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REVIEW ARTICLE

Clinical relevance and therapeutic potential of IL-38 in immune and non-immune-related disorders

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ABSTRACT. Interleukin-38 (IL-38) is the most recent member of the IL-1 family that acts as a natural inflammatory inhibitor by binding to cognate receptors, particularly the IL-36 receptor. In vitro, animal and human studies on autoimmune, metabolic, cardiovascular and allergic diseases, as well sepsis and respiratory viral infections, have shown that IL-38 exerts an anti-inflammatory activity by modulating the generation and function of inflammatory cytokines (e.g. IL-6, IL-8, IL-17 and IL-36) and regulating dendritic cells, M2 macrophages and regulatory T cells (Tregs). Accordingly, IL-38 may possess therapeutic potential for these types of diseases. IL-38 down-regulates CCR3+ eosinophil cells, CRTH2+ Th2 cells, Th17 cells, and innate lymphoid type 2 cells (ILC2), but up-regulates Tregs, and this has influenced the design of immunotherapeutic strategies based on regulatory cells/cytokines for allergic asthma in future studies. In auto-inflammatory diseases, IL-38 alleviates skin inflammation by regulating γδ T cells and limiting the production of IL-17. Due to its ability to suppress IL-1β, IL-6 and IL-36, this cytokine could reduce COVID-19 severity, and might be employed as a therapeutic tool. IL-38 may also influence host immunity and/or the components of the cancer microenvironment, and has been shown to improve the outcome of colorectal cancer, and may participate in tumour progression in lung cancer possibly by modulating CD8 tumour infiltrating T cells and PD-L1 expression. In this review, we first briefly present the biological and immunological functions of IL-38, and then discuss the important roles of IL-38 in various types of diseases, and finally highlight its use in therapeutic strategies.

Key words: interleukin-38 (IL-38), interleukin-36 receptor (IL-36R), autoimmune diseases, cancer, respiratory viral infections, metabolic and cardiovascular diseases, asthma

Interleukin-1 (IL-1) family is one of the best characterized cytokine families. This family consists of 11 members that are involved in different aspects of the immune system; some have agonistic activity (*e.g.*, IL-33, IL-36γ, IL-36β, IL-36α, IL-18, IL-1β, IL-1α) while some are considered to have antagonist activities (*e.g.* IL-38, IL-36 receptor antagonist [IL-36Ra], and IL-1 receptor antagonist [IL-1Ra]) [1]. Besides a broad range of activities from pro-inflammatory to anti-inflammatory, cytokines of the IL-1 family have various functions. A similar structure exists in all the family members that includes an extracellular region consisting of three immunoglobulin-like domains, a transmembrane domain, and an intracellular portion with a Toll-IL-1-receptor (TIR) domain which initiates signalling pathways [2]. While some of the members of the IL-1 family, such as IL-18 and IL-1β, have been extensively studied, others, such as IL-37 and IL-38, have just recently been investigated.

Among all the members of the IL-1 cytokine family, the role of IL-38 in different diseases has not yet been completely elucidated. Most of the findings indicate an anti-inflammatory role for IL-38 through binding to IL-36R or IL-1R1 as receptors, while other investigations suggest that IL-38 may have both pro- or anti-inflammatory functions depending on the dose, the receptor type, and the length of the cytokine (full length vs. truncated form) [3, 4]. The IL-1 cytokine family, and more specifically IL-38, may possess therapeutic potential. As indicated in *figure 1*, we first briefly describe the structure, signalling pathways, and biological function of IL-38 based on recent findings, and then clarify the clinical and therapeutic roles of IL-38 in numerous types of immune and non-immune disorders.

The biology of IL-38

IL-38 structure

IL-38, also known as IL-1F10 (interleukin-1 family member 10), belongs to the IL-1 cytokine family. The IL-38 gene is located on human chromosome 2q13-14.1,

