REVIEW
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Advances in the biological function of interleukin 38 and its study in immune diseases

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Author contributions

Tian-Xiao Cui wrote the manuscript and designed the figures. Cui-Ting Gong, Ye Yerdingqmk, Mizaniye Kaharv and Xiao-Juan Zhou revised the manuscript. Ji-Yun Zhang gave final approval to the manuscript. All authors contributed to the article and approved the submitted version.

Competing interests

The authors declare no conflicts of interest.

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Abbreviations

RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; CVD, cardiovascular disease; IBD, inflammatory bowel disease.

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Abstract

IL-38 is a newly discovered anti-inflammatory cytokine that belongs to the IL-1 family's IL-36 subfa + mily. Nonetheless, recent studies have shown that it can interact with multiple receptors to impede downstream signaling pathway activation, thereby restraining the differentiation and maturation of Th17 cells. While IL-38 enhances the immunosuppressive activity of Treg by inhibiting the transformation of CD4 + T cells to Th17 cells, it can also exert its immune regulatory role by binding to the corresponding IL-38 receptor on the cell surface, which in turn inhibits classical signaling pathways such as NF-κB, P38, or JNK activation.IL-38 has been shown to alleviate disease progression in Rheumatoid Arthritis (RA), Systemic lupus erythematosus (SLE), cardiovascular disease (CVD), and other diseases by reducing the production of inflammatory cytokines and limiting the inflammatory response that is dependent on T cell subsets. Moreover, an increasing body of evidence suggests that IL-38 is a promising therapeutic target for these diseases. This article primarily reviews the immunological function of IL-38 and its involvement in related diseases, providing insights and theoretical support for chronic inflammatory and autoimmune diseases.

Keywords: systemic lupus erythematosus; interleukin-38; Th17 cells; receptors

Introduction

IL-38 is a newly identified member of the IL-1 family. The human IL-38 gene, consisting of four exons, is situated in the chromosome 2p13 region that corresponds to the IL-1 encoding gene and is flanked by the IL-1Ra and IL-36Ra genes [1, 2]. Furthermore, the sequence of IL-38 gene exhibits high homology to IL-1Ra and IL-36Ra, with 41% and 43% homology [3]. IL-38 is primarily expressed in healthy human skin, spleen, tonsils and other organs. Recent studies have demonstrated that the overexpression or knockdown of IL-38 plays a role in the development of immune diseases, including inflammatory bowel disease (IBD), SLE, Ankylosing Spondylitis (AS), RA, and psoriasis [4-7]. All of these inflammatory responses involve activation or inhibition of multiple cytokines by immune cells, focusing IL-38's potential to regulate inflammatory diseases. The aim of this review is to comprehensively examine the various immunological functions of IL-38 and provide an update on the current progress in understanding the role of IL-38 in immune diseases.

IL-38 immunomodulatory functions

So far, there are three candidate receptors have been proposed for IL-38 which are IL-1R1, IL-36R and IL-1RAPL1 [8]. Among them, IL-36R has been proved to be a specific receptor for IL-38. After IL-38 and L-36R bind and recruit interleukin-1RAcP, forming a "cytokine-IL-IL-IL-1RAcP" ternary complex, activating MYD88, then regulating intracellular mitogen-activated protein kinase (MAPK), NF-κB and other signaling pathways (Figure 1) [9-11]. IL-38 can also combine with IL-1R1 and subsequently form a trimer with IL-1PAcP. The trimer, bound to the TIR receptor of the cytoplasm, regulates downstream extracellular regulatory protein kinase (ERK) 1/2, p38 MAPK, NF-κB, and JNK signaling pathways through MYD88 (Figure 1) [10, 12]. The third potential receptor for IL-38 is IL-1RAPL1, which is expressed in the brain. The binding of IL-38 to IL-1RAPL1 inhibited IL-6 secretion and c-Jun N-terminal kinase (JNK)/AP1 pathway (Figure 1) [13]. IL-38 has plenty of similar functions with IL-36Ra, and the latter one can recruit SIGIRR. Although it is not reported whether IL-38 has the ability to recruit SIGIRR (Figure 2) [14].

