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REVIEW

Advances in Interleukin-6 Family Cytokines and the Role in Respiratory Diseases

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Abstract: The interleukin-6 (IL-6) family of cytokines includes IL-6, IL-11, IL-27, IL-31, etc. These cytokines are intimately linked with inflammatory diseases and exhibit pleiotropic properties. Several factors, including air pollution, smoking, and an aging population, are contributing to the changing epidemiology of respiratory diseases. A high incidence of respiratory disease represents a significant burden on society and the economy. The prominent role of IL-6 family members in respiratory diseases has been extensively studied, and they influence the disease process through multiple mechanisms and has significant clinical relevance in respiratory diseases. Here, we describe the role of IL-6 family cytokines and their signaling pathways on various immune cells, as well as the research progress on IL-6 family cytokines in respiratory diseases in recent years. The aim of this review is to provide an in-depth analysis of the key role of the IL-6 family in respiratory diseases and to provide a solid theoretical basis for further research and clinical practice in this field.

Keywords: IL-6 family cytokines, respiratory diseases, biological function, inflammation, immune response

Introduction

Cytokines have been widely studied for their functional diversity for decades. As small (15–20 kD) soluble proteins, they fulfill a multitude of important functions in immunity, development, cancer therapy, cellular senescence and other processes by binding to the corresponding receptor to complete signal transduction or acting on distant target organs through the circulatory system.[1,2] Interleukin-6 (IL-6) family cytokines, as important members of interleukins, are not only involved in immune regulation, hematopoiesis and inflammatory processes, but are also closely related to the onset and progression of numerous diseases.[3]

The IL-6, IL-11, IL-27, IL-31, leukemia inhibitory factor (LIF), oncostatin M (OSM), ciliary neurotrophic factor (CNTF), cardiotrophin-1 (CT-1), and cardiotrophin-like cytokine factor 1 (CLCF1) are all part of the IL-6 family cytokines.[4] The IL-6 family plays a multifaceted and crucial role in the immune system, and is closely related to the activation and differentiation of immune cells and the regulation of immune responses, affecting the immune homeostasis of the body. IL-6, as a representative member of the family, initially known as B cell stimulatory factor 2 in 1976, that differentiates activated B cells into immunoglobulin-producing cells.[5] The molecule was first designated IL-6 in 1988. Following the detection of pathogens at the site of infection or tissue damage by Toll-like receptors (TLR), myeloid cells, including macrophages and dendritic cells, produce IL-6, which plays a critical role in the process of adaptive immune response, myeloma cells' proliferation and survival of plasma cells.[4] The sources and functions of the IL-6 family members are summarized in Table 1. Exploring the IL-6 family cytokines in detail will help to unravel its mechanism of action in the immune response and provide important clues to understanding the role it plays in disease processes.

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Table 1 Origin and Primary Function of IL-6 Family Members

IL-6 Family Cytokines	Source	Function	References
IL-6	T cells, B cells, monocytes, fibroblasts, keratinocytes, endothelial cells, cancer cells	Promote B cell differentiation; Participate in monocyte and T cell differentiation; Regulate the production of inflammatory mediators	[5]
IL-11	Epithelial cells, endothelial cells, bone marrow stromal cells, fibroblasts	Regulates B cell differentiation; promotes Hematopoietic stem cell proliferation, megakaryocyte maturation and platelet production	[3,6]
IL-27	Dendritic cells, monocytes, and macrophages	Promote the differentiation of initial CD4+T cells into Th1 cells; Enhance the cytotoxic activity of NK cells, inhibit tumor cell proliferation, and induce tumor cell apoptosis	[7]
IL-31	T cells	Inducing the production of various cytokines and chemokines, affecting the differentiation and function of T cells, and regulating the release of neurotransmitters	[8]
LIF	Embryonic fibroblasts, bone marrow stromal cells	Inducing hematopoietic differentiation of normal and myeloid leukemia cells; Inducing differentiation of neuronal cells; Regulating mesenchymal epithelial cell transformation	[9]
OSM	Monocytes	Regulate the proliferation of hematopoietic stem cells; Inhibit tumor cell proliferation; Regulate neuronal activity; Participate in liver development	[10]
CNTF	Neurons and retinal cells	Neuroprotection; regulate muscle fibers	[11]
CT-1	Cardiomyocytes, endothelial cells, adipocytes, osteoclasts, neuronal cells	Promote the survival of motor neurons; Promote the proliferation and activation of immune cells	[12]

The maintenance of human health depends on the proper functioning of the immune system. Imbalances in the immune response are frequently the underlying cause of a multitude of diseases.[13] Airborne inhalants interact with immune cells in the airways, resulting in disturbance to the human immune system that may lead to the development of disease. If the inflammatory response is out of control, the overproduction of cytokines can cause tissue damage. Therefore, elucidating the changes in immune-related factors in respiratory-related diseases can be of great assistance in subsequent clinical treatment. IL-6 family plays a crucial role in the pathogenesis, diagnosis, treatment, and prognosis of respiratory diseases. Several studies have shown that in the early stages of respiratory infectious diseases, IL-6 levels in serum and sputum increase significantly within hours after the onset of the disease. Real-time monitoring of IL-6 levels can provide key clues for early diagnosis, enabling early detection and treatment of the disease and effectively reducing the risk of disease progression. For example, monitoring of COVID-19,[14] asthma,[15] chronic obstructive pulmonary disease (COPD),[16] viral infection,[17] pulmonary tuberculosis,[18] acute respiratory distress syndrome (ARDS)[19] through the IL-6 family.

This paper will further elucidate the role of the IL-6 family in respiratory diseases, based on the molecular structure and pleiotropic properties of the IL-6 family of cytokines, as well as their relationship with immune cells.