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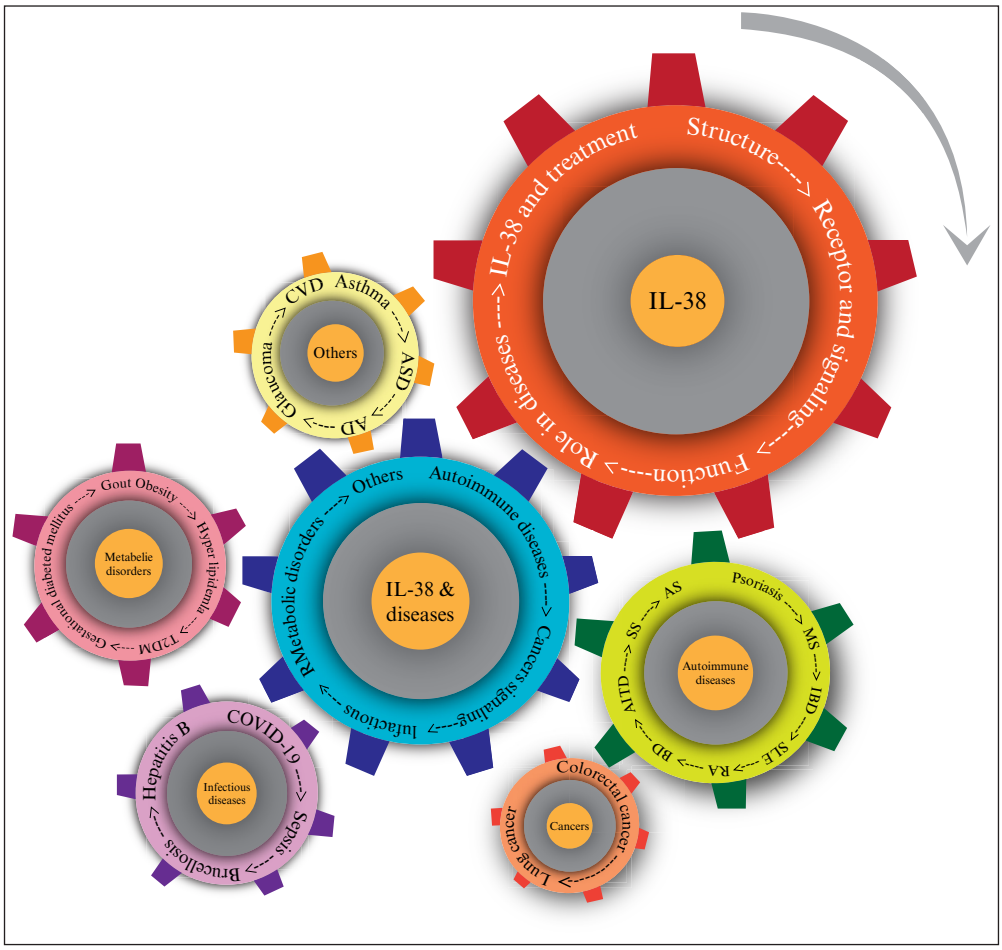

Figure 1
Overview of the contents of this manuscript. In this review, we first briefly describe the structure, signalling pathways, and function of IL-38, and subsequently describe the clinical relevance and therapeutic potential of IL-38 in relation to immune and non-immune-related disorders.
MS: multiple sclerosis; IBD: inflammatory bowel disease; SLE: systemic lupus erythematosus; RA: rheumatoid arthritis; BD: Behçet's disease; AITD: autoimmune thyroid disease; SS: Sjögren's syndrome; AS: ankylosing spondylitis; T2DM: type 2 diabetes Mellitus; GDM: gestational diabetes mellitus; EAE: experimental autoimmune encephalomyelitis; CVD: cardiovascular disease; MDVF: mean deviation of visual field; AD: Alzheimer disease; ASD: autism spectrum disorder.

between the genes encoding IL-1Ra and IL-36Ra [5]. The gene encodes a 152 amino acid protein with 16,943 Da molecular mass [6]. It is expressed in proliferating B cells of the tonsils, as well as the basal epithelia of some tissues such as the skin, spleen, foetal liver, salivary glands, placenta, and thymus [7]. IL-38 demonstrates almost 37-41% and 43% homology with IL-1Ra and IL-36Ra, respectively [3, 5]. IL-38 shares a common structure with other members of the IL-1 cytokine family and has a 12 β-stranded trefoil structure in the C-terminus; the structure of the N-terminus remains unknown [8]. IL-38 lacks a conventional signal peptide and caspase-1 consensus cleavage site [6].

