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REVIEW ARTICLE

Role of IL-18 in Asthma

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ABSTRACT

Asthma is a common heterogeneous disorder characterized by chronic airway inflammation, remolding and hyperresponsiveness. Although substantial advance has been achieved in understanding its complex pathogenesis, which involves genetic factors, environmental exposures, and immune system imbalances, the effective clinical therapeutics of asthma remains challenging. IL-18, a pleiotropic cytokine of IL-1 superfamily produced mainly by monocyte-macrophage system, is an imperative participant in the pathology of asthma through interacting with IL-18R, and is likely to be the potential targets for the diagnosis and therapeutics of asthma. In this review, we addressed briefly the phenotypes and endotypes of asthma. Then we introduced the regulation mechanisms of the IL-18 production, and summarized the roles of IL-18 in the pathogenesis of different asthma endotypes, in particular emphasizing the roles of IL-18 alone and IL-18 in synergy with other cytokines. Furthermore, we highlighted the effects of IL-18 on airway pathological characteristics and disorder severity of asthma. Finally, we discussed the future research directions and challenges based on IL-18 therapy, which is expected to provide novel ideas for the precise treatment of asthma.

Keywords: IL-18; asthma; pathogenesis; diagnosis; therapy

1. Introduction

Asthma is a chronic respiratory disorder affecting over 300 million people worldwide, and its prevalence is increasing in economically developing counties [1]. The main pathologic characteristics of asthma are chronic airway inflammation, airway remodeling and hyperresponsiveness, which lead to the recurrent episodes of wheezing, breath shortness, chest tightness, cough [2], and even life-threatening acute respiratory distress [3]. The pathogenesis of asthma involves the interplay of genetics, environment and microbiota of host gut and airway [4]. Additionally, imbalanced immune responses induced by various cells such as macrophages [5], innate lymphoid cells (ILC) [6], helper T cells [7], regulatory T cells (Treg) [8] and natural killer (NK) T cells [9], lead to the release of inflammatory cytokines and aggravation of inflammation in asthma. Therefore, the complex pathological mechanisms of asthma bring challenges to it's clinical treatment.

IL-18, a pleiotropic cytokine of IL-1 superfamily, exerts its biological activity by interacting with IL-18 receptor α (IL-18Rα)/IL-18Rβ complex, and thus activating downstream signaling pathways [10]. Recently, the role of IL-18 in asthma has attracted much attention. This review aims to analyze the role of IL-18 in the pathogenesis of asthma, and systematically explore the effect of IL-18 on airway pathology in asthma. Meanwhile, we will also evaluate the possibility of IL-18 as a potential therapeutic target, particularly its application prospects in alleviating asthma symptoms and blocking inflammatory signaling. This review hopes to provide novel ideas for future research, reveal the potential of IL-18 in the treatment of asthma, and promote the development of precise therapeutics.

2. Asthma phenotypes and endotypes

2.1 ASTHMA PHENOTYPES

Asthma is a heterogeneous respiratory condition, and asthma phenotype refers to observable characteristics resulting from the interaction between individual genetics and environment. Asthma is classified into two major phenotypes, allergic asthma and non-allergic asthma, based on observable clinical characteristics such as onset age, triggers and symptoms. In general, early-onset allergic asthma is most prevalent during childhood and into young adulthood, after which the non-allergic form predominates among adults [11].

2.2 ASTHMA ENDOTYPES

Asthma endotypes are defined based on underlying molecular and immunological mechanisms. Understanding asthma endotypes is crucial for the development of targeted therapies and personalized treatment strategies. As suggested by Hammad H and Lambrecht BN [12], the chronic airway inflammation in approximately a half of asthmatics is driven by IL-4-, IL-5- and IL-13-producing Th2 cells or ILC2, which is defined as type 2-high asthma. These type 2 cytokines promote pathological features of the asthma such as eosinophilia, mucus hypersecretion, airway hyperresponsiveness, IgE production and susceptibility to exacerbations. Type 2-low asthma is dominated by non-type 2 immune responses such as Th1 and Th17 pathways, and involves IL-1β, IL-6 and neutrophilic inflammation. Usually, patients with type 2-low asthma are characterized by unresponsiveness to corticosteroids and resistance to asthma therapy.