IL-6 Family Cytokines and Their Receptors

The pleiotropic effects of IL-6 can be explained by the widespread expression of Glycoprotein 130 (gp130) on various cells, nearly all of IL-6 family cytokines utilize the common signaling receptor gp130.[20,21] IL-6 can signal through two distinct pathways: the classical pathway, which involves the binding of membrane-bound IL-6R (mIL-6R) molecules to gp130, and the trans pathway, which involves the binding of soluble IL-6R (sIL-6R) molecules to gp130.[22] The gp130-IL-6R-IL-6 complex is an IL-6-IL-6R complex that fuses two gp130 proteins.[23] This complex can activate Janus kinase (JAK), which in

turn activates three possible signaling pathways (Figure 1): Firstly, JAK induces autophosphorylation of tyrosine, which subsequently activates Signal transducer and activator of transcription 3 (STAT3);[24] Secondly, JAK activates the Ras/Raf pathway, causing hyperphosphorylation of MAPK and enhancing its serine/threonine kinase activity;[25] Finally, there is activation of the PI3K-PKB/Akt pathway,[26] In this pathway, JAK phosphorylates and activates PI3K, which then phosphorylates certain phosphatidylinositols to phosphatidylinositol (4,5)-bisphosphate (PIP2) and phosphatidylinositol 3-phosphate (PIP3) are also involved in this process. PIP3, in turn, phosphorylates and activates PKB/Akt, which is adsorbed by the cell membrane, thereby promoting NF-κB.[27] In addition, Zhang et al demonstrated that IL-6 can bind to CD5, activating STAT2 through gp130 and JAK2, and subsequently activating STAT3 which results in the expression of CD5 in a positive feedback loop. This process plays a pivotal role in the progression of cancer.[28] IL-6 exerts biological functions through multiple signaling pathways. It is reported that IL-6 has a protective effect on neuronal cells through the JAK/STAT3, MAPK/ERK and PI3K/AKT signaling pathways.[29] In addition, IL-6 increased autophagy in vitro in a dose-dependent manner and activated the JAK-STAT pathway to induce cardioprotective autophagy and signaling.[30] IL-6-induced activation of STAT3 or STAT5 is a key mechanism of PI3K inhibitor resistance in lymphomas, suggesting that IL-6 can be used as a potent biomarker to predict therapeutic response to PI3K inhibitors.[31]

In addition to IL-6, other IL-6 family members perform a variety of biological functions through their receptors. The principal sources of IL-11 are bones, connective tissues and tumor cells. As an important oncogene, IL-11 involved in the development of a variety of tumors.[32] In tumor cells, IL-11 receptor is highly expressed, enabling tumor cells to be highly sensitive to IL-11, further promoting tumor cell proliferation, invasion and metastasis, etc. Interleukin-27 is secreted by activated antigen-presenting cells, play a role in the regulating $CD4^+$ T cell differentiation and the immune response. IL-27 may exert pro-inflammatory or anti-inflammatory effects in a variety of autoimmune diseases.[33] IL-27 is composed of p28 and Epstein-Barr virus induced 3 (EBI3), and its receptors include glycoprotein 130 and Wsx1.[33] IL-31 plays an important role in the development of endometrial cancer, lung cancer, cutaneous T-cell lymphoma, follicular

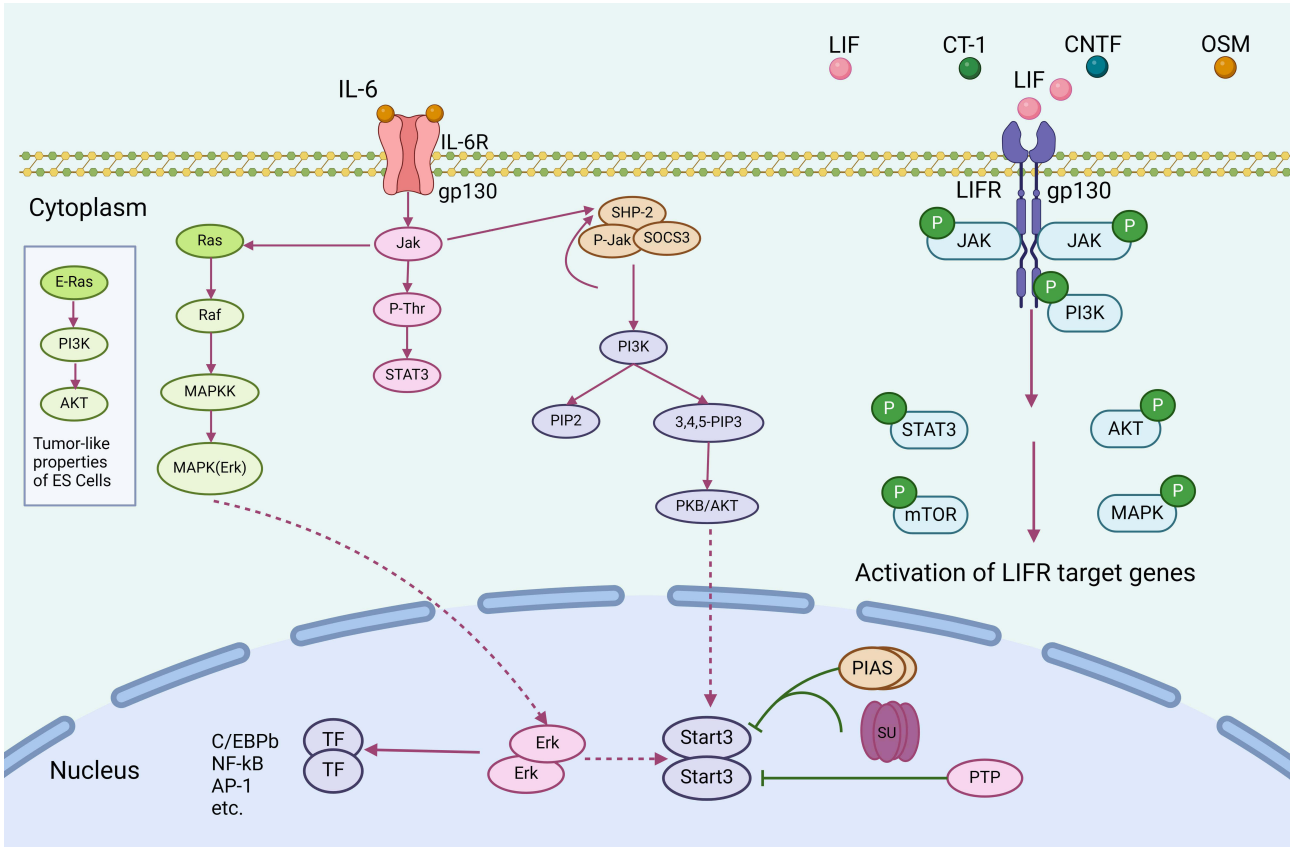

Figure 1 IL-6 family cytokine signaling pathway. Created in BioRender. Ji, T. (2025) https://BioRender.com/r61v345.