IL-38 receptor and signalling

Several receptors have been proposed as IL-38 receptor candidates, including interleukin-36 receptor (IL-36R), interleukin-1 receptor 1 (IL-1R1), and interleukin-1 receptor accessory protein-like 1 (IL-1RAPL1) [9, 10]. IL-38 receptor candidates and their signalling pathways are shown in *figure 2*. IL-36R, also known as interleukin-1 receptor-related protein 2 (IL-1Rrp2), IL-1R6, or interleukin 1 receptor-like 2 (IL1RL2), is mainly expressed in dendritic cells, T cells (especially naïve CD4 T cells), synovial fibroblasts, and keratinocytes [11-14]. The binding of IL-36γ, IL-36β, and IL-36α as pro-inflammatory agonists results in the production of inflammatory cytokines such as tumour necrosis factor-α (TNF-α), IL-17A, and interferon-γ (IFN-γ) which promote the activation of neutrophils, T cells, dendritic cells, and macrophages [15, 16]. On the other hand, the binding of IL-38 and/or IL-36Ra to IL-36R inhibits the downstream signalling pathways. This feature affects the biological functions of IL-36 (*figure 2.1*) [17]. A study conducted by Tian *et al.* indicated that IL-36R antagonist could suppress the NLRP3 inflammasome pathway, therefore, exerting

