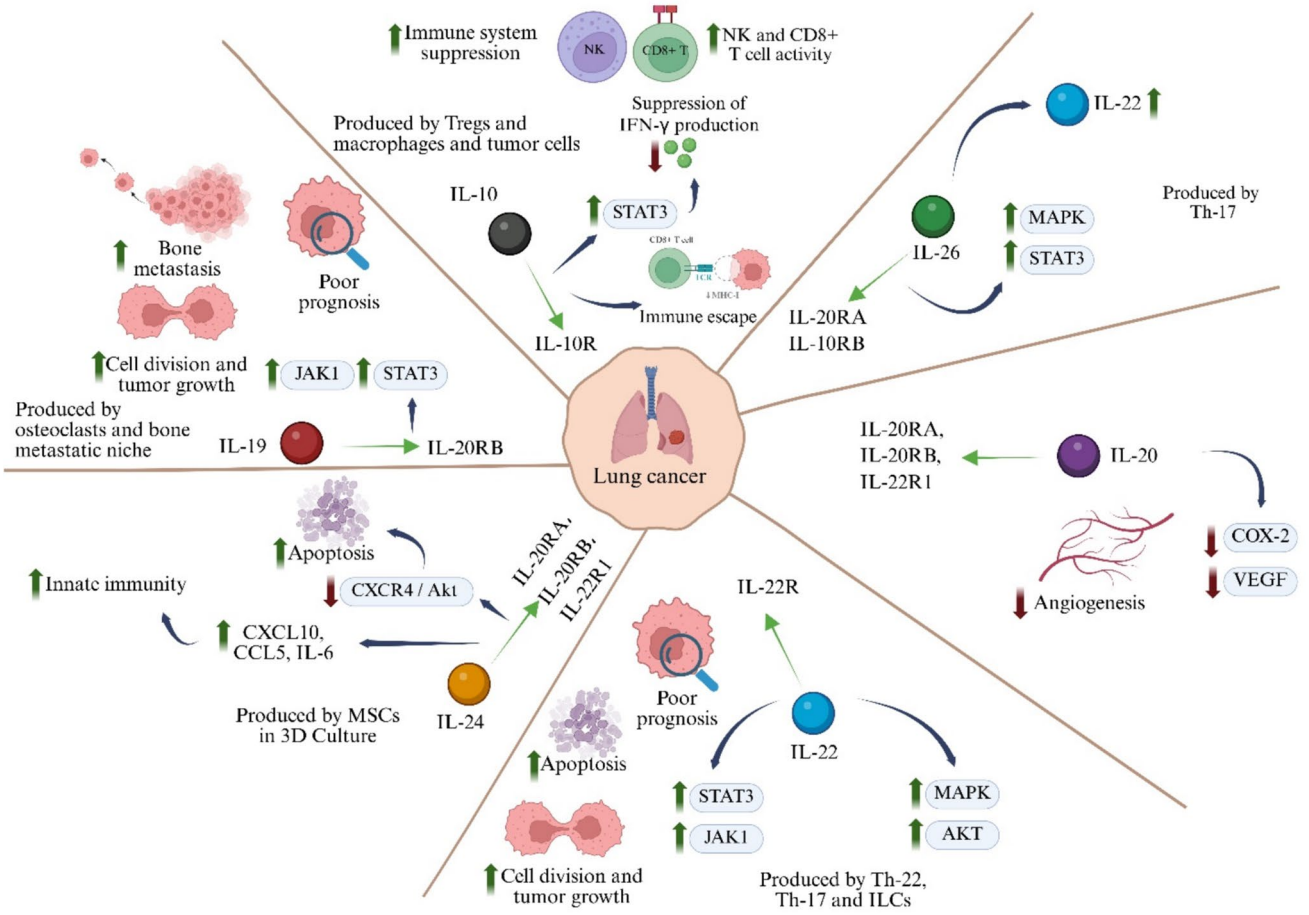


Fig. 2 Influences of IL-10 family cytokines in lung cancer and related signaling pathways. Created with BioRender.com

IL-22/STAT3 signaling pathway. This persistent dysregulation may hinder bacterial clearance and promote chronic infection, even with current treatments (Litman et al. 2021; Rajamanickam et al. 2023; Bojanowski et al. 2024).