Mora et al. [13] conducted an experiment to compare the levels of IL-38 in the supernatant of apoptotic lung center A549 or breast cancer cells MDA-231 (called apoptotic cell conditioned medium, ACM) with that in the necrotic medium. They found that when T cells were cultured in macrophage ACM, they secreted lower levels of IFN-γ and IL-10, and slightly increased levels of IL-17. However, when cultured in ACM lacking IL-38, the opposite effect was observed. Additionally, T cells produced less IL-17 when cultured in ACM overexpressing IL-38. The peripheral blood mononuclear cells stimulated by IL-36 γ downregulated IL-8 expression under the regulation of either IL-38 or IL-36Ra, suggesting that IL-38 is capable of suppressing the IL-36 γ -induced secretion of IL-8. Lipopolysaccharides (LPS) can increase the levels of IL-6 and IL-8 [15]. However, the expression of IL-6 and IL-8 was decreased when macrophages were present inside A549 cells with high levels of IL-38 expression, while the removal of IL-38 from A549 cell rings significantly increased the expression of these cytokines [13]. THP-1 cells that were transduced with lentiviral particles overexpressing human IL-38 (THP-1-IL-38) exhibited a notable reduction in the expression of IL-6 and IL-23p19 following LPS stimulation. It is noteworthy that IL-38 was detected in the supernatant of THP-1-IL-38 cells (17-18 kd). When THP-1 cells were stimulated with LPS, the medium of THP-1-IL-38 cells significantly downregulated the production of IL-6, TNF α , and IL-23. Additionally, THP-1 cells treated with epithelial HEK cell medium, which overexpressed IL-38, could also downregulate IL-6 secretion [16], indicating that IL-38 could be released via autocrine or paracrine pathways. Most current views suggest that IL-38 plays a protective role in chronic inflammatory and immune contexts by acting on Th1 and Th17 activation and function and may inhibit the expression of various proinflammatory cytokines, such as IL-6, IL-8, TNF, and multiple chemokines [17]. Furthermore, the level of IL-6 secretion by macrophages may influence the maturation of Th17 [18, 19], a co-transformation factor necessary for the differentiation and expansion phase of Th17 cells. Treg cells are induced to differentiate by TGF-β , express CD4, CD25, Foxp3, and secrete cytokines such as IL-10. Tregs are also regulated by cytokines such as IL-38 and IL-27, which can increase the number of Tregs by preventing them from converting to Th17 cells, thereby affecting the body's physiological functions. Although the literature supports that IL-38 is secreted by B cells, its immunological effects on B cells need to be studied under autoimmune conditions. For example, at low concentrations, IL-38 reduces IL-17, IL-22, and IL-36 γ -derived IL-8 levels in PBMCs. However, at high concentrations, it has the opposite effect. Moreover, IL-38 was able to increase IL-6 expression in DCs, and high levels of IL-36R expression by DCs cells play a crucial role in Th17 cell differentiation [20]. Therefore, The mechanism of the cytokines' role in immunity and chronic inflammation mentioned above requires further investigation. Notably, the immunomodulatory effects of IL-38 may depend on its concentration/dose and form. On one hand, it has been reported that IL-38 can inhibit the secretion of IL-22 and IL-17 by PBMCs at concentrations of 10 ng/mL and 100 ng/mL, with the greatest inhibition of IL-22 observed at 10 ng/mL [15]. Moreover, Han and colleagues [21] observed that the inhibitory effect of IL-38 decreased with increasing concentrations of the cytokine. Furthermore, the full-length form of IL-38 (aa1-152) was found to be anti-inflammatory at a concentration of 250 ng/mL, whereas truncated IL-38 (aa20-152) was able to inhibit IL-6 production by macrophages at concentrations ranging from 0 to 20 ng/mL in response to different concentrations of IL-1 or LPS. However, full-length IL-38 (aa1-152) significantly increased IL-6 secretion by macrophages at doses of 0 to 20 ng/mL, with the greatest inhibitory effect observed at dose levels of 20 and 10 ng/mL (Figure 2) [13]. In summary, we conclude that IL-38 exerts anti-inflammatory effects at low concentrations, as well as truncated IL-38 (aa20-152) and mature IL-38 (aa7-152), but has pro-inflammatory effects at high concentrations. Therefore, administering IL-38 requires careful consideration of the balance between dose and IL-38 form (see Figure 2 for the mode of action of IL-38 signaling under different conditions). Currently, many studies have identified the signaling pathways of IL-38 action, but the specific mechanism of action remains unknown. It is speculated that IL-38 is likely to play a role in immune regulation through the pathways mentioned above, although in some cases, it can also induce pro-inflammatory cytokines, depending on its form, concentration, and external stimulus. Further research is needed to understand why IL-38 can have distinct immunological functions.