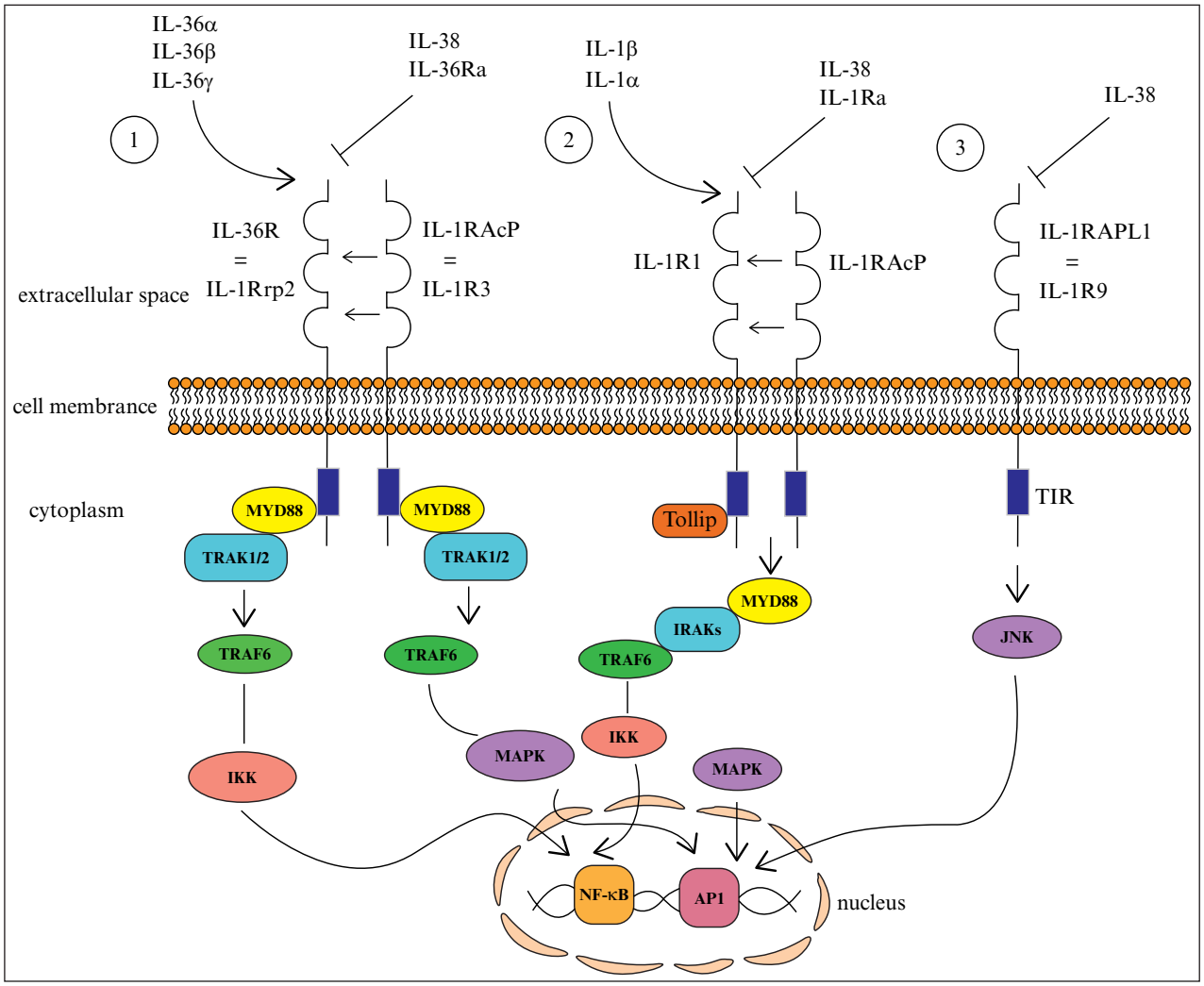

Figure 2
IL-38 receptor candidates and downstream signalling pathways. (1) IL-36R is a heterodimeric receptor consisting of an IL-1Rrp2 subunit and IL-1RAcP as a co-receptor. The binding of IL-36β, IL-36γ, and IL-36α as pro-inflammatory agonists results in the production of inflammatory cytokines while the binding of IL-38 and IL-36Ra to IL-36R inhibits the downstream signalling pathways. MYD88 recruitment through the TIR domain finally leads to activation of MAPK and NFκB that bind to DNA and induce the production of pro-inflammatory cytokines. (2) IL-1R1 and IL-1RAcp are two subunits of IL-1R. IL-1 binding to IL-1R1 induces the recruitment of co-receptor chain IL-1R3 (IL-1RAcP) that results in a conformational change in the TIR domain. Finally, recruitment of MyD88 and IRAK-1, and Tollip leads to the activation of NF-κB. (3) The IL-1RAPL1 signalling pathway mainly functions through activation of JNK/AP1.
IL-36R: interleukin-36 receptor; IL-1RAPL1: interleukin-1 receptor accessory protein-like 1; IL-1R1: interleukin-1 receptor 1; IL-1Rrp2: interleukin-1 receptor-related protein 2; IL-1RAcP IL-1: receptor accessory protein: NF-κB nuclear factor-κB; MAPK: mitogen-activated protein kinases; TIR: Toll/IL-1 receptor; IRAK: IL-1 receptor-associated kinase; Tollip: Toll-interacting protein; AP-1: activator protein 1; IκB: inhibitor of nuclear factor-κB; IKK: kinase; JNL: c-Jun N-terminal kinase; TRAF: tumour necrosis factor receptor-associated factor; MyD88: myeloid differentiation factor 88.

atheroprotective functions both *in vitro* and *in vivo* [18]. Moreover, IL-36Ra deficiency led to delayed wound healing due to increased infiltration of inflammatory cells such as macrophages and neutrophils [19]. As an anti-inflammatory factor, IL-36Ra can improve asthmatic symptoms by inhibiting the nuclear factor-κB (NF-κB) signalling pathway in murine models [20]. Structurally, IL-36R is a heterodimeric receptor consisting of an IL-1Rrp2 subunit and IL-1 receptor accessory protein (IL-1RAcP) as a co-receptor [21-23]. The inhibitory function of IL-38 appears to be mediated by IL-36R, co-receptor IL-1R9, and IL-1 receptor accessory protein-like 1 (IL-1RAPL1) [14]. IL-38 does not form a complex with IL-1R3 and uses IL-1R9 as a co-receptor, which is different from other IL-36 family members. However, a complex consisting of IL-38, IL-1R9, and IL-1R6 has not yet been indicated [24, 25]. IL-36α, IL-36β and IL-36γ signalling through IL-36R (IL-1Rrp2) and IL-1 receptor accessory protein (IL-1RAcP) activates NF-κB and mitogen-activated protein kinases (MAPK). In contrast, IL-36Ra binding to IL-36R, with a higher affinity compared with IL-36γ or IL-36α, hinders the recruitment of the co-receptor (IL-1RAcP) and consequently inhibits the corresponding intracellular signalling [21-23]. As an anti-inflammatory cytokine, IL-38 binds to IL-1Rrp2 which blocks the

NF-κB signalling cascade. However, whether IL-38 impedes the recruitment of the co-receptor (IL-1RAcP) is unclear [6, 26]. Except for single Ig IL-1-related receptor (SIGIRR), which has just one extracellular Ig-like domain, all members of the IL-1 receptor family, such as IL-1Rrp2, have one transmembrane domain and three extracellular immunoglobulin (Ig)-like domains [27]. In addition, these receptors contain a conserved intracellular Toll/IL-1 receptor (TIR) signalling domain (excluding IL-1R2). Similarly, the co-receptor IL-1RAcP is comprised of three immunoglobulin-like domains followed by a cytoplasmic TIR domain [28]. Three immunoglobulin domain-containing IL-1 receptor-related (TIGIRR)-1, TIGIRR-2, and SIGIRR have an extra C-terminal cytoplasmic extension [29, 30]. Further studies have indicated that TIGIRR-2 may act as a receptor for IL-38 [4]. IL-36R structure and its downstream signalling pathway are shown in *figure 2.1*.