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B-cell lymphoma and other tumors.[34,35] The pleiotropic properties of IL-31 have been used in a wide variety of diseases, especially in atopic dermatitis, where IL-31R is a heterodimer, consisting of IL-31R bound to OSMR, and IL-31 binds first to IL-31R and subsequently to OSMR.[36,37]

OSM is a multifunctional cytokine that can promote tumor extracellular matrix remodeling, inflammatory response, differentiation, drug resistance and metastasis.[38,39] It stimulates the secretion of chemokines by vascular endothelial cells and the migration and adhesion of neutrophils to the vasculature.[40] OSM is a potential drug target due to its inhibitory effect on cell proliferation.[41] OSM is a heterodimeric receptor complex composed of gp130 and OSMR or LIFR, which are involved in intracellular signaling.[42] LIF is a member of the pleiotropic interleukin-6 cytokine family, and the LIF/LIF receptor signaling pathway plays an important role in the processes of tumorigenesis and progression [9]. CNTF functions through the CNTF receptor α (CNTFRα), which initiates multiple signaling pathways, including MAPK/ERK,[43] AKT/PI3K,[44] JAK/STAT.[45] It is involved in a variety of physiological processes, such as the survival and differentiation of many cells. CT-1 can form heterodimers with gp130 and LIFR, then exerts its function.[46] CLCF1 is a member of the IL-6 receptor family, and its receptor CNTFR can form a ternary complex with LIFR and gp130. CLCF1 is responsible for the phosphorylation of LIFR and gp130 through the activation of the CNTFR-LIFR-gp130 complex, which in turn initiates downstream signaling.[47]

The literature has demonstrated that IL-6, IL-11, CNTF, CLCF1, and CT-1 can bind to specific cytokines and present their ligands to a receptor complex containing gp130.[48] In contrast, LIF, OSM, IL-27 and IL-31 interact directly with signaling receptor subunits without the aid of ligand subunits.[49] IL-6 and IL-11 are the only IL-6 class cytokines found to be mediated by gp130 homodimers, and the remaining IL-6 class cytokines can be signaled via heterodimeric forms such as gp130/LIFR or gp130/OSMR. OSM can recruit two receptor complexes, namely heterodimers of LIFR-gp130 and OSMR-gp130. LIF and OSM can bind directly to their signaling receptor subunits without other α-receptor subunits[50,51] (Figure 2).

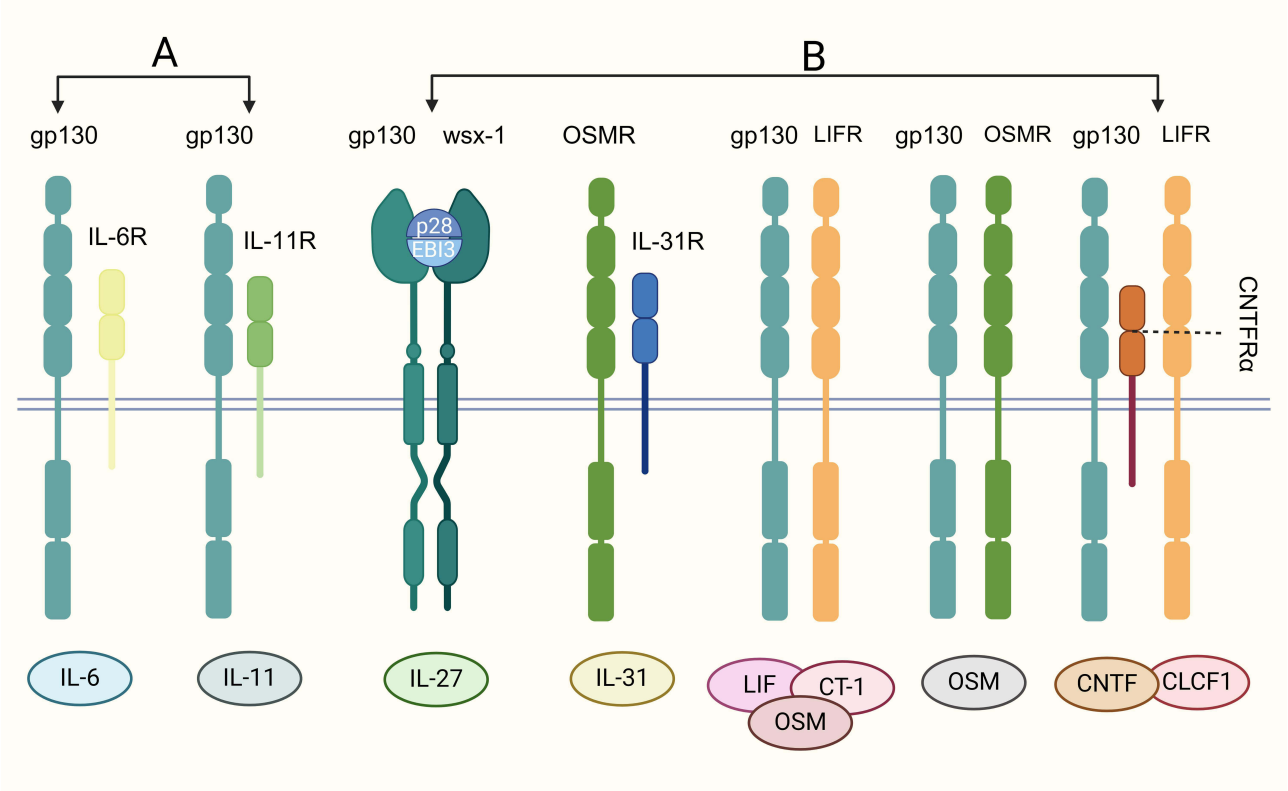

Figure 2 IL-6 family cytokines and their receptors. (**A**) Signaling mediated only by gp130. (**B**) Signaling mediated by gp130 and other receptors. Created in BioRender. Ji, T. (2025) https://BioRender.com/b59x959.

IL-6 Family Regulates Innate Immune Cells

The IL-6 family has been demonstrated to play a pivotal role in intrinsic immunity (Figure 3). An understanding of the role played by IL-6 family cytokines in intrinsic immunity enables a more comprehensive understanding of the pathogenesis of a wide range of diseases.

Neutrophils

The role of the IL-6 family cytokines on neutrophils is mainly reflected in its recruitment, activation and differentiation regulation. Researchers found that IL-27/IL-27R protect the host respiratory against chlamydial infection by inhibiting neutrophil recruitment.[52] In addition, Chiba demonstrated that IL-27 directly activates hematopoietic stem cells and promotes their differentiation into bone marrow precursor cells.[53] This process results in an increase in neutrophils due to acute osteomyelitis in mice during the phase of malaria infection. In an animal model of gram-negative pneumonia, the researchers found that OSM regulates neutrophil secretion of CXCL5 through the STAT3 signaling pathway, thereby

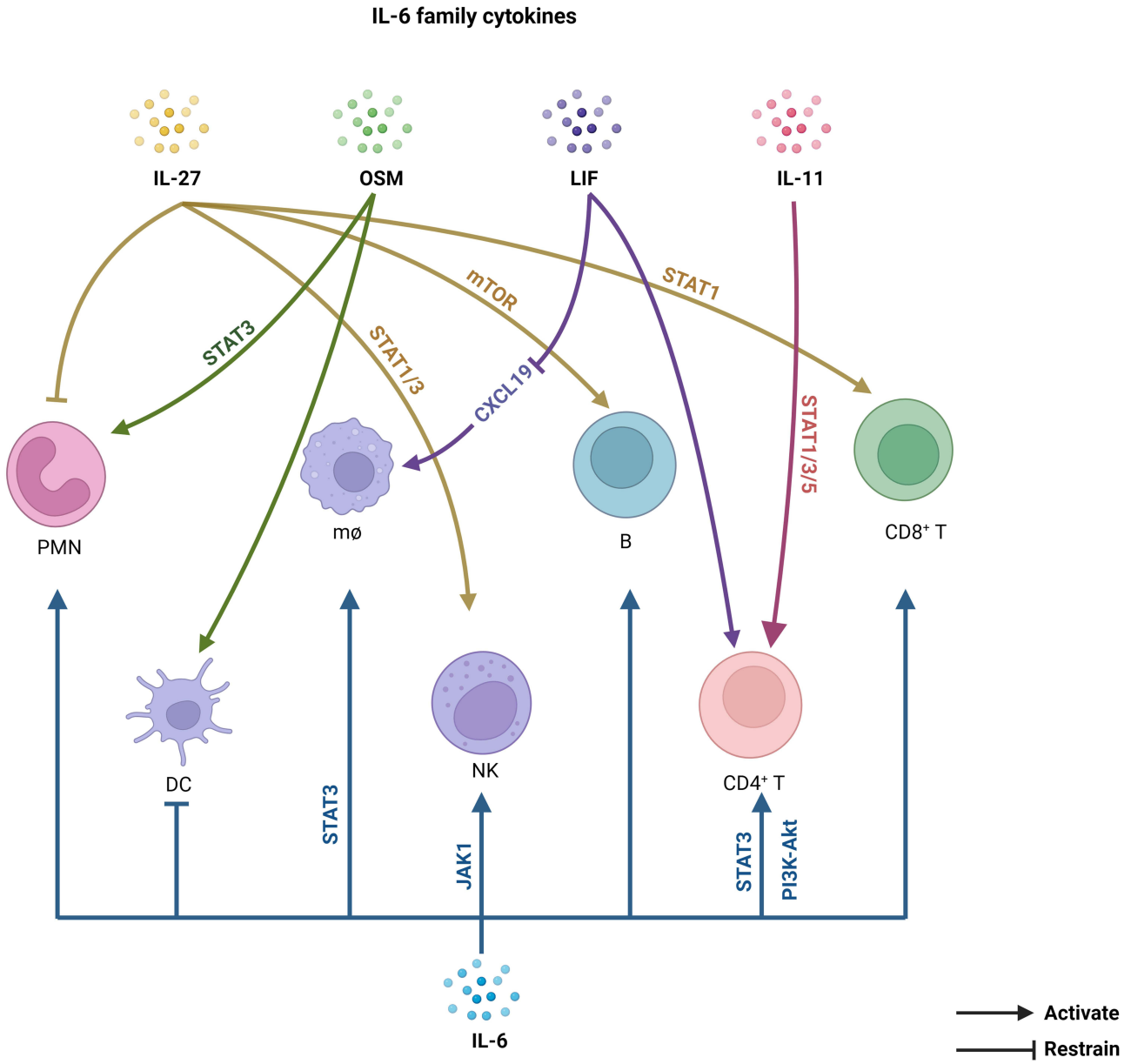

Figure 3 IL-6 family and immune cells. Created in BioRender. Ji, T. (2025) https://BioRender.com/h49b292.

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promoting neutrophil aggregation to the lungs.[54] IL-6 regulates both neutrophil activation and apoptosis and can lead to blood and neutrophil aggregation at sites of infection or trauma.[55] Human neutrophils express high levels of mIL-6R on their surface, and it is thought that they are the main source of sIL-6R. An investigation into the role of IL-6 in neutrophils may facilitate an appreciation of its mechanisms in disease development. Leukocyte infiltration can result in elevated levels of sIL-6R, which can facilitate leukocyte recruitment when it binds to IL-6. Additionally, it may also lead to activation of other chemokines. Thus, it promotes IL-6 trans-signaling in stromal tissue cells.[56] This regulatory mechanism ensures that the organism protects itself against excessive damage and promotes neutrophil recruitment to monocytes.[57] In the study of Haemophiles influenzae, the inflammatory cell death mode of neutrophils promotes the production of IL-6 trans-signaling (IL-6TS) in the lungs, through the induction of the production of sIL-6R by neutrophils. Meanwhile, chronic IL-6TS is not only an important marker of the inflammatory response, but also an important factor in promoting the inflammatory response and airway remodeling.[58]

Dendritic Cells

Dendritic cells (DCs) play an important role in a variety of infectious diseases, organ transplantation, and oncology. They present antigens to T cells and initiate inflammatory responses. The effects of the IL-6 family cytokines on dendritic cells include promotion of differentiation and maturation and enhancement of antigen presentation. Studies have shown that the effects of OSM on immune system are primarily achieved through the promotion of DCs maturation.[59] Infiltrating DCs represent a significant source of CNTFs in the cornea. Research has demonstrated that corneal damage in individuals with diabetes significantly impairs the regenerative capacity of the sensory organs, as well as the infiltration of DCs.[60] There is a wealth of evidence indicating that IL-6 plays a pivotal role in activating STAT3. Furthermore, STAT3 has been shown to possess the capacity to impede the differentiation, maturation and antigen presentation of DCs.[61] It has been demonstrated that under ex vivo conditions, IL-6 inhibits the production of DCs.[62] Moreover, IL-6 inhibits the activation of NF-κB and the expression of CCR7 in DCs, while promoting the expression of IL-1 receptor antagonists and tumor necrosis factor soluble p55 receptors.[63] Studies have shown that the development of certain diseases may be associated with abnormalities in IL-6-mediated DCs, including colorectal cancer,[64] breast tumor[65] etc.