3. Biological functions of IL-18

3.1 IL-18 PRODUCTION AND REGULATION

IL-18 is constitutively expressed by monocytes, macrophages and epithelial cells. In addition, blood $CD4^+$ T cells [13], basophils, mast cells [14], neutrophils and B cells [15] also express IL-18. IL-18 is synthesized as an inactive precursor in the cytoplasma, while the activation and release of IL-18 depends on caspase-1, the central component of the inflammasome, which cleaves IL-18 precursor into biologically mature IL-18 [16]. The production of IL-18 is regulated by multiple signaling pathways. On the one hand, extracellular pathogen invasion and endogenous damage factors such as heat shock proteins and uric acid crystals, activate Toll-like receptors (TLR) and NOD-like receptors (NLR), which subsequently induces the activation of caspase-1 via downstream signaling cascades [17], and directly promotes the activation and release of IL-18 [18,19]. Indeed, TLR and NLR also act as a signal amplifier in inflammatory response by regulating the secretions of other proinflammation cytokine such as IL-1β, TNFα and IL-6 [18-21]. On the other hand, the excessive activation of TLR and NLR induces the secretion of IL-18 [22], and further exacerbates airway chronic inflammation and hyperresponsiveness in asthma, which seems to be ameliorated by blocking TLR- and NLR-related pathways [23-26]. Therefore, an in-depth understanding of the regulatory mechanism of IL-18 is helpful to reveal its role in asthma and provide potential therapeutic targets for asthma.

3.2 INTERACTION AND COMPARISON OF IL-18 WITH OTHER CYTOKINES

As presented in Table 1, IL-18 closely interacts with various cytokines, and particularly exhibits its proinflammatory properties in synergy with IL-12, which induces the production of IFNγ [27], even Th2-type cytokine IL-9 and IL-13 [28] from Th1 cells. IFNγ is a classical Th1-type cytokine that helps defend against pathogens such as bacteria and viruses, also exacerbates the chronic inflammation in type 2-low asthma by recruiting neutrophils [7].

Table 1: Interaction of IL-18 with other cytokines and their resultant effects in asthma

Cytokines	Cell reactions	Involvement in asthma endotypes
IL-18/IL-18+IL-2 /IL-18+IL-3	Induction of IFNγ production from Th1 cells and IL-4, IL-5, IL-9 and IL-13 from Th2 cells, mast cells and eosinophils.	Involved in type 2-high asthma
IL-18+IL-4	Induction of IgE production from B cells.	Involved in type 2-high asthma
IL-18+IL-5	Induction of eosinophil development, transformation and maturation.	Involved in type 2-high asthma
IL-18+IL-12	Induction of IFNγ, IL-9 and IL-13 production.	Involved in both type 2-high and -low asthma
IL-18+IL-15	Induction of NK cell proliferation.	Involved in both type 2-high and -low asthma
IL-18+IL-12+IL-15	Induction of NK cell death.	Involved in both type 2-high and -low asthma
IL-18+IL-23	Induction of Th17 cell differentiation, and IL-17A and IL-22 production.	Involved in type 2-low asthma

Intriguingly, studies involves type 2-high asthma demonstrate that IL-18 alone or in synergy with IL-2 or IL-3 is also capable of activating Th2 cells, mast cells and eosinophils, and thus inducing the production of IL-4, IL-5, IL-9 and IL-13, which mediate airway inflammation and hyperresponsiveness by promoting eosinophil recruitment and airway mucus secretion [27,29]. It is also reported that IL-18 in synergy with IL-4 induces the production of IgE from B cells, and with IL-5 induces eosinophilic inflammation [27].

On the other hand, studies involving type 2-low asthma demonstrate that IL-18 alone or in synergy with IL-23 promotes the differentiation of Th17 cells, induces IL-17A and IL-22 production and thus contributing to airway hyperresponsiveness and neutrophilic airway inflammation [30-33].

Furthermore, IL-18 also acts synergistically with IL-15 in stimulating NK cell proliferation [34]. NK cells may partially promote airway inflammation in both type 2-high and -low asthma by secreting IL-4, granzyme B and IFNγ, and by inhibiting eosinophil apoptosis [35]. However, IL-18 in synergy with IL-12 and 15 induces NK cell death [36].

Therefore, IL-18 not only triggers the inflammatory response independently, but also forms a multi-factor inflammatory network by cooperating with other cytokines in asthma according to its cytokine milieu. This is rather different from other proinflammatory cytokines such as IL-4, IL-25, IL-33 and TSLP, which drive only Th2 responses [7], suggesting the important node of IL-18 in asthma. Hence, inhibition or neutralization of IL-18 brings potential therapeutic value for achieving more comprehensive asthma control.

4. The role of IL-18 in the pathological characteristics of asthma

4.1 IL-18 AND AIRWAY INFLAMMATION

Airway inflammation in asthma results from various cellular inflammation. It has been demonstrated that IL-18 alone activates neutrophils to release CXCL8 [37], activates airway epithelial cells to release MCP-1α [38], activates eosinophils to release IL-6, CXCL8 and CCL2 [39,40], and in synergy with anti-CD3 induces Th1 cells to release CXCL8 and IL-13 [41]. These cytokines can induce substantial neutrophil and eosinophil recruitment in the airway, and thereby exacerbating the local inflammatory response. In fact, IL-18 also enhances eosinophil survival [39] though without modulation effects on neutrophil survival [37].

Additionally, elevated level of IL-18 in asthma patients induces mast cells and basophils to release a variety of mediators such as histamine and prostaglandins, leukotrienes [42], consequently leading to increased vascular permeability, mucosal edema and mucus secretion, and thereby exacerbating airway constriction and hyperresponsiveness. More importantly, IL-18-deficient mice exhibit diminished chronic inflammation and airway remodeling in ovalbumin (OVA)-induced asthma model [43].

Furthermore, the inflammasome activation in asthma also contributes to the release of another proinflammatory cytokine IL-1β, which induces airway epithelial cells release plentiful chemokines such as CXCL8, CCL5, MCP-1α and MCP-1β [38,44]. Therefore, the proinflammatory effect of IL-18 plays an important role in airway inflammation exacerbation of asthma,
which makes IL-18 a key factor that maintains the chronic inflammation.

4.2 IL-18 AND AIRWAY REMODELING

Airway remodeling is one of the common chronic pathological changes in asthma, which is characterized by the thickening of the airway induced by airway epithelial cell proliferation, matrix protein deposition and smooth muscle cell hypertrophy, thus resulting in persistent, irreversible airflow obstruction [45]. Indeed, IL-18 has been demonstrated to induce bronchial epithelial cell activation and differentiation [46], airway fibrosis and mucus metaplasia [47] via exacerbating chronic inflammation in the airways. Additionally, IL-18 also promotes the production of matrix metalloproteinases (MMP) such as MMP1, MMP2 and MMP9 [48], which contribute to the degradation and deposition of the extracellular matrix and angiogenesis, and thus inducing airway wall thickness, airway constriction and airflow limitation [49]. Notably, IL-18-deficient mice exhibit diminished airway remodeling in OVA-induced asthma model [43]. These suggest IL-18-mediated pathological changes affect airway structure.

4.3 IL-18 AND AIRWAY HYPERRESPONSIVENESS

Airway hyperresponsiveness is the core pathological feature of asthma, which refers to the abnormal sensitivity of the airway to environmental stimuli such as allergens

and cold air [50]. Actually, airway hyperresponsiveness results from airway remodeling in asthma [51].

IL-18 plays an important role in airway hyperresponsiveness via various mechanisms. On the one hand, IL-18 seems to promote the contraction of airway smooth muscle cells [52], thereby triggering bronchospasm and leading to the symptoms of wheezing and dyspnea in asthmatic patients. On the other hand, IL-18 induces the production of IL-13 and IL-4 from activated Th2 cells [53], basophils and mast cells [54], which exacerbates airway inflammation and hyperresponsiveness. Furthermore, blocking IL-18 signaling NLRP3/caspase-1 seems to alleviate airway hyperresponsiveness in mouse asthma model [30], and the airway hyperresponsiveness is inhibited in IL-18-deficient mice [43], indicating the critical role of IL-18 in asthma pathology.

4.4 IL-18 AND ASTHMA SEVERITY

Studies based on human demonstrate that the gene polymorphism of *IL-18* is not only relevant to asthma [55,56], but also to the severity of asthmatic adults [57]. While *IL18R1* gene is negatively associated with lung function and is highly expressed in severe asthma patients [58]. Elevated serum level of IL-18 in adults with moderate and severe asthma [59] but not in children with asthma [60] is correlated with asthma attack. Upregualted IL-18 and IL-18R expressions are observed in the lungs of fatal asthma patients but not of well-controlled mild asthma patients [61]. However, these characteristics are not applicable to asthmatic children [62-64]. Particularly, serum IL-18 levels in patients with mild and moderate asthma exacerbation decrease after therapy [65] and low serum IL-18 level may predict the effectiveness of Dupilumab in severe asthma [66]. Furthermore, IL-18 level in sputum of patients with asthma [46] and with severe eosinophilic asthma [67] is elevated, which is lower in patients with severe refractory asthma than that with mild asthma [68]. On the contrary, IL-18 level in bronchoalveolar lavage fluid is lower than that in healthy control subjects, and high serum free IL-18 is associated with decreased omalizumab efficacy [69]. These suggest that serum IL-18 level and *IL-18* gene polymorphism are more likely to be used as a potential biomarker to reflect asthma severity.

Studies based on mice reveal that IL-18 increases allergic sensitization, serum IgE, Th2 cytokines and airway eosinophilia in asthmatic mice [70]. The *IL-18* gene knockout [43] and NLRP3 inflammasome inhibition [71,72] alleviate airway inflammation, remodeling and hyperresponsiveness. Till now, there is only one report that IL-18 deficiency selectively enhances allergen-induced eosinophilia and lung damage in mice [73]. These further support the potential of IL-18 as a therapeutic target in asthma.

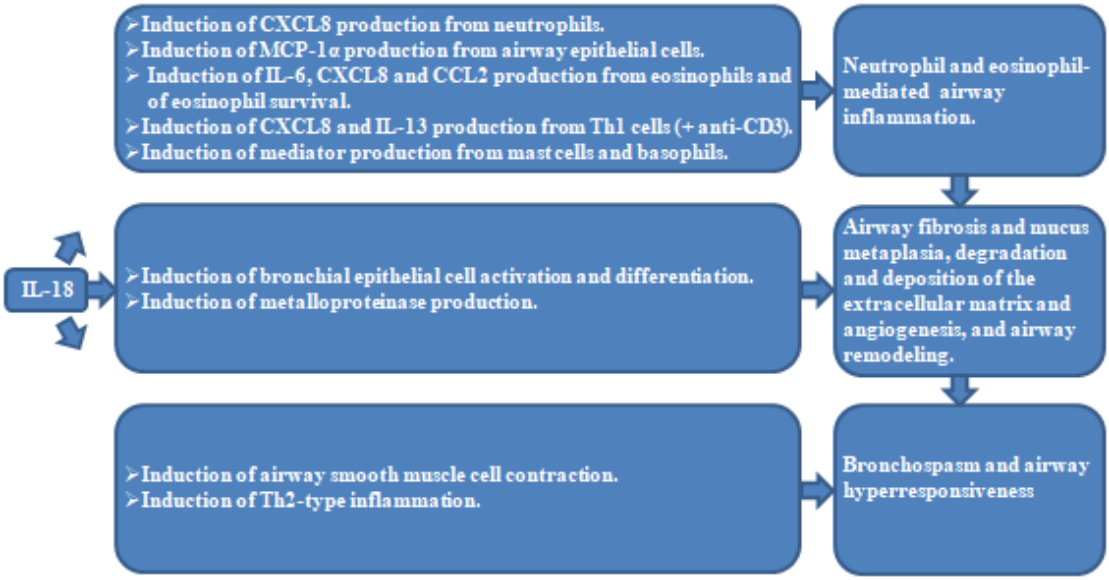

Figure 1: The role of IL-18 in the pathological characteristics of asthma

As depicted in Figure 1, these studies provide a rationale for the development of IL-18-based therapeutic strategies for asthma in the future. The IL-18 inhibitors or IL-18R blockage may effectively alleviate the symptoms of asthma. These results provide valuable reference for the design of novel therapeutic regimens, and provide reliable data support for preclinical studies.

5. Future research directions and challenges

5.1 POTENTIAL RESEARCH DIRECTIONS

Future studies can further explore the specific role of IL-18 in different asthma phenotypes and endotypes, in particular the differences in the performance of refractory asthma and atypical asthma, e.g., patients with refractory asthma often do less respond to conventional therapeutics and may have unique inflammatory mechanisms in which the specific role of IL-18 has not been fully defined. These studies may help identify more effective therapeutic targets and provide novel ideas for the development of more precise therapy.

In addition, the synergistic mechanism of IL-18 with other proinflammatory cytokines is also a direction worthy of further exploration. IL-18 interacts with IL-4, IL-33 and other cytokines to form a multi-factor network and regulate airway inflammation and hyperresponsiveness. Understanding the interaction between these factors, particularly the specific signaling pathways in different immune cells will reveal the multi-level effects of IL-18 in asthma, and provide a more comprehensive understanding of the complex mechanism of IL-18 and a

richer scientific basis for the multi-target therapeutics of asthma.

5.2 RESEARCH CHALLENGES

Indeed, IL-18-related preparations have been applied in clinical trials for the therapy of inflammatory dermatological disease [74]. Although the development of IL-18 as a therapeutic target for asthma is promising, its practical application still faces many technical and clinical challenges. Firstly, how to mimic the complex mechanism of IL-18 *in vivo* accurately is an urgent problem to be figured out. Given that IL-18 has multiple functions in inflammatory response and immune regulation, how to reproduce its multi-level roles effectively in animal models is crucial to understand its specific mechanism in the pathogenesis of asthma. The development of experimental techniques such as more precise gene editing techniques and three-dimensional tissue culture models, may help to better understand the complex biological roles of IL-18.

On the other hand, how to reduce the potential impact of IL-18 inhibitor or IL-18R blocking on immune system is an important issue that is worthy of deep consideration. The complete inhibition of IL-18 activity or IL-18R blocking is likely to impair the individual ability to defense pathogen. Therefore, future research is warranted to find precise methods that can effectively suppress airway inflammation without impairing immune function.

In addition, the safety and efficacy of IL-18 in clinical application still need to be further verified in human trials. Although current preclinical studies have shown its potential efficacy, there are not enough data to support its full clinical application [75]. Future clinical trials with more rigorous design are warranted to evaluate the long-term effects of different doses and different durations of medication on patients to ensure that the treatment is both safe and effective. The resolution of these challenges will be the key to the successful application of IL-18 targeted therapy in asthma.

6. Conclusions

IL-18 plays a key role in the pathogenesis and development of asthma by inducing airway inflammation, remodeling and hyperresponsiveness. These effects make IL-18 a potential therapeutic target and provide a new possibility for the treatment of asthma in the future. However, although the potential of IL-18-targeted therapy is gradually being recognized, its clinical application still needs to be supported by more experimental data and clinical trials. Particularly in terms of efficacy and safety, further verification and refinement are warranted.

Conflicts of interest

The authors have no conflicts of interest to declare.

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