IL-1R1 has also been introduced as a receptor candidate for IL-38. IL-1R1 and IL-1RAcP (the receptor accessory protein) are two subunits of IL-1R. Structurally, both IL1R1 and IL-1RAcP have a ligand-binding site, a single-pass transmembrane region, and a cytoplasmic Toll-IL-1 receptor domain [31, 32]. IL-38 inhibits the binding of IL-1β and IL-1α cytokines, although IL-1R1 showed a lower affinity for IL-38 compared with IL-1Ra or IL-1 [3, 10]. IL-1 binding to IL-1R1 induces the recruitment of co-receptor chain IL-1R3 (IL-1RAcP) which gives rise to a conformational change in the cytoplasmic Toll-IL-1 receptor domain followed by recruitment of MyD88 and IL-1 receptor-associated kinase 1 (protein kinase IRAK-1) and the Toll-interacting protein (Tollip) which finally results in the activation of NF-κB [33-35]. IL-1Ra inhibits the binding of pro-inflammatory cytokines (such as IL-1), and acts as a receptor antagonist [36]. IL-1R1 structure and its downstream signalling pathway are presented in *figure 2.2*.

Interleukin 1 receptor accessory protein-like 1 (IL-1RAPL1), also known as IL-1R9 or orphan receptor TIGIRR-2, is abundantly expressed in the brain and probably plays a role in brain development and memory or learning functions [29, 37-39]. IL-1R9 mutations are associated with mental disorders such as schizophrenia and autism [40-42]. IL-1RAPL1 probably plays a role in regulating calcium-dependent exocytosis and neurotransmitter release since the C-terminal segment of IL-1RAPL1 interacts with neuronal calcium sensor-1 protein (NCS 1) [43]. The IL-1RAPL1 signalling pathway acts via activation of JNK/AP1 and RhoA [44-46]. A study conducted by Han *et al.* indicated that IL-38 inhibits IL-17 production by γδ T cells mainly through IL-1 receptor accessory protein-like 1 (IL1RAPL1) [47]. Another study has revealed that truncated IL-38 suppresses the IL-1RAPL1 signalling pathway, comprised of JNK/AP1, leading to inhibition of Th17 activation after release from apoptotic cells [4]. *In vivo* experiments have indicated a suppressing role of IL-38 in IL-17 production by dermal γδT cells through IL-1RAPL1 signalling inhibition, and IL-1RAPL1 is a probable receptor for IL-38 [47]. IL-1RAPL1 structure and its downstream signalling pathway are presented in *figure 2.3*.