Macrophages

LIF has been reported to regulate $CD8^+$ T lymphocyte infiltration in tumors by down-regulating CXCL19 and promoting the production of macrophages. Further studies have found that LIF inhibitors can play an anti-tumor role by neutralizing antibodies, enhancing T-lymphocyte recruitment, and binding to immune test sites.[66] A deficiency in the OSM receptor has been demonstrated to inhibit pressure-loaded cardiac hypertrophy, potentially through the macrophage OSM/LIFR/STAT3 pathway.[67] The IL-6-activated STAT3 signaling pathway has been reported to mediate inflammatory responses via macrophages.[68] Dharmesh Hirani has reported that hyperoxia can disrupt the interactions between macrophages and alveolar epithelial cells by increasing the levels of various macrophage-regulated cytokines, including IL-6, which promotes the differentiation of macrophages into a pro-inflammatory MI-like phenotype. He highlighted that hyperoxia results in an imbalance in the microenvironment of alveolar epithelial cells, with IL-6 plays an important role in this process.[69] Macrophages play a pivotal role in the pathogenesis of pulmonary fibrosis. In a murine model of macrophage inflammation established by the investigators, Xuanfei Baidu Decoction exhibited anti-inflammatory properties, reducing the expression of the type 2 macrophage marker protein CD206 and the lipopolysaccharide-induced IL-6.[70]

NK Cells

It has been reported that IL-27 activates NK cells via the STAT1/3 pathway, and then inhibit tumor growth by suppressing the immune response.[71] Concurrently, numerous studies have indicated that IL-6 exerts a certain inhibitory effect on the cytotoxic function of NK cells. NK and CD8T cells are unable to effectively kill antigen-presenting cells, resulting in a delayed interaction with the host and an exacerbation of the inflammatory response.[72] It was observed that NK cells exhibited a notable increase following the knockout of IL-6, while the inhibition of IL-6 was found to enhance the killing effect of NK cells in a transgenic mouse model of epidermal growth factor receptor mutant.[73] Xu [74] posited that the knockdown of IL-6 would result in alterations to the regulatory mechanism of the JAK/STAT3 pathway, thereby

reducing the expression of PD-L1 in castration-resistant prostate cancer cells and reducing the binding of IL-6 to PD-1 on the surface of NK cells, consequently affecting the content of NK cells in the tumor microenvironment. The secretion of IL-6 by tumor cells can inhibit the activity of NK cells through the JAK1 pathway.[75] Consequently, the inhibition of IL-6 and its downstream pathway can more effectively fulfil the role of NK cell immune surveillance, thereby significantly inhibiting tumor growth and metastasis.

IL-6 Family Regulates Adaptive Immune Cells

IL-6 induces B cells to mature into antibody-secreting cells, promotes the survival and maintenance of plasma cells.[55] The enhancement of humoral immunity by IL-6 is related to its effect on follicular helper T (TFH) cells. TFH is a specific subset of $CD4^+$T cells that express CXCR5 and are primarily distributed in B cell follicles. They can stimulate the proliferation of B lymphocytes and the class transformation of immunoglobulins.[76] Therefore, IL-6 can facilitate the connection between B cells and T cells, indicating that IL-6 plays an important role in regulating adaptive immune cells. The literature indicates that both LIF and IL-11 can promote the differentiation of Treg and TH2 cells. IL-6 can inhibit the development of Tregs and the differentiation of TH17 cells in conjunction with TGF-β, which may be related to the SOCS3 to directly inhibit the pro-TH17 activity of IL-6.[77,78]

CD4+T Cells

$CD4^+$T cells are a type of helper cell that differentiate into specific subsets when stimulated by antigens and respond to cytokine signals. IL-6 plays a pivotal role in determining the differentiation of T cells. The absence of IL-6 has been observed to favor the generation or expansion of antigen-specific Treg cells and to inhibit the development of effector T cell responses.[79] Recombinant human IL-6 can induce $CD4^+$T cells to secrete IL-10 and promote the production of Treg. The anti-inflammatory cytokine IL-10 can more effectively trigger STAT3 phosphorylation in Treg cells, resulting in a stronger response.[80,81] Harker[82] posited that the IL-6 signal subunit gp130 plays an important role in the survival and functional characteristics of virus-specific $CD4^+$T lymphocytes. In the context of chronic viral infection, IL-27 is necessary to maintain the number of virus-specific $CD4^+$T cells.[82,83]

CD8+ T Cells

The researchers observed that in animal models, IL-11 gene knockout resulted in an increase in $CD8^+$T cell infiltration and a reduction in the incidence of colon cancer.[84] IL-27 can activate $CD8^+$T cells through STAT1, inducing transcription factors such as T-bet and EOMES, and plays a role in the anti-tumor immune response.[85] The IL-6-dependent STAT3 signaling pathway inhibits the translocation of FOXO1 in the nucleus, promotes the maturation of memory T cells,[86] and regulates memory $CD8^+$T cells.[87] When the function of $CD8^+$T cells is inhibited, the overexpression of SUMO2 can activate the IL-6 signaling pathway, thus demonstrating that reliance on IL-6 can improve the biological function of $CD8^+$T.[88] IL-6 specifically induces STAT8 activation in naive $CD3^+$T cells and participates in the activation of $CD8^+$T cells.[89] Regulate the secretion of IL-6 to control the transformation of $CD4^+$T lymphocytes to Foxp3+Tregs, enhance the inhibitory effect on $CD8^+$T lymphocyte proliferation in vitro, and regulate the number of Treg in the tumor microenvironment.[86] This represents a novel approach to T cell immune-related immunotherapy. IL-6R is a universal marker used to describe the cytotoxicity of helper T cells, Tc1 and Tc17 cells exhibit classic cytotoxic characteristics related to $CD8^+$T cells and stably express CD8 family transcription factor RUNX3.[90] In pre-clinical models, the combined use of PD-L1 and IL-6R has been demonstrated to result in tumor regression and a significantly improved anti-tumor $CD8^+$T cell response compared to anti-PD-L1 alone.[91]

B Cells

B cells are capable of differentiating into plasma cells and producing antibodies, which has a beneficial effect on the host.[92] As the primary source of IL-6, B cells can facilitate the transformation of TFH and TH17 cells and induce the differentiation of plasma cells. IL-6 derived from effector B cells plays an important role in the pathogenesis of autoimmune diseases such as multiple sclerosis[93] and systemic sclerosis.[94] Xiao[95] demonstrated that defective B cells impair the production of IL-10 and enhance the synthesis of IL-6, IL-1β and IL-12, which stimulate TH1 and TH17

responses and inhibit the production of Treg cells. This, in turn, exacerbates the severity of autoimmune encephalomyelitis and enhances graft rejection. In addition, the secretion of IL-6 by B cells may be involved in the occurrence and development of fibrosis.[96] Some literatures have indicated that while the stimulation of the agonist R848 through the TLR7 pathway can induce the production of IL-10 and IL-6 in healthy B cells, the production of IL-10 in B cells in children with autoimmune dermatomyositis is inhibited, while the production of IL-6 is still increased.[97] Furthermore, IL-6 can stimulate B cell proliferation, promote plasma cell production and antibody production, and may induce pathogenic IgG autoantibody response.[98] The researchers discovered that the augmentation of glycolysis in B cells in rheumatoid arthritis induced by IL-27 may result in the overactivation of B cells by activating the mTOR signal pathway.[99]

The Role of IL-6 Family Cytokines in the Respiratory System

IL-6 family cytokines play important roles in the pathogenesis of multitude of diseases. Consequently, a comprehensive investigation of the interrelationship between IL-6 family cytokines and their receptors and the development of disease will facilitate the formulation of more efficacious clinical treatment strategies. Respiratory diseases have become a significant public health concern, with high morbidity, disability and mortality rates. These diseases impose a a significant burden on families and societies.[100] An understanding of the role of IL-6 family cytokines in respiratory diseases will facilitate the development of more effective strategies for the management of these conditions (Table 2 and Figure 4).