IL-38 in connective tissue diseases

Rheumatoid arthritis

Rheumatoid arthritis is an immune disease associated with immune deficiency in human joints, with a typical pathological manifestation being the proliferation of synovial cells. The level of IL-38 mRNA in the synovial membrane is significantly higher in patients with rheumatoid arthritis than in those with osteoarthritis, and it correlates significantly with the number of leukocytes in the synovial fluid [22]. Additionally, the level of IL-38 mRNA in the synovium of patients with rheumatoid arthritis was significantly higher than that in patients with osteoarthritis and significantly correlated with the number of leukocytes in the synovium [23, 24]. The expression of Il-38 mRNA was significantly increased in the joints of rheumatoid model mice [25]. Furthermore, the mouse IL-38 cDNA was subcloned into the SSV9 SCCMV plasmid to produce adenovirus encoding IL-38 (AAV IL-38). After the intra-articular injection of AAV IL-38 in CIA mice, IL-38 was consistently expressed locally only in the ankle joint, and the clinical activity score and incidence of arthritis were significantly decreased. Overexpression of IL-38 decreased the expression of Il-17, IL-23p19, IL-22, nuclear factor kappa-B ligand, and CXCL1 [16]. Additionally, IL-38-/-k/BXN mice were treated with AAV IL-38, and the clinical activity score deteriorated significantly, while the scores of inflammation and bone erosion increased significantly. However, the

score of arthritis inflammation decreased significantly in the phase of inflammation subsiding. The density of IBa1+ monocytes/macrophages was significantly decreased in the inflammatory synovial region [16]. These results indicate that IL-38 expression is increased in patients with arthritis and mouse models of arthritis and has a negative regulatory role in the pathogenesis of arthritis.

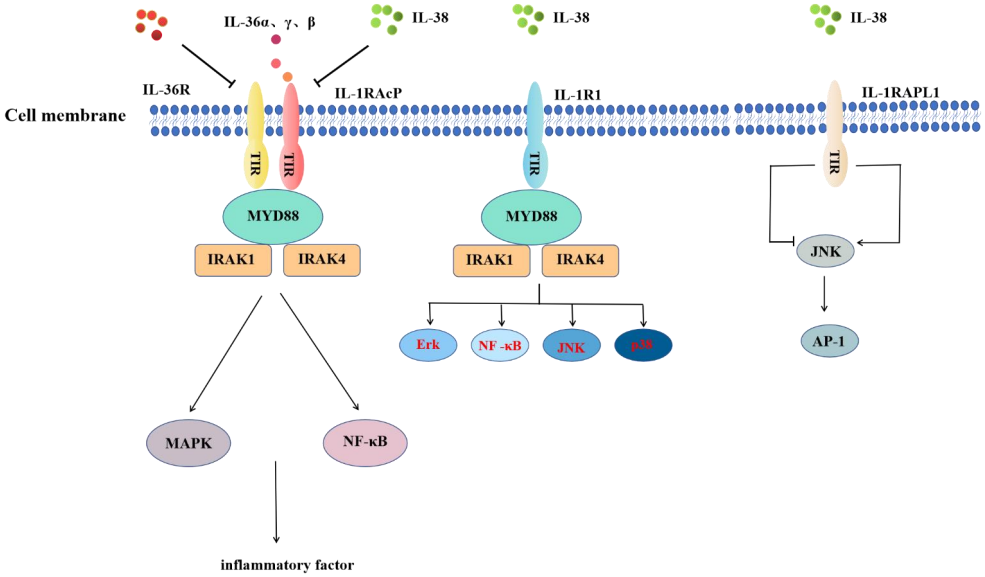

Figure 1 The receptor and signaling pathway of IL-38

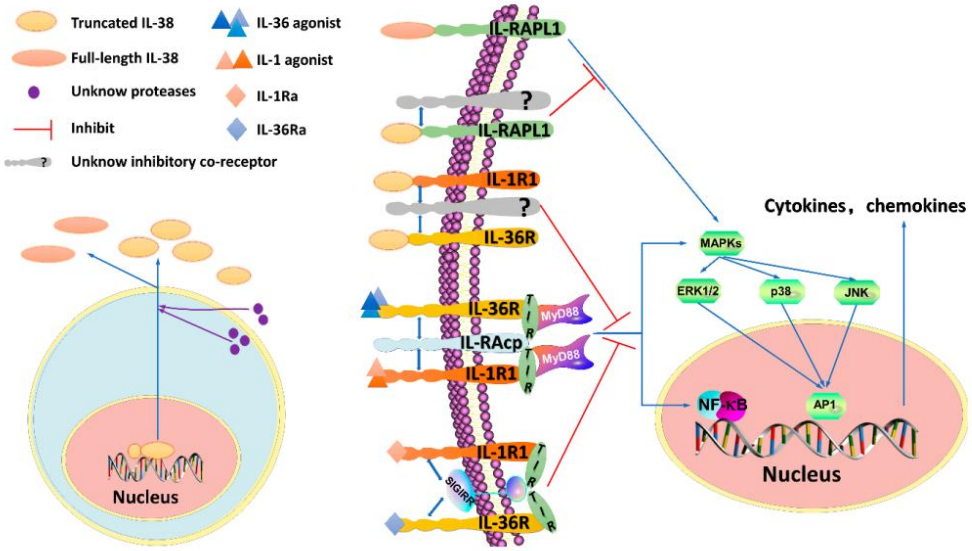

Figure 2 Mode of action of IL-38 signaling under different conditions

Systemic lupus erythematosus

SLE is a multifactorial immune disease. In a follow-up study, IL-38 protein levels were found to be significantly higher in patients with persistent disease activity or at different time periods than in patients without disease activity [26]. This suggests that serum IL-38 levels have a strong early warning effect on disease activity. Serum IL-38 levels were significantly lower in treated SLE patients. Analysis against unstimulated SLE PBMCs enhanced the production of IL-6, chemokine CCL2, and APRIL and activated cells via TLR-9 (CpG-ODN) [27]. In MRL/LPR mice, the expression of IL-38 mRNA was lower in the kidney and PBMCs compared to control mice. Recombinant IL-38 can inhibit the activation of the NF- κ B signaling pathway in peripheral blood B cells of SLE patients and reduce the secretion of anti-ds-DNA antibodies and pro-inflammatory factors [28]. Additionally, the degree of inflammatory infiltration in renal lesions in lupus mice was significantly alleviated by IL-38 treatment [29]. In the inflammatory autoimmune environment, IL-38 mainly inhibits the cytokines secreted by Th1, Th17, and γ δ T cells (TNF, IL-1, IFN- α , IL-17A) and down-regulates the expression of IL-6, IL-8, IL-22, and IL-23, thus playing a protective role [30]. In conclusion, these data suggest that IL-38 may delay the time and extent of lupus progression, thereby improving patients' long-term prognosis.

Spondyloarthritis

Spondyloarthritis is a group of chronic inflammatory rheumatic diseases, of which AS is a clinical type, characterized by inflammation and ossification of the spinal joints and ligaments of the lumbar, cervical, and thoracic segments, as well as sacroiliac joints. Unfortunately, there is no curative treatment strategy for this condition. In recent years, some views have emerged regarding the

potential association between IL-38 polymorphisms and AS. For instance, IL-38 polymorphism rs3811058 has been found to be prevalent in Chinese and European populations, but not in Asians [31-33]. However, some studies have suggested that IL-38 may not be associated with AS in the French population [33]. Therefore, exploring the correlation between IL-38 and the diagnosis and treatment of AS may be a promising area for future research.

IL-38 in other autoimmune diseases

Psoriasis. Psoriasis is a chronic immune disease characterized by abnormal skin rash. Patients with psoriasis have been shown to have significantly higher levels of IL-38 than healthy controls [34]. Imiquimod (IMQ) activates intrinsic immunity and the application of IMQ-containing adalat cream to the skin of mice causes leukocyte infiltration and keratosis of the skin, similar to human psoriatic lesions [35]. However, Palomo et al applied Aldara cream containing IMQ to the ear skin of female IL-38-/- mice and their wild-type pups, causing psoriasis-like reactions in both groups [36]. This study also observed a reduction in IL-38 mRNA expression in the epidermis of mice after IMQ induction. However, the study showed no effect of IL-38 on the expression of inflammatory cytokines in the skin [36]. Therefore, the role of IL-38 in psoriasis needs further confirmation.

Inflammatory bowel disease. There are two principal types of inflammatory bowel disease (IBD): Ulcerative colitis (UC) and Crohn's disease (CD). IL-38 is highly expressed in the mucosa, submucosa, muscular layer, and serous layer of IBD patients [37], while IL-36 expression is markedly decreased during the active stage of UC [38]. Furthermore, IL-36 is one of the cytokines that is preferentially expressed in the inflamed large intestine, as demonstrated by DNA microarray analysis [39]. Hence, it is plausible that IL-36, IL-36Ra, and IL-38 contribute to the development of IBD. Studies have shown that IL-36R knockout mice exhibit a Th cell immune response compared to wild-type mice, which may be attributed to reduced IL-2 expression, thereby inhibiting Th1 differentiation and promoting Th17 maturation [40]. The application of IL-38 recombinant protein to IL-36R knockout mice has been found to restore IL-22 expression in dextran sulfate sodium-induced mice, thus promoting inflammation repair. Conversely, IL-36 has no significant effect on Th1 and Th2 polarization in IBD. Therefore, IL-38 may be an anti-inflammatory cytokine in IBD [23]. With further study of the IL-38/IL-36R signaling pathway in inflammatory bowel disease, we speculate that this pathway may become an emerging target for intervention in IBD and UC in the future.

Others. Thyroid-associated ophthalmopathy (TAO) lesions primarily involve the extraocular muscles, causing edema, chronic inflammatory cell infiltration, degeneration, hypertrophy, and fibrosis. mRNA for IL-38 in orbital connective tissue is significantly lower in TAO patients than in controls and is negatively correlated with disease activity. In addition, IL-38 not only reduces levels of fibrosis-related factors, but also neutralizes phosphorylation in the TGF- β /Smad signaling pathway [41]. Asthma, a chronic inflammatory ailment of the bronchi, is characterized by long-standing inflammation of the airways, airway hyperresponsiveness, and structural alterations in the bronchi that can be reversed. The underlying pathological feature of asthma entails persistent inflammation of the airways, a process that involves the participation of several cell types, particularly mast cells, eosinophils, and T lymphocytes. Several investigations have suggested that the levels of IL-38 during an acute asthma attack are lower than those observed during a remission period. Furthermore, the severity of lung function has been shown to be inversely related to the levels of IL-38. In a fundamental experimental study, intraperitoneal injection of IL-38 into the experimental group of mice caused a reduction in the overall number of infiltrating inflammatory cells, with eosinophils in bronchoalveolar lavage fluid displaying a significant decrease in number. IL-38 can also modulate the p38, STAT1, STAT3, ERK1/2, and NF- κ B pathways, as well as upregulate the expression of airway genes in airway epithelial cells, leading to the inhibition of pro-inflammatory cytokine activation and ultimately suppressing the production of inflammatory cytokines, chemokines, and adhesion molecules [42-44]. IL-38 expression was found to be significantly higher in septic sweat glands (HS), while IL-36 procytokine and IL-36Ra levels were significantly higher only in areas of HS lesions. Studies have suggested that a new pathway of IL-23/Th17 exists in HS and that there is a protective effect when IL-38 is present under this condition [45]. Therefore, the IL-38-IL36R axis probably plays a role in HS and could be a possible therapeutic target. Based on the above results, it can be inferred that IL-38 may confer a protective effect against inflammatory autoimmune diseases. However, given the limited research information in this area, further studies using better animal models are warranted to explore the function of IL-38 and its receptors, as well as the possible immune mechanisms involved.

IL-38 in other diseases

IL-38 has been shown to have a potential therapeutic effect on various chronic inflammatory diseases. In mice with oxygen-induced retinopathy (OIR), IL-38 has been observed to inhibit the development of pathological neovascularization [46]. In addition, IL-38 has been found to have anti-inflammatory properties, reduce insulin resistance, and regulate abnormal lipid metabolism in atherosclerotic lesions, thus controlling the size of these lesions in coronary heart disease [8]. Given the diverse mechanisms of action of IL-38 in chronic inflammatory diseases, further studies are needed to explore the potential functions and immune mechanisms of IL-38 and its receptors. Therefore, better animal models are required for this purpose.

Conclusion

Currently, research on IL-38 is still in its early stages. Although IL-38 has been reported to have potential therapeutic effects on autoimmune diseases, cardiovascular diseases, and metabolic diseases, its clinical application remains limited. This review aims to provide insight into the potential mechanisms of IL-38, including its ability to modulate Th1/Th17-mediated dysfunction via the IL-38/IL-36R signaling pathway and suppress inflammatory responses in T cell subsets. Furthermore, the review aims to clarify the structure, function, receptor complex, relationship with IL-1F members, related drugs, and their effects of IL-38 in humans. Despite recent progress, many questions regarding the mechanisms of IL-38 action still require further investigation. As research on IL-38 continues to deepen, it will provide valuable guidance for the clinical application of IL-38 in the treatment of autoimmune diseases.

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