IL-38 function

In order to elucidate the biological function of IL-38, van de Veerdonk *et al.* evaluated cytokine production in Candida albicans-induced memory T-lymphocytes after adding recombinant IL-38 [10]. The authors reported reduced levels of cytokines in T lymphocyte, such as IL-22 and IL-17 by about 37% and 39%, respectively, which was accompanied by a potential failure in Th17-related response [10]. Remarkably, this effect declined at higher concentrations of IL-38 which suggests a dose-dependent effect for this cytokine. In addition, IL-38 decreased IL-8 production induced by IL-36γ in peripheral blood mononuclear cell (PBMC) cultures by about 42%. Similarly, IL-36Ra demonstrated the same effect and suppressed IL-8 production by about 73%. Overall, these data suggested an anti-inflammatory role for IL-36Ra and IL-38 through IL-36R [10]. Additionally, IL-38 may inhibit inflammatory cytokine production, including TNF-α, monocyte chemoattractant protein-1 (MCP-1), IL-1β, and IL-17 in LPS-induced THP1 cells [9]. IL-38 also ameliorates skin inflammation by regulating γδ T cells and limiting the production of IL-17 [47]. Furthermore, IL-38 secreted from apoptotic cells restrained cytokine production in macrophages, thereby regulating subsequent inflammatory responses [4]. Moreover, regarding the pathological pathways of several diseases, IL-38 is believed to suppress inflammation created at the early stages of disease [48]. In this regard, in murine sepsis models, IL-38 was found to be associated with enhanced immunosuppressive responses, probably through increasing the activity of $CD4^+CD25^+$Tregs [49]. In myocardial infarction (MI)-induced mice, exposure of dendritic cells (DCs) to LPS and IL-38 may influence DC functions by decreasing CD40 and CD86 molecules and IL-23, IFN-γ, and TNF-α cytokines [50]. Importantly, in a mouse model of allergic asthma, IL-38 was shown to decrease the accumulation of eosinophils and the number of Th2, Th17, and innate lymphoid type 2 cells [ILC2], but increased the proportion of Tregs [26]. In septic mice induced by CLP, IL-38 stimulated and amplified Tregs and Th2 responses, but decreased the proliferation of effector T cells [49]. Previous studies have mostly suggested an anti-inflammatory role for IL-38 through binding to IL-36R or IL-1R1 as receptors, however, a few studies have revealed that IL-38 may have both pro- or anti-inflammatory functions depending on the dose, the receptor type, and the length of the cytokine (full length vs. truncated form) [3, 4]. For example, one study reported higher levels of LPS-induced IL-6 in human blood monocyte-derived DCs via IL-36Ra or IL-38 [10]. N-terminal truncation may affect IL-38 function as truncated IL-38 showed a higher level of bioactivity compared to the full-length form [4, 47]. Mora *et al.* indicated that although the IL-38 precursor can increase IL-6 production by human macrophages, the truncated form of IL-38 contributed to reduced levels of IL-6 through targeting JNK phosphorylation and subsequent AP1 activation following its binding to IL1RAPL1 [4]. It is not well understood why IL-38 has such contradictory effects on different cells and further studies are required. The biological function of IL-38 is summarized in *figure 3*.