Covid-19

Due to its intricate pathogenesis, Pneumonia is the most prevalent infectious disease globally. Consequently, the diagnosis and prognosis of the disease cannot be fully evaluated and accurately determined.[107] COVID-19 is an acute respiratory infectious disease caused by SARS-CoV-2.[108] Studies have demonstrated that the concentration of IL-6 in the serum of critically ill patients increased significantly, and that the death cases exhibited an abnormal increase. This suggests that IL-6 can be used as an important index to predict the disease development and has important clinical significance for follow-up treatment.[109] Tocilizumab can be used to treat patients with severe COVID-19 by blocking signaling through IL-6R.[110] In COVID-19, IL-6 has been demonstrated to induce a number of abnormalities in the immune response. These include the dysfunction of NK and $CD8^{+}$T cells, accompanied by a down-regulation of perforin

Table 2 The Role of IL-6 Family Cytokines in the Respiratory Diseases

Disease	Function	Reference
COVID-19	1. IL-6 can obviously induce the disorder of the immune response. On the one hand, IL-6 can cause the dysfunction of NK and CD8T cells, accompanied by the down-regulation of perforin and granzyme. On the other hand, IL-6 can also inhibit the differentiation of regulatory T cells. 2. The level of IL-27 is closely related to the high mortality of COVID-19.	[101]
Lung cancer	1. The increase of IL-6 will lead to the excessive activation of JAK/STAT3 pathway, thus promoting the proliferation, angiogenesis and metastasis of tumor cells. 2. The carcinogenic effect of IL-11 is related to STAT3.	[102]
COPD	1. IL-6 is a marker of chronic obstructive pulmonary disease complicated with neutrophils and can lead to inflammatory response and airway remodeling. 2. The expression of IL-11Rα was decreased in the COPD.	[58,103]
Asthma	1. IL-6 can mediate the occurrence and development of hormone resistant asthma by regulating the secretion of HMGB1 and phosphorylation of STAT3. 2. The increase of IL-11 level is positively correlated with the severity of the disease.	[104,105]
Pulmonary fibrosis	1. Inhibition of IL-6/STAT3 pathway can prevent inflammation and pulmonary fibrosis induced by macrophages. 2. IL-11 can promote the proliferation of resting fibroblasts and transform them into invasive fibroblasts and induce the process of epithelial-mesenchymal transformation.	[70,130]

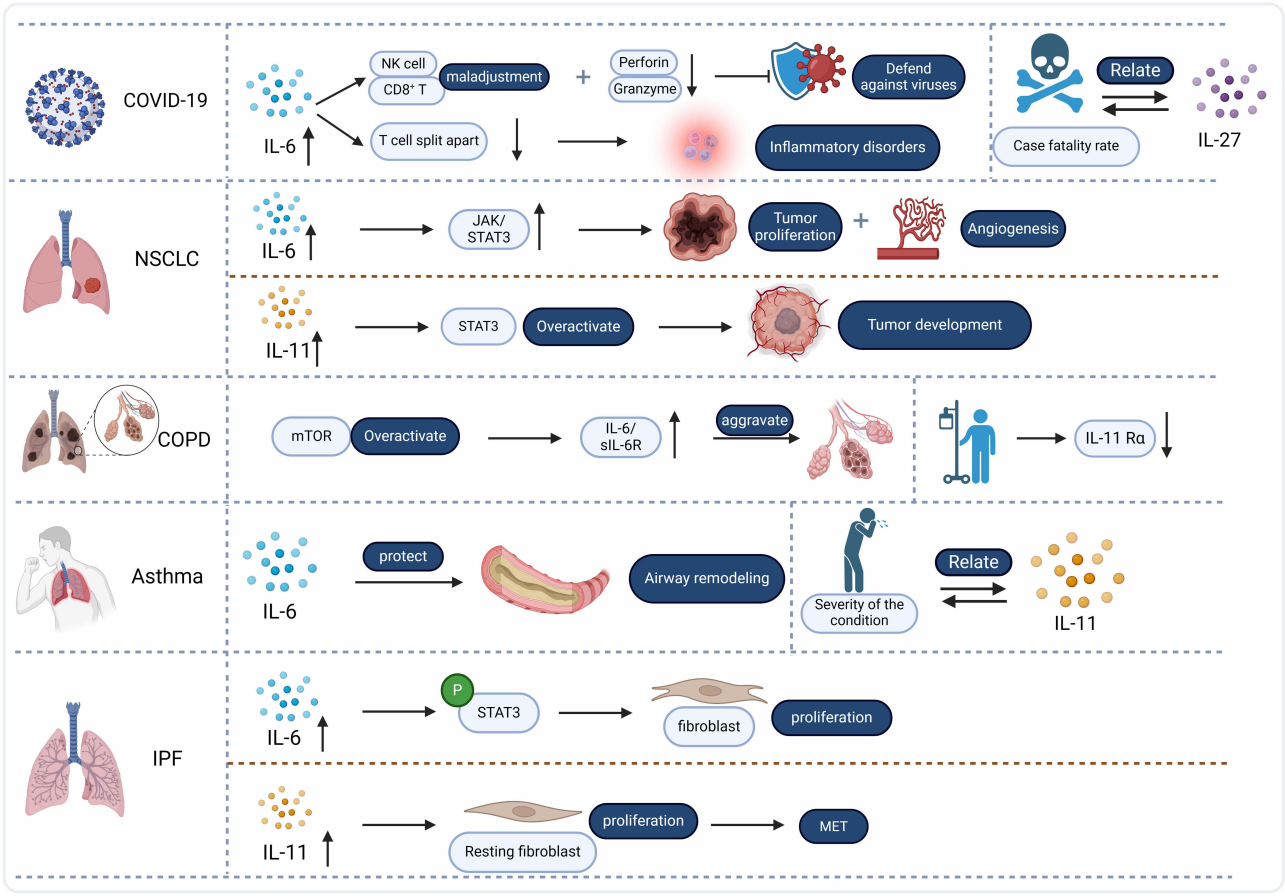

Figure 4 The role of IL-6 family cytokines in the respiratory diseases. Created in BioRender. Ji, T. (2025) https://BioRender.com/v73l303.

and granzyme,[101] which impairs the antiviral defense response. Conversely, IL-6 also inhibits the differentiation of regulatory T cells[111] and causes uncontrolled inflammation. Previous studies have demonstrated that the level of IL-27 is significantly elevated in non-survivors of COVID-19, with a strong correlation between elevated IL-27 levels an high mortality rates.[112] It is noteworthy that a separate study found that the concentration of IL-27 among survivors of COVID-19 was considerably higher than that observed in patients who succumbed to the disease.[113] It is, of course, possible that the observed difference may be attributed to the differing periods over which the subjects were studied. Nevertheless, this is an important area that requires further investigation.

Lung Cancer

Lung cancer is the most prevalent malignant tumor worldwide, with the highest mortality rate.[114] It is classified into two main categories: non-small cell lung cancer (NSCLC) and small cell lung cancer. NSCLC accounts for 85% of all cases. The elevated level of IL-6 in the peripheral blood of patients with non-small cell lung cancer is associated with the prognosis. Some studies have indicated that IL-6 and its receptor components gp80 and gp130 are overexpressed in non-small cell lung cancer, suggesting that the downstream molecule-mediated IL-6 pathway may play an important role in the occurrence and development of NSCLC.[115] In a study by Wen Liu,[116] it was proposed that IL-6 regulates the expression of NF-κB and up-regulates TIM-4, which enhances the ability of lung cancer cells to invade and metastasize. In the tumor microenvironment, the elevation of IL-6 results in the overactivation of the downstream JAK/STAT3 pathway, thereby facilitating tumor cell proliferation, angiogenesis and metastasis,[102] However, the precise mechanism of IL-6 in tumor-infiltrating immune cells remains unclear. The IL-6/STAT3 signaling pathway plays an important role in the tumor microenvironment. It has been demonstrated that the block of the IL-6/STAT3 pathway can prevent the

cachexia induced by Kras mutation in lung adenocarcinoma.[117] STAT3 exerts negative regulatory effects on neutrophils, NK cells, effector T cells and DCs, while exerting positive regulatory effects on Treg cells and myelogenous suppressor cells.[118] IL-11 is a significant factor in tumor promotion. Zhao proposed that overexpression of IL-11 has a tumor-promoting effect on A549 and H1299 lung cancer cell lines.[119] In a subsequent study, it was found that both miR-495 and miR-5688 could upregulate the expression of IL-11, thereby promoting the occurrence and development of tumor.[120] It is proposed that IL-11 may be a pivotal factor in the promotion of tumor growth in a hypoxic environment. The carcinogenic effect of IL-11 is mechanistically related to STAT3.[121,122] The key participants of the targeted signal network have the potential to significantly inhibit metastasis. Focusing on the role of IL-6 family cytokines and their signaling pathways in lung cancer may have important clinical implications.

Copd

COPD is a heterogeneous, universal, and preventable disease. The principal manifestations are persistent respiratory symptoms and airflow limitation.[123] The researchers observed a reduction in the expression of IL-11Rα in patients with COPD, and identified a correlation between the polymorphism of the IL-11 promoter region and the pathogenesis of COPD.[103] Celli conducted a longitudinal study on inflammatory markers in patients with COPD. The results demonstrated that the concentration of IL-6 in serum increased after three years, which was associated with an increased mortality rate in COPD.[124] In the mouse emphysema model, the expression of sIL-6R and IL-6 is related to the overactivation of the mTORC1 signal pathway.[125] IL-6TS is implicated in the pathophysiology of COPD. Winslow[58] demonstrated that IL-6TS is a marker of chronic obstructive pulmonary disease complicated with neutropenia and can lead to inflammatory response and airway remodeling. IL-6 has been demonstrated to promote the proliferation, viability and anti-apoptosis ability of cultured human and mouse smooth muscle cells, with these effects dependent on the activity of STAT3-AKT and the expression of FOXO1. Conversely, the absence of IL-6 in body fluid has been demonstrated to inhibit the excessive proliferation of smooth muscle cells, increased airway resistance and bronchial and vascular remodeling in offspring.[126] The researchers confirmed that the release of MCP-1 from pulmonary vascular endothelial cells is a consequence of the IL-6 pathway, rather than other pathways.[127] Previous studies have found that Asp358Ala, a functional variant in the IL-6R gene, regulates IL-6 signal transduction, the level of MCP-1 in pulmonary vascular endothelial cells is significantly elevated in the context of Asp358Ala gene knockout. Furthermore, IL-6 inhibitor Tocilizumab has been shown to exert a pronounced downregulation of MCP-1 expression, thereby suggesting that IL-6 may potentially mediate pulmonary vascular inflammation through Tocilizumab.[128] The target of IL-6-related pathway has been preliminarily confirmed, but further studies are required to elucidate the role of IL-6 transcription factors and related pathways in the occurrence and development of COPD in a larger cohort of patients.

Asthma

Asthma is a disease that poses a significant threat to human health, affecting approximately 347 million individuals across all age groups.[129] The level of IL-11 in patients with moderate and severe asthma was elevated, and it was positively correlated with the disease severity.[105] IL-11 can inhibit TH1 polarization and promote TH2 polarization. It can also stimulate the secretion of TH2 cytokines such as IL-4 and IL-10, commonly associated with a TH2 response in asthma.[106] The role of the IL-6 signaling pathway in the pathogenesis of asthma has become increasingly prominent.[130] Some experiments have shown that IL-6 knockout mice exhibited pronounced airway hyperresponsiveness, eosinophil accumulation, and a TH2 response.[131] Some researchers have demonstrated that toluene diisocyanate (TDI) can up-regulate the expression of p-STAT3 in the lung, which can be inhibited by IL-6 repressor antibody and anti-IL-6 receptor. It is therefore proposed that IL-6 can regulate the phosphorylation of STAT3, thereby mediating the occurrence and development of hormone-resistant asthma. Furthermore, blocking IL-6 signaling is of great significance in the prevention and treatment of airway inflammation and remodeling induced by TDI.[104] Excessive inflammation can cause tissue damage and exacerbate infection.[132] Conversely, the body's response to allergic inflammation can prevent respiratory tract infection.[133] Although the IL-6 effect mainly comes from its immune response, a trans-signal transduction pathway of IL-6R will produce opposite curative effect.[134] Therefore, it is of great significance to maintain the equilibrium of IL-6 within the body.

Pulmonary Fibrosis

Fibrosis is defined as the pathological accumulation of extracellular matrix during the repair of wounds. This process involves the transmission of signals between numerous cells and tissues. Idiopathic pulmonary fibrosis (IPF) is a progressive lung disease with a high mortality rate and a lack of effective treatment.[135] In vitro studies have demonstrated that IL-11 can promote the proliferation of resting fibroblasts, transform them into invasive fibroblasts, and induce the process of epithelial-mesenchymal transformation.[136] In a mouse model of IPF, the inhibition of IL-11 or the specific blocking of IL-11 pathway has been shown to reduce the infiltration ability of fibroblasts in vitro and to reverse pulmonary fibrosis and inflammation.[136,137] Furthermore, it has been demonstrated that macrophages from diseased lungs secrete sIL-6R α and promote IL-6 transcription, which plays a key role in the pathogenesis of pulmonary fibrosis.[138] Activated M2 macrophages can feedback regulate the invasion and metastasis of trophoblasts,[139] and macrophages promote fibrosis by releasing inflammatory factors and profibrotic factors.[140] Milara[141] found that IL-6 can promote the proliferation and migration of primary cultured human fibroblasts by STAT3 phosphorylation. Therefore, the researchers postulated that the inhibition of IL-6/STAT3 pathway can prevent inflammation and pulmonary fibrosis induced by macrophages.[70] IL-6Rα is found in macrophages and induces the expression of sIL-6Rα. Its role in pulmonary fibrosis is unclear, but it is highly expressed in patients. It is an important marker that warrants further study.[138] In addition, OSM contributes to the accumulation of pro-fibrotic macrophages and the enhancement of pulmonary fibrosis, and therapeutic strategies targeting OSM may be beneficial in preventing the accumulation of M2-like macrophages and the progression of fibrotic lung disease.[142]

Discussion

The level of IL-6 family members has diagnostic and prognostic value, with the main member of IL-6 playing a pivotal role in the body. IL-6 plays a pivotal role in maintaining the body's homeostasis. Signalling pathways associated with IL-6 provide promising targets for therapeutic intervention in inflammatory diseases and tumours.[143] In the event of an infection or tissue damage, IL-6 is released rapidly, initiating the acute phase and immune response.[144] IL-6 has a dual effect (pro- and anti-inflammatory). IL-6 activates the downstream JAK/STAT3 signalling pathway, which promotes the inflammatory response. Conversely, IL-6 binding to sIL-6R activates the gp130 receptor, which is widely expressed on the membrane, and thus regulates the anti-inflammatory response. However, when there is an imbalance in the levels of IL-6 in the body, this can lead to the development of several different diseases. Therefore, it is important to understand how IL-6 maintains a dynamic equilibrium within the body.

At present, drugs targeting immunomodulatory factors have achieved good results in a variety of clinical settings. A large number of scholars have mainly focused on the blocking therapy of IL-6 and IL-6-related signal pathways, and have successfully applied drugs to many chronic immune diseases. Furthermore, it is employed in treatment of numerous diseases, including rheumatoid arthritis, juvenile idiopathic arthritis, Karsman's disease, and others. Tocilizumab is a novel humanized monoclonal antibody against IL-6 receptor. It has been demonstrated to be efficacious in the treatment of Castleman's disease in numerous cases.[145,146] A literature report in 2004 proved[147] the efficacy of Tocilizumab in the treatment of Crohn's disease. However, due to the occurrence of gastrointestinal perforation in several parallel arthritis studies,[148] the use of Tocilizumab in the treatment of Crohn's disease has been limited. Consequently, research on the efficacy of Tocilizumab in the treatment of Crohn's disease has been largely stalled. A review of numerous studies conducted both domestically and internationally indicates that IL-6 blocking plays a significant role in the pathogenesis of a multitude of diseases. However, due to inherent limitations in both cognitive and technical domains, it is challenging to develop an accurate and effective treatment for a specific disease. Nevertheless, the aberrant expression of IL-6 cytokines has been observed in a spectrum of diseases, suggesting that this could serve as a potential starting point for the identification of more efficacious therapeutic strategies. There is a lack of small molecule inhibitors targeting IL-6 on the market. By focusing on the design and optimization of synthetic small molecules to complement or even replace current monoclonal antibody-based therapies.[149] By resolving the mechanism of action of IL-6, we can perform more effective and personalized IL-6-targeted therapies and improve patient prognosis in IL-6-mediated diseases.

Respiratory disease is a prevalent ailment that poses a significant threat to human health. Although there is a wide range of treatment options and the technology is well-developed, it is challenging to achieve accurate treatment outcomes. IL-6 has the capacity to activate both human innate and acquired immune responses, as well as exerting specific biological effects contingent upon the prevailing conditions. IL-6 has important research significance in the development, diagnosis, treatment and prognosis assessment of respiratory diseases. In addition to the major respiratory diseases mentioned above, the role of IL-6 family members in other respiratory diseases has also been reported. A recent Mendelian randomization study has shown a causal relationship between reduced IL-6 signaling and reduced risk of tuberculosis, suggesting that IL-6 antagonists do not increase the risk of tuberculosis but should be investigated as therapeutic adjuvants.[150] The circNOX4/miR-329-5p/FAP axis promotes NSCLC progression through induction of IL-6.[151] In addition, the researchers found in a mouse model that targeting progranulin attenuated silica particle-induced lung inflammation and fibrosis by reducing IL-6.[152] Aspirin-exacerbated respiratory disease (AERD) is a serious condition involving type 2 inflammatory dysregulation. It has been found that patients with AERD have elevated IL-6 and OSM in nasal fluid, both of which correlate with nasal albumin levels and may contribute to pathology by negatively impacting epithelial barrier function.[153] It will be seen from this that the complex role of IL-6 in disease requires in-depth studies combining immunology, molecular biology, clinical medicine, and other disciplines to reveal its diverse biological functions. With a deeper understanding of IL-6's mechanism of action, targeted drugs may be developed to reduce side effects and improve therapeutic efficacy.

Overall, the study of the IL-6 family in respiratory diseases is significant, not only in helping to understand the pathogenesis and progression of the disease, but also in providing new targets and strategies for clinical treatment. Future studies can further explore the interactions of the IL-6 family with other factors and utilize the double-edged sword of IL-6 to develop more effective therapeutic approaches.

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Disclosure

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