IL-10 family cytokines in TB

In TB, cytokines from the IL-10 family including IL-10, IL-19, IL-20, IL-22, IL-24, and IL-26, play varied roles in modulating immune responses to *Mycobacterium tuberculosis* (Mtb). IL-10, an anti-inflammatory cytokine, shapes granuloma function and limits early inflammation, with its absence potentially enhancing bacterial control during later infection stages. IL-19, part of the IL-20 subfamily, is elevated in TB patients and may reflect ongoing immune activation in response to Mtb. IL-22, primarily produced by Th22 cells, is reduced systemically in TB and especially in multidrug-resistant cases, suggesting impaired mucosal repair and immune regulation. IL-24 and IL-20, also members of the IL-10 family, are less studied in TB but likely contribute to the regulation of inflammation and epithelial responses. Notably, IL-26 exhibits direct antimicrobial activity against Mtb and enhances innate immunity by promoting cytokine and chemokine release from macrophages and dendritic cells. Collectively, these cytokines orchestrate a complex balance between protective immunity, inflammation, and tissue repair during TB infection (Hawerkamp et al. 2020; Imperiale et al. 2020; Wong et al. 2020; Ding et al. 2023).

Therapeutic targeting of IL-10 family cytokines

In chronic respiratory conditions such as asthma, COPD, and pulmonary fibrosis, abnormal cytokine expression is associated with greater disease severity, leading to growing interest in targeting these molecules therapeutically. Asthma,

Table 4 Summary of IL-10 family cytokines in lung cancer

Cytokine	Source/expression site	Function in lung cancer	Mechanism/pathway	Clinical implication	Refs
IL-10	Tumor cells, Tregs, immune cells	Immunosuppressive TME; supports tumor escape	Downregulated IFN-γ, upregulated STAT3 activation, promotes Th2 polarization	Poor prognosis; upregulated irAEs during ICI therapy	(Mirlekar 2022; Wang et al. 2022a; Niu et al. 2024)
IL-19	Osteoclasts in bone metastatic niche	Upregulates tumor growth and bone metastasis	IL-20RB → JAK1/STAT3 signaling	Targetable axis in metastatic lung cancer	(Fan et al. 2021; He et al. 2022)
IL-20	NSCLC tissue; tumor microenvironment	May prevent angiogenesis; dual role in tumor progression	Downregulated COX-2, VEGF; epigenetically regulated via IL-20RA/B–IL-22R1 axis	Linked to IL-20RA/B, IL-22R1 expression	(Baird et al. 2011; Fan et al. 2021; He et al. 2022)
IL-22	Th22 cells, tumor-infiltrating lymphocytes	Promotes proliferation, migration; therapy resistance	JAK/STAT3, MAPK, AKT signaling	Poorer prognosis; resistance to EGFR-TKIs	(Yao et al. 2022; Wang et al. 2024, Xu et al. 2024)
IL-24	MSCs, epithelial and immune cells	Tumor-suppressive: induces apoptosis, prevents metastasis	p38 MAPK, CXCR4/AKT, Upregulated cGAS–STING	Prognostic biomarker; gene therapy potential	(Suo et al. 2021; He et al. 2024b; Raguraman et al. 2024)
IL-26	Th17 cells in MPE	Enhances tumor progression; decreases cytotoxicity	STAT3–RORγt; Downregulated granzyme B in $CD8^+$ T cells	Biomarker in MPE; upregulated CEA, NLR association	(Niu et al. 2021; Gowhari Shabgah et al. 2022)

characterized by classic Th2-mediated inflammation, frequently presents with a deficiency in endogenous IL-10 which is a key anti-inflammatory cytokine. Notably, patients with severe asthma exhibit markedly lower IL-10 levels in both bronchoalveolar lavage fluid and pulmonary cells (de Brito et al. 2022; Hendriks 2023). This deficiency plays a role in perpetuating uncontrolled allergic inflammation, indicating that enhancing IL-10 function might help alleviate asthma symptoms. In contrast, some members of the IL-10 family cytokines are overexpressed in asthma and contribute to disease progression. For example, IL-19, part of the IL-20 subfamily, is upregulated in airways exposed to allergens and promotes Th2-mediated immune responses. Recent studies in rodent models have demonstrated that inhibiting IL-19 or its receptor, IL-20R1, can reduce allergen-induced airway hyperresponsiveness and inflammation. This represents the initial evidence that inhibiting IL-19 signaling can alleviate allergic inflammation in the lungs, highlighting anti-IL-19 approaches as a promising new direction for asthma treatment (Weng et al. 2019; Matsuda et al. 2022). In COPD, an inflammatory condition commonly linked to smoking, an imbalance in IL-10 family cytokines is also observed. Both smokers and individuals with COPD exhibit reduced IL-10 levels in their airways compared to healthy non-smokers, potentially intensifying inflammatory responses. As a result, preclinical studies have investigated strategies to boost IL-10 levels. In murine models of lung injury caused by smoke or dust exposure, administration of IL-10 either through inhalation or targeted delivery to the lungs markedly reduced inflammation and accelerated tissue recovery (Jacobs et al. 2022; Schwab et al. 2025).

IL-22, a member of the IL-20 subfamily, is elevated in the airways of individuals with COPD and illustrates the complex, context-dependent roles of IL-10 family cytokines. While IL-22 can promote inflammation under certain conditions, it also plays a protective role by supporting lung immunity and epithelial repair. Its importance is particularly evident in the defense against respiratory infections—COPD patients who frequently experience bacterial exacerbations often exhibit a weakened IL-22 response (Nguyen et al. 2020; Petta et al. 2023). In one study, administering exogenous IL-22 to cigarette smoke-exposed mice improved the production of antimicrobial peptides and enhanced bacterial clearance during pneumococcal infection, underscoring its potential as a therapeutic strategy to reduce COPD-related exacerbations (Pichavant et al. 2015). In pulmonary fibrosis, a condition marked by abnormal tissue repair and scarring, IL-10 family cytokines demonstrate contrasting functions. IL-19 is significantly overexpressed in fibrotic lung tissue and has been shown to directly worsen fibrotic processes by stimulating fibroblast proliferation, enhancing their invasiveness, and promoting their transformation into collagen-producing myofibroblasts. These findings suggest that targeting

IL-19 signaling could help limit fibrosis progression (Wang et al. 2022b). Conversely, IL-22 exhibits protective effects in fibrosis models. Mice lacking IL-22 develop more severe pulmonary fibrosis following bleomycin exposure, while treatment with recombinant IL-22 leads to reduced collagen accumulation and mitigates fibrotic damage (Qu et al. 2022). IL-10 has been a focal point in studies of COVID-19 immunopathology. Interestingly, patients with severe disease often show elevated systemic IL-10 levels, which are thought to reflect an inadequate compensatory anti-inflammatory response. To more effectively harness IL-10's immunoregulatory properties, researchers have explored its potential as a therapeutic agent in COVID-19-related ARDS. Unlike corticosteroids, which suppress immune function broadly, IL-10 may selectively dampen the excessive cytokine storm while maintaining essential antiviral T-cell activity. Recent studies proposed that IL-10 is particularly well suited to precisely modulate the cytokine surge in COVID-19, thereby limiting lung tissue damage (Shih et al. 2023). In addition to their role in viral infections, IL-10 family cytokines play critical functions in other pulmonary infections. IL-22, in particular, is essential for defending against bacterial pathogens by promoting the production of antimicrobial peptides and maintaining epithelial barrier integrity. In models of bacterial pneumonia including those mimicking COPD exacerbations, therapeutic administration of IL-22 enhanced bacterial elimination and improved survival outcomes (Pichavant et al. 2015). IL-26, another member of the IL-10 family cytokines, has recently been identified as an innate antimicrobial mediator. Secreted primarily by TH17 cells, IL-26 can directly interact with and kill pathogens; for instance, it has been shown to bind to *Mycobacterium tuberculosis* and diminish its viability within human macrophages. In addition, IL-26 stimulates macrophages and dendritic cells to release TNF-α and chemokines, thereby enhancing the host immune response against tuberculosis (Hawerkamp et al. 2020). In lung cancer, the IL-10 family cytokines serves as both a therapeutic target and an immunomodulatory tool. Tumors frequently exploit IL-10's immunosuppressive properties to escape immune detection; however, when administered at high doses, IL-10 can paradoxically enhance antitumor responses by activating $CD8^+$ T cells. Pegilodecakin, a pegylated form of recombinant IL-10, has been evaluated in phase II clinical trials for NSCLC alongside PD-1 checkpoint inhibitors. Although this combination boosted certain immune functions (such as increased IFN-γ and Granzyme B production by T cells), it produced inconsistent clinical outcomes and was associated with a higher incidence of immune-related adverse events compared to checkpoint inhibitor therapy alone (Naing et al. 2018; Spigel et al. 2021). Several other IL-10 family cytokines exhibit more direct anti-tumor activity. IL-24, also known as MDA-7, acts as a tumor-suppressive cytokine by selectively inducing apoptosis in cancer cells while sparing normal tissues. It also impairs metastatic potential. In lung cancer models, IL-24 overexpression significantly reduced tumor cell migration and invasion by suppressing key oncogenic signaling pathways, including PI3K, MAPK, and FAK. Therapeutic strategies involving IL-24 such as gene therapy vectors and IL-24-engineered CAR T cells are currently being investigated to harness its potent anti-cancer effects (Zhang et al. 2024; Raguraman et al. 2025). In contrast, IL-22 is generally associated with promoting lung tumor development. In NSCLC, IL-22 signaling activates pathways that support cell survival, proliferation, and resistance to apoptosis, thereby facilitating tumor growth and metastasis. As a result, therapeutic strategies aimed at inhibiting the IL-22/IL-22 receptor (IL-22R) axis are being explored as adjunct treatments to counteract IL-22's tumor-promoting influence (Petta et al. 2023) (Fig. 3).

Agents targeting IL-10 family signaling beyond the IL-10 receptor

The IL-10 family of cytokines exerts anti-inflammatory and immune-modulating actions primarily through the JAK1-TYK2–STAT3 pathway, alongside various secondary signaling routes. As a result, therapeutic strategies have shifted from focusing solely on receptor-targeting biologics to directly intervening in these intracellular processes. Small-molecule JAK inhibitors exemplify this approach. One such drug, Baricitinib (a JAK1/JAK2 inhibitor) suppresses STAT3 activity downstream and, according to a meta-analysis of randomized trials, significantly reduced mortality rates and the requirement for mechanical ventilation in patients with COVID-19 (Lin et al. 2022). Tofacitinib, a JAK1/JAK3 inhibitor, has also been shown to mitigate cytokine storm responses. In a double-blind study involving hospitalized patients with COVID-19 pneumonia, the combined rate of death or respiratory failure by day 28 was 18.1% among those receiving tofacitinib, compared with 29.0% in the placebo group, corresponding to a risk ratio of 0.63. Selective inhibition of JAK1 is represented by upadacitinib (Guimarães et al. 2021; De Greef et al. 2023). In a trial involving mechanically ventilated patients, ruxolitinib 15 mg reduced 28-day mortality from 70% with placebo to 51%. However, the study lacked sufficient power, and the difference was not statistically significant. Taken together, available trials indicate that JAK inhibitors can attenuate the COVID-19-associated cytokine storm and may enhance survival outcomes (Rein et al. 2022). Furthermore, Napabucasin, originally developed as an investigational anti-cancer agent, has demonstrated promising potential for repurposing against both COVID-19 and TB in computational and experimental evaluations. In the context of COVID-19, molecular docking and dynamic simulations highlighted napabucasin as

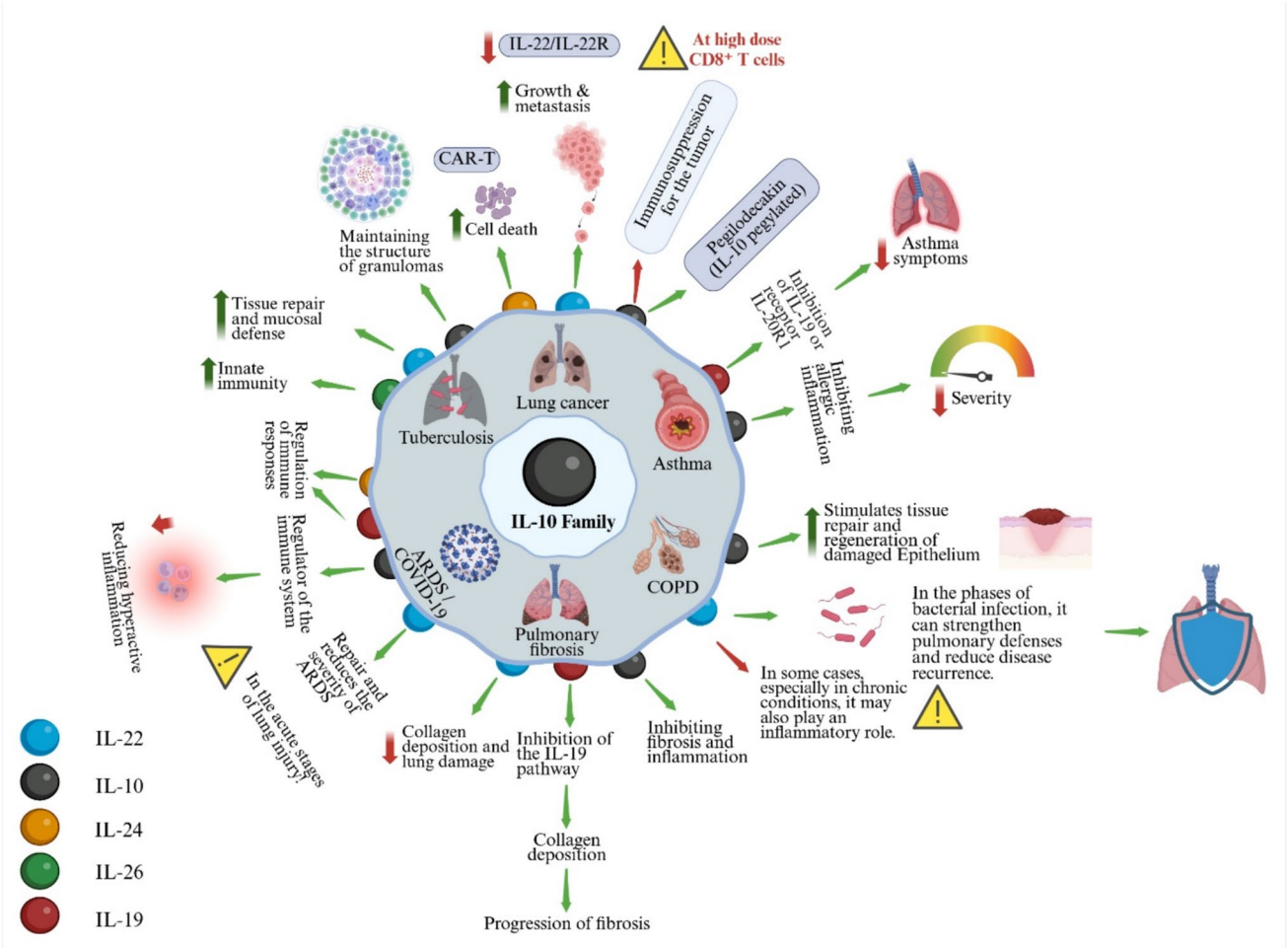


Fig. 3 IL-10 family cytokines as therapeutic targets in chronic respiratory diseases. Created with BioRender.com

one of seven candidate inhibitors of the SARS-CoV-2 main protease (Mpro), showing strong binding affinity and stable interactions, which indicates a possible role in suppressing viral replication, although further laboratory and clinical studies are required. For TB, napabucasin exhibited moderate activity against *M. tuberculosis* H37Ra (MIC 2.5 µg/mL), and structural modifications led to more potent derivatives, with compound 3 s achieving significantly enhanced activity (MIC 0.3125 µg/mL). These optimized derivatives also proved effective against the *M. tuberculosis* H37Rv strain and drug-resistant clinical isolates, highlighting napabucasin's potential as a valuable scaffold for the development of new treatments targeting both viral and bacterial pathogens (Li et al. 2019; Chowdhury et al. 2020). In addition, Napabucasin (BBI608), a novel small-molecule that inhibits STAT3 and stemness-related signaling, has exhibited notable therapeutic potential in small cell lung cancer (SCLC), especially in tumors resistant to cisplatin. Research findings revealed that napabucasin curtailed cell proliferation and colony formation, triggered S-phase cell cycle arrest, and induced apoptosis in resistant SCLC cells. Its mechanism of action involved the suppression of stemness regulators SOX2 and c-Myc, as well as the downregulation of anti-apoptotic proteins such as Mcl-1 and survivin, thereby reducing drug resistance. Interestingly, loss of SOX2 expression weakened the cytotoxic effect of napabucasin, whereas reintroducing SOX2 restored drug sensitivity, underscoring SOX2's pivotal role in its activity. Animal studies further confirmed that napabucasin inhibited the growth of cisplatin-resistant xenograft tumors by promoting apoptosis and decreasing SOX2 expression. Overall, these results highlight napabucasin's ability to disrupt stemness pathways and overcome chemotherapy resistance, supporting its potential as a treatment option for refractory SCLC (Li et al. 2022). In addition to the canonical JAK–STAT pathway, IL-10 also engages the PI3K–AKT–mTOR cascade, which supports cell survival. A study on airway inflammation highlighted that IL-10 produced by B cells can drive allergic sensitization and proposed that disrupting the Bcl-3/IL-10 interaction might offer therapeutic benefit. The same review further

Table 5 Pharmacologic agents modulating IL-10 family signaling beyond receptor interactions

Patient/context	Intervention	Type of study	Molecular mechanism	Outcomes	Comparator/control	Ref
Hospitalized COVID-19 patients	Baricitinib (JAK1/JAK2 inhibitor)	Meta-analysis of RCTs	Suppresses STAT3 activity downstream of IL-10	Reduced mortality and reduced requirement for mechanical ventilation	Standard care alone	(Rajamanickam et al. 2023)
Hospitalized COVID-19 pneumonia	Tofacitinib (JAK1/JAK3 inhibitor) 10 mg	Double-blind RCT	Inhibits downstream inflammatory signaling, mitigates cytokine storm	28-day death/respiratory failure: 18.1% vs 29.0% (RR 0.63)	Placebo	(Guimarães et al. 2021)
Mechanically ventilated COVID-19	Ruxolitinib 15 mg	RCT	JAK inhibition attenuates cytokine storm	28-day mortality: 51% vs 70% (NS)	Placebo	(Rein et al. 2022)
COVID-19 & TB (preclinical/experimental)	Napabucasin (BBI608)	Computational and lab studies	STAT3 inhibitor; SARS-CoV-2 Mpro binding; activity vs *M. tuberculosis*	Strong docking to SARS-CoV-2 Mpro; anti-TB activity (MIC 2.5 → 0.3125 µg/mL with derivatives)	In-silico/experimental controls	(Li et al. 2019; Chowdhury et al. 2020)
Small cell lung cancer (cisplatin-resistant)	Nintedanib (tyrosine kinase inhibitor, 150 mg BID)	Preclinical in vitro and xenografts	STAT3 and stemness signaling inhibition (↓SOX2, c-Myc, Mcl-1, survivin)	Reduced proliferation, colony formation, induced apoptosis, inhibited xenograft growth	Cisplatin-resistant controls	(Li et al. 2022)
Progressive fibrosing interstitial lung diseases (non-IPF)	Nintedanib (tyrosine kinase inhibitor, 150 mg BID)	RCT	Inhibits VEGF, FGF, PDGF receptors; suppresses PI3K/Akt signaling (preclinical)	Slowed decline in FVC vs placebo; diarrhea in 72 percent dose reduction/interruption in 48 percent discontinuation 16.7 per 100 patient-years; AEs mainly mild-to-moderate	Placebo	(Wuyts et al. 2025)

described how, in preclinical models, broad-spectrum PI3K inhibitors (nintedanib, CL27c, LY294002) and isoform-specific agents (CZC24832, GSK-2269557, IPI-145) suppressed pro-inflammatory cytokines including IL-13, IL-6 and TNF-α, indicating that PI3K inhibition may influence IL-10 family signaling indirectly (Hendriks 2023; Li et al. 2023; Song et al. 2025). Nintedanib acts as an intracellular tyrosine kinase inhibitor, blocking VEGF, FGF, and PDGF receptors, and has demonstrated suppression of PI3K/Akt signaling in preclinical studies. A randomized controlled trial involving 663 individuals with progressive fibrosing interstitial lung diseases (excluding IPF) showed that nintedanib, administered at 150 mg twice daily, significantly slowed the decline in forced vital capacity (FVC) compared with placebo. Gastrointestinal events were common, with diarrhea reported in 72% of participants; nearly half (48%) required treatment interruption or dose adjustment, and it represented the leading cause of discontinuation. Overall, adverse effects were generally mild to moderate in severity, though diarrhea remained the predominant issue, and discontinuation occurred at a rate of 16.7 per 100 patient-years (Wuyts et al. 2025) (Table 5).

Limitations

While this review synthesizes the existing body of research, its scope is constrained by variability between experimental models and patient cohorts used in the studies. A substantial portion of the data originates from in vitro systems or animal models, which may not accurately reflect the complexities of human respiratory disease. The multifunctional nature of IL-10 family cytokines, combined with their shared receptor components, further complicates efforts to delineate the specific roles of individual cytokines. Moreover, the absence of robust, large-scale clinical trials directly evaluating these cytokines in respiratory conditions limits the clinical relevance and translatability of current insights. Variability in cytokine expression patterns and functional outcomes across disease subtypes and progression stages underscores the necessity for more individualized, precision-based therapeutic strategies.

Conclusion and future perspectives

The IL-10 cytokine family acts as a context-dependent regulator of airway immunity, orchestrating both inflammatory control and epithelial repair through overlapping yet distinct functions in health and disease. A consistent feature across chronic respiratory conditions is diminished IL-10 expression, whereas elevated levels of IL-19, IL-20, IL-24, and IL-26 drive epithelial damage, neutrophil recruitment, and airway remodeling. Among these mediators, IL-22 is particularly notable for its dual capacity to either promote barrier restoration or exacerbate pathological responses, highlighting the critical role of disease stage and context in therapeutic strategies. Overall, current evidence highlights the therapeutic potential of selectively modulating IL-10 family signaling to fine-tune immune responses in respiratory disorders. Promising approaches include boosting IL-22 activity to support epithelial healing, suppressing IL-26 in neutrophil-dominated inflammation, and exploiting IL-24's anti-tumor properties in lung cancer. The figures and tables in this review emphasize the importance of stratifying patients by cytokine signatures and inflammatory endotypes to maximize treatment benefit.

Looking ahead, research priorities should include the development of dynamic cytokine biomarkers, confirmation of their utility in large clinical populations, and integration of cytokine-based therapies with standard care. Precision targeting of IL-10 family pathways may provide a powerful means to restore epithelial integrity, control chronic inflammation, and improve clinical outcomes across diverse respiratory diseases.

Acknowledgements We thank all the authors who participated in this research.

Author contributions P.G. and M.A.K.T.: conceived and designed the manuscript. P.G., A.A., and S.A.: wrote the manuscript. M.A.K.T. and M.M.H.: methodology and drew the figures. P.G., M.A.K.T., and M.A.: revised the manuscript. D.S.L., H.K., and M.D.: supervision and project administration.

Funding Not applicable.

Data availability No data were used for the research described in the article.

Declarations

Conflict of interest The authors declare no competing interests.

Ethical approval and consent to participate Not applicable.

Consent for publication Not applicable.

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