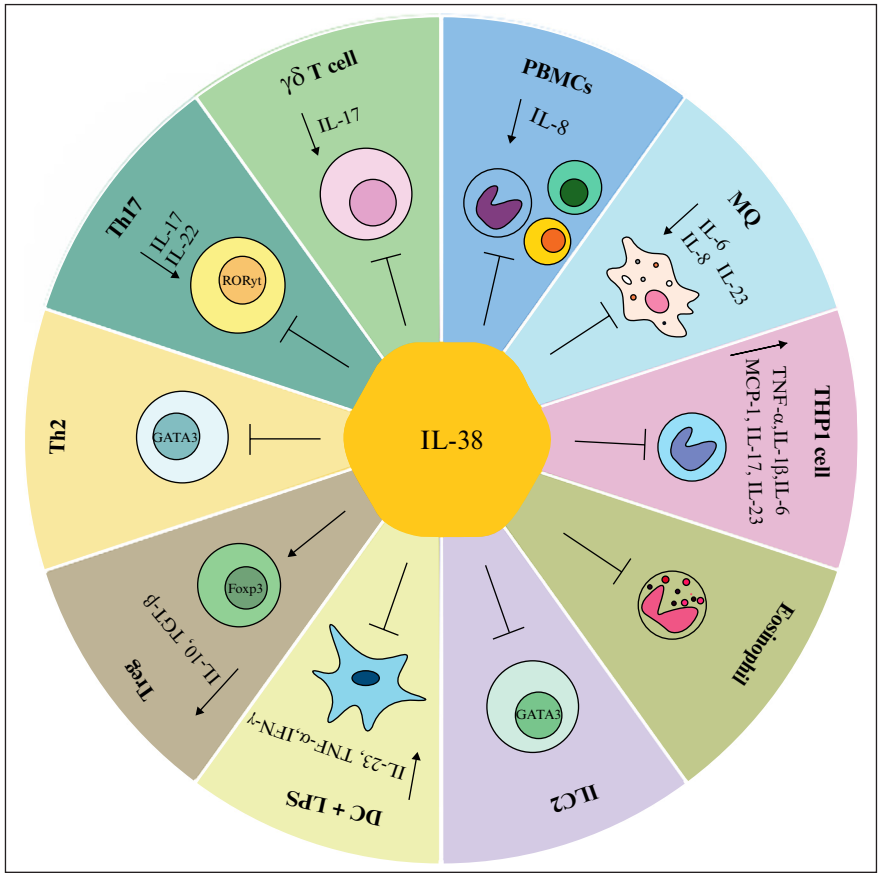

Figure 3
The biological function of IL-38 as an immune modulator. IL-38 exerts a suppressing effect on a majority of cells and regulates the inflammatory cytokines in both healthy and pathological conditions. In the presence of IL-38, pro-inflammatory cytokines (*e.g.* TNF-α, IFN-γ, IL-6, IL-8, IL-17, IL-22, and IL-23) are mostly down-regulated. IL-38 reduces the number of Th2 cells and inhibits Th2-related cytokines in a mouse model with allergic asthma, but amplifies Th2 responses in septic mice induced by CLP. IL-38 also augments the immunosuppressive activity of Tregs and increases the production of anti-inflammatory cytokines including IL-10 and TGF-β.
IL-38: interleukin 38; Treg: regulatory T cell; IL-10: interleukin 10; TGF-β: transforming growth factor beta; Th17: T-helper 17 cell; IL-4: interleukin 4; IL-5: interleukin 5; IL-13: interleukin 13; Th2: T-helper 2 cell; IL-17: interleukin 17; IL-22: interleukin 22; PBMC: peripheral blood mononuclear cell; MQ: macrophage; IL-6: interleukin 6; IL-8: interleukin 8; IL-23: interleukin 23; THP-1: a human acute monocytic leukaemia cell line; TNF-α: tumour necrosis factor alpha; IFN-γ: interferon gamma; IL-1β: interleukin 1 beta; MCP-1: monocyte chemoattractant protein-1; CCR3: CC chemokine receptor type 3; ILC-2: type 2 innate lymphoid cell; DC: dendritic cell; LPS: lipopolysaccharide.

Clinical manifestations of IL-38 in immune and non-immune disorders

As explained in the manuscript and summarized in *table 1*, several studies have specified the critical roles of IL-38 in the pathogenesis of various types of diseases including autoimmune diseases, cancers, infections, allergic asthma, and metabolic and cardiovascular diseases. In this section, we will summarize the recent research in this field.

IL-38 and autoimmune diseases

The anti-inflammatory role of IL-38 appears to be suitable for the treatment of autoimmune disease due to the suppression of inflammatory cytokines of the IL-1 family [51].
In systemic lupus erythematosus (SLE) patients, it has been reported that TNF-α, IL-23, IL-1β, and IL-6 expression, in supernatants derived from PBMCs stimulated by IL-38, were significantly down-regulated compared with those without IL-38. Similarly, the levels of these inflammatory cytokines and IgG deposition were reduced in pristane-induced lupus mice that received IL-38 compared to controls [52]. Additionally, IL-38 silencing by siRNA in PBMCs from healthy controls down-regulated IL-38 mRNA. This resulted in increased expression of CCL-2, APRIL, and IL-6, indicating regulatory effects of endogenous IL-38 in SLE disease [53]. Lupus-like clinical symptoms, such as proteinuria and leukocyturia (indicators of renal inflammation), and skin lesions were reported to be attenuated after administration of murine recombinant IL-38 into MRL/lpr mice as a mouse model for spontaneous lupus-like disease. Interestingly, treatment with IL-38 significantly reduced serum levels of IL-22 and IL-17 in SLE mice. However, IgG renal deposition and serum IgG and anti-dsDNA antibody concentrations were unchanged

Table 1.
The role of IL-38 in various types of diseases.

Category	Diseases	Function(s) of IL-38
Autoimmune diseases	Psoriasis	Suppression of inflammatory cytokines of the IL-1 family, therefore the anti-inflammatory role of IL-38 appears to be suitable for the treatment of psoriasis
	MS	Role in the development of MS in an EAE mouse model/ increase in IL-38 at early stages to suppress inflammation
	IBD	Regulation of NF-κB and p-STAT3 signalling pathways
	SLE	Alleviation of SLE symptoms by inhibiting inflammatory cytokines
	RA	Increase of IL-38 in serum and synovium in RA patients/ alleviation of the inflammatory responses
	BD	Protective anti-inflammatory role/ reduction of IL-38 level in serum of BD patients
	AITD	Suppression of IL-17A by downregulating IL-23R in PBMCs/ reduction of inflammation in orbital fibroblasts
	SS	Improvement in patients with primary SS mainly through inhibiting Th17-related responses
	AS	Association between IL-1 complex gene polymorphisms and clinical manifestations of AS
Cancers	Colon	Correlation between a high level of expression of IL-38 and better overall survival, smaller tumour size, and extent of tumour differentiation
	Lung	Association with high tumour grades, advanced stage, reduced overall survival, and disease-free survival as well as invasion of pleural and vessel/correlation with PD-L1 positive cases
Infectious diseases	Respiratory viral infections	Reduced naïve T cell to Th17 differentiation / up-regulation of Tregs/ suppression of IL-6 and CRP production
	Sepsis	Increase in Treg activity/ increase in Th2 responses/ decrease in effector T cell proliferation
	Hepatitis B	Reduction of proinflammatory cytokines (TNF-α, IL-17, IFN-γ, IL-22, IL-6)/ association with better liver function (reduction of ALT and AST) in mice Association between higher level of IL-38 and AST, resulting in better response to treatment in chronic patients
Metabolic and cardiovascular diseases	Obesity	Suppression of inflammatory cytokines/ inhibition of adipocyte differentiation/ increase in insulin sensitivity
	Hyperlipidaemia	Suppression of IL-6, IL-1β and CRP/ decrease in triglyceride (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL)/ alleviation of atherosclerotic lesions in mice models
	T2DM	Promotion of insulin sensitivity via suppressing IL-36 function
	GDM	Production of IL-38 as a response to local inflammation during GDM development
	Gout	Reduction of swelling and redness mainly through decreasing IL-1β and IL-6
Other diseases	Asthma	Induction of M2 macrophages and Tregs/ inhibition of Th2 cytokine secretion/ decrease in the number of ILC2, Th2 and Th17 cells
	ASD	Decrease of IL-38 in the amygdala/ increase of IL-38 in serum of ASD children Inhibition of IL-1β and CXCL8 expression in human adult microglia culture
	AD	Increase of IL-38 in newly diagnosed AD patients compared to control subjects of the same gender Increase of IL-38 in AD patients with treatment compared to newly diagnosed patients, in males but not females
	Glaucoma	Positive correlation with MDVF
	CVD	Regulation of dendritic cell function/ inhibition of cardiomyocyte apoptosis

MS: multiple sclerosis; IBD: inflammatory bowel disease; SLE: systemic lupus erythematosus; RA: rheumatoid arthritis; BD: Behçet's disease; AITD: autoimmune thyroid disease; SS: Sjögren's syndrome; AS: ankylosing spondylitis; T2DM: Type 2 diabetes mellitus; GDM: gestational diabetes mellitus; EAE: experimental autoimmune encephalomyelitis; CVD: cardiovascular disease; MDVF: mean deviation of visual field; AD: Alzheimer disease; ASD: autism spectrum disorder.

before and after IL-38 administration [54]. The data may suggest a protective role for IL-38 in improving SLE symptoms by inhibiting such inflammatory cytokines.

In addition to genetic and environmental factors that are proposed to involve in the development of rheumatoid arthritis (RA), various pro- and anti-inflammatory cytokines, including IL-1, TNF-α, IL-17, IL-6, and IL-37, play significant roles in the progression of RA [55-57]. It has been reported that the clinical symptoms were exacerbated in C57/BL6 IL-38 gene-deficient mice with autoantibody-induced RA compared with WT B6 mice [58]. This may suggest a possible protective role for IL-38 in RA. The effective role was also reported after injection of adeno-associated virus (AAV) 2/8 encoding IL-38 in mice arthritis models which was associated with reduced clinical inflammatory scores mainly through a reduction in macrophage infiltration and

Th-17 cytokine production [59]. On the other hand, the levels of all three IL-36Ra, IL-36 agonists, and IL-38 were higher in the synovium of patients with RA and mice with collagen-induced arthritis. These cytokines correlated with the expression of M-CSF, IL-1β, CCL4, CCL3, and IL-1Ra cytokines [11]. Moreover, a significant increase in serum levels of IL-38, IL-36β, IL-36α, IL-36Ra, and IL-33 was also reported in RA patients compared with healthy controls [60]. Xu *et al*. demonstrated that IL-38 could be used as a diagnostic marker for RA since IL-38 plasma levels increased in RA patients compared with healthy controls, and these correlated with disease severity [61]. To clarify the inhibitory role of IL-38 in RA, SIRT1/HIF-1α signalling pathway-related proteins were examined in animal models with collagen-induced arthritis. