Progress of IL-27 in the Pathogenesis of Chronic Rhinosinusitis

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Abstract

Chronic rhinosinusitis (CRS) is a chronic inflammatory disease that occurs in the mucosa of the nasal cavity and paranasal sinuses and is regulated by a variety of immune cells and immune factors. As a newly discovered inflammatory factor in recent years, interleukin-27 (IL-27) has special immunoregulatory function and plays a role in infectious diseases, immune diseases and tumors. IL-27 promotes and/or inhibits cellular differentiation of regulatory T cells (Treg) and helper T cells (Th), thus exhibiting dual pro-inflammatory and anti-inflammatory effects. This article reviews the biological characteristics of IL-27 and its role in CRS.

Keywords: Interleukin-27; Chronic rhinosinusitis; Polyps; Cytokines

Introduction

Chronic rhinosinusitis (CRS) is a common chronic inflammatory disease of the upper respiratory tract that occurs in the mucosa of the nasal cavity and paranasal sinuses and is highly heterogeneous. CRS is mainly characterized by symptoms such as nasal congestion, purulent nasal discharge, and hyposmia, and lasts for more than 12 weeks [1]. According to the phenotype, CRS can be divided into two categories: with nasal polyps (CRSwNP) and without nasal polyps (CRSsNP); according to intracellular inflammation, CRS can be divided into type 1 (T1), type 2 (T2) and type 3 (T3) [2]. The global prevalence of CRS ranges from 5.5% to 28%, and the prevalence of CRS in China is about 8%, About 107 million people are affected by CRS in their physical and mental health and quality of life[3,4]. According to surveys, there are regional differences in the types of manifestations and incidence of CRS. Having CRS will not only affect the quality of life, but also causes a series of complications such as crani-o-oculo-pulmonary disease, posing a serious threat to the life safety of patients [5]. In recent years, with the deepening of immune molecular biology, it has been found that the pathogenesis of CRS is closely related to the abnormal level of immune factors in patients. The imbalance of immune homeostasis leads to the disturbance of immune barrier function, followed by the increase of mucosal epithelial permeability, the decrease of antibacterial substance secretion and the decrease of antibacterial response, which finally induces the occurrence and development of CRS [6]. Studies have shown that IL-27-mediated immune response is closely related to CRS. In this paper, the pathogenic mechanism of IL-27 involved in CRS is reviewed in order to provide a new direction for immune molecule targeted therapy of CRS.

Characterization and Function of IL-27

Overview of IL-27 components

IL-27 was discovered and named in 2002 as a cytokine belonging to the IL-6/IL-12 family [7]. IL-27 is a heterodimeric cytokine composed of the soluble cytokine receptor-like component (Epstein-Barr virus-induced gene 3 (EBI3)) and a helical protein(IL-27p28). EBI3 is inactive in IL-27 and can effectively function only when the two binds [7,8]. IL-27 is mainly derived from activated antigen presenting cells such as monocytes, macrophages and dendritic cells, and can also be derived from different types of cells and tissues such as other myeloid cells, lymph nodes, spleen, and placenta [8,9]. IL-27 production is mainly triggered by Toll-like receptors (TLR) and interferon-γ (IFN-γ). TLRs play an important role in immune responses, and their agonists induce IL-27 production by stimulating antigen presenting cells to express mRNA for IL-27p28 and EBI3; IFN-γ alone or in concert with TLR agonists enhances IL-27 production [10].

IL-27 receptors and signaling pathways

IL-27 receptor (IL-27R) is a heterodimer composed of IL-27Ra and glycoprotein (gp) 130 [1]. IL-27Ra is a type I cytokine receptor expressed predominantly by T and B cells and binds specifically to IL-27. As a signal transduction chain, gp130 is present in all cells and can bind to other cytokines, such as IL-6, IL-11, leukaemia inhibitory factor, and tumor suppressor M, thus showing different immune-inflammatory responses [8,11].
IL-27 achieves signal transduction mainly through the Janus kinase/signal transducer and activator of transcription (JAK/STAT) and Mitogen-activated protein kinase (MAPK) pathways, resulting in different biological effects [10,12]. The pathway through which IL-27 undergoes signaling depends on the type of binding cells, such as activation of the JAK/STAT pathway in monocytes and macrophages, which increases the expression of inflammatory cytokines and chemokines in monocytes and reduces the production of tumor necrosis factor (TNF) and IL-12p40 in macrophages; in naive CD4+ T cells, IL-27 promotes IFN-γ and IL-2 production by phosphorylating signaling through STAT1/2/3/4/5; and in naive B cells, IL-27 signals through STAT1/3 [8,12].

**Effect of IL-27 on CRS**

As a common type of local chronic inflammation, the pathogenesis of CRS is complex. At present, it is believed that the occurrence of CRS is related to microbial infections such as bacteria and viruses, structural abnormalities of the nasal cavity and paranasal sinuses, allergic reactions and genetic factors. Long-term chronic inflammation makes the local immune environment of the body disordered and tissue remodeling, further aggravating the disease progression [13-15]. IL-27 has dual immunomodulatory effects on CD4+ T cells, and the differential inflammatory effects expressed depend on different stages of the inflammatory response or on different stimulation conditions. It is well-known that Th cells mainly differentiate into Th1 cells and Th2 cells, but also Th17 and Th22 cells. Among them, Th1 cells mainly secrete IFN-γ, IL-2 and TNF-β; Th2 cells mainly secrete IL-4 and IL-6; and Th17 cells mainly secrete IL-17. In China, CRS is mainly characterized by regulatory T cells (Treg) suppression and helper T cells (Th) 1/Th2/Th17 mixed inflammation, and different inflammatory factors play different roles in different types of CRS, such as CRSsnP showing Th1 type response, and CRSwNP is mainly characterized by Th2 polarization [1,16]. The following review will focus on the role of IL-27 in different cell types of CRS.

**Effect of IL-27 on Th1 cytokines**

IL-27 was initially thought to promote Th1 cell differentiation. With the in-depth study of domestic and foreign scholars, it has been found that IL-27 can also inhibit Th1 cell differentiation, and its dual effects depend on different cellular environments. Patients with CRSnNP are usually characterized by a Th1-type response. IL-27 promotes Th1 cell differentiation through STAT1, p38 MAPK, and ICAM-1/LFA-1/ERK1/2 signaling pathways, in which IL-27 induces the expression of the specific transcription factor T-bet and its target genes IL-12p35 and IFN-γ through the STAT1 signaling pathway, thereby allowing T cells to promote Th1 cell inflammation [11,17]. IFN-γ is a potential immunomodulatory cytokine, and domestic and foreign scholars have a comprehensive study on the expression and mechanism of IFN-γ in CRS patients. Michael B, et al. treated epithelial cultures from CRS patients and controls with IFN-γ in air-liquid interface (ALI) cultures, and IFN-γ-stimulated ALI cultures showed by stratification that tight junctions between adjacent cells were open, i.e., pro-inflammatory cells regulated barrier function of epithelial cells in CRS patients [18]. Lee M, et al. induced mesenchymal transition of nasal epithelial cells with IFN-γ via the JAK-STAT-1-ICSBP-p38 and ERK pathways in CRS patients with marked neutrophil infiltration [19]. Liu, et al. in a mouse model of ovalbumin induced asthma, prophylactic intranasal IL-27 injection attenuates airway inflammation and hyperresponsiveness by up-regulating Th1 cell differentiation [20]. Increased IFN-γ can disrupt the epithelial barrier and inhibit epithelial cell apoptosis in CRS patients, and these defects in the epithelial layer of the nasal mucosa may provide an opportunity for bacteria and related substances on the mucosal surface to spread and penetrate CRS tissues, coupled with the synergistic effect of cytokines and inflammatory factors, which can make the nasal mucosa swollen, increased glandular secretion and inflammatory cell infiltration, and then lead to a vicious cycle of CRS inflammation. However, the direct effect of IL-27 on TH1 cytokines in CRS has not been reported and needs to be confirmed by in vivo/in vitro studies.

**Effect of IL-27 on Th2 cytokines**

CRSwNP usually presents as a Th2-type inflammatory response with eosinophilia and is mainly characterized by a high rate of asthma association and easy recurrence after surgery. GATA-3 is an important transcription factor in Th2 response, type-2 innate lymphoid cells (ILC2). IL-27 inhibits Th2 cell differentiation by inhibiting GATA-3 while up-regulating T-bet expression [12,21]. Qiao Feng, et al. reported that the increased expression of T-bet and GATA-3 in CRS mucosal tissues promoted the excessive differentiation of Th1 and Th2 cells, resulted in massive cytokine production and secretion, and further induced the inflammatory response by activating the p38 MAPK/NF-kB signaling pathway to initiate the expression of inflammatory factors [22]. ILC2 is a key regulatory cell that develops Th2 responses in vivo, and IL-27 inhibits ILC2 function by activating the STAT1 pathway to suppress the secretion of Th2 cytokines [8]. Evidence suggests that elevated ILC2 is detected in nasal polyp tissue and is significantly higher than in nasal mucosa tissue from CRSnNP patients, and ILC2 co-exists with Th2 cells and is an accelerator of the inflammatory response in CRSnNP [23]. Luo X, et al. directly inhibited ILC2 proliferation and function in AR through the interaction of L-27 with IL-27R, thereby reducing the secretion of Th2 cytokines [24]. In allergic inflammation models, IL-27 suppressed ILC2 proliferation and cytokine production and significantly suppressed their accumulation in papain-induced airway inflammation; mice exhibited more severe allergic responses following IL-27Ra knockdown of WSX-1 [25,26]. In addition, Yoshimoto T, et al. found that intranasal administration of IL-27 inhibited airway hyperresponsiveness and inflammation in ovalbumin sensitized animals, and IL-27 not only directly inhibited the development of Th2 cells, but also induced their IFN-γ producing Th1 cells [21]. Artsis D, et al. showed that loss of WSX-1 resulted in increased proliferation of CD4+ T cells and...
production of Th2 cytokines [27]. The direct regulatory effect of IL-27 in chronic inflammatory diseases such as bronchial asthma and allergic rhinitis has been reported, the so-called "same airway, the same disease", bronchial asthma, allergic rhinitis and CRSwNP have many similarities in pathogenesis, therefore, IL-27 is expected to be an effective drug for the treatment of CRSwNP.

IL-27 Inhibits Th17 cell differentiation

Th17 is a subset of Th cells, and IL-17 (also known as IL-17A) is an important effector molecule secreted by Th17 cells. IL-17A is strongly proinflammatory, and the effect of IL-27 on Th17 is mainly involved in inducing and regulating immune responses in vivo by activating STAT1/3. STAT3 is a critical transcription factor for Th17 cell differentiation, which impacts downstream molecules to promote maturation and IL-17 secretion of Th17 cells, and induces anti-apoptotic signals in the survival of Th17 cells [28]. Ouyang H, et al. showed that the protein level of IL-17 in AR group was higher than that in control group, while the protein level of IL-27 was lower than that in control group, that is, IL-27 was negatively correlated with IL-17, and revealed that IL-27 inhibited Th17 differentiation mainly through STAT1/3, NF-κB, MEK and JNK pathways [29]. Defects in IL-27 signaling augment Th17 responses in murine inflammatory models, thereby exacerbating allergic inflammatory responses [25]. Associated studies have shown that IL-17A levels are increased in Asian CRSsNP or CRSwNP patients compared to controls [2,3]. Ramezanpour M, et al. observed decreased epithelial resistance, increased permeability of macromolecules, and discontinuity of normal tight junction proteins in human nasal epithelial cell monolayers in human nasal epithelial cells, suggesting that Th17 cytokines may lead to barrier dysfunction, allowing inflammatory factors to penetrate the mucosal barrier, break the tight junction integrity, and further promote the development of CRSwNP [30]. Pothoven, et al. showed that IL-17 promotes the development of CRS by binding to receptors on the epithelial cell surface and activating the canonical NF-κB and MAPK pathways to promote eosinophil infiltration in CRS [31]. The above results suggest that IL-17 promotes the development of CRS by promoting mucosal barrier disruption and neutrophil infiltration, which produces a series of inflammatory factors. Inflammatory responses were mitigated when IL-27 inhibition of IL-17 was enhanced. According to the above studies, we can conclude that IL-27 can slow inflammatory response in CRS by inducing neutrophil apoptosis and protecting mucosal barrier function through IL-17.

IL-27 promotes Treg cell differentiation

Increasing evidence suggests that Treg homeostasis and function are compromised during allergic inflammation. Foxp3 is a characteristic transcription factor of Tregs and mainly acts as a suppressor effector T cell. CD4+ Tregs are divided into two major groups based on the presence or absence of forkhead box protein 3 (Foxp3): CD4+ Foxp3+ Tregs and type 1 regulatory T cells secreting IL-10 but lacking Foxp3 expression [32]. Downregulation of Foxp3 and hypofunction of Tregs suppression caused by reduced Tregs may be responsible for the persistent eosinophilic inflammatory response and upregulation of GATA-3 and T-bet in CRSwNP tissues [33]. Chang L, et al. have injected Treg into eosinophilic CRS mice and found that intravenous Treg subsets significantly reduced eosinophil counts in the mucosa of eosinophilic CRS mice, demonstrating the effect of Treg on CRSwNP [34]. Suzuki, et al. found that intranasal administration of IL-27 increased the percentage of CD25+ Foxp3+ cells and Foxp3 gene expression in CD4+ cells and increased the production of Tregs cytokines IL-10 and IL-35, suggesting that IL-27 can promote the differentiation of Tregs in vivo [35]. Nguyen, et al. found that intranasal administration of IL-27 to Foxp3-null Tregs failed to suppress airway inflammation in a mouse model of cockroach antigen-induced allergic inflammation and provided Foxp3 Treg to significantly reduce the development of airway inflammation, further confirming that IL-27 suppresses effector T cell proliferation by promoting Foxp3+ Tregs [36]. The above suggests that IL-27 may reduce nasal and airway mucosal inflammation by promoting Treg cell differentiation, thereby altering the course of the disease.

Summary and outlook

Studies of CRS have jumped from the phenotype-based era of initial research to the endotype-based information era, and identifying CRS endotypes can help to select the best treatment modality and predict treatment outcomes and reduce the risk of complications. The occurrence of CRS involves many factors such as local anatomy, immune inflammatory response and cytokines. Abnormal levels of inflammatory factors in the body will damage the immune barrier, while different inflammatory cells and secreted inflammatory factors further affect the phenotype, diagnosis and treatment of CRS, which brings great challenges to the treatment of CRS. Therefore, it is necessary to seek novel targeted agents that prevent the production or action of inflammatory cells and cytokines in CRS and further provide new options for clinical CRS treatment.

As a bidirectional regulator of pro-inflammatory and anti-inflammatory, IL-27 exhibits two distinct functions in CD4+ T cells: one is to promote Th1-type immune responses and the other is an inhibitor of immune/inflammatory responses. IL-27 can induce the growth, proliferation and apoptosis of Th cells through signaling pathways such as JAK-STAT and MAPK, which can foresee that IL-27 plays an important role in CRS disease and needs to be further explored and practiced in the future in order to make IL-27 a new target for CRS immunotherapy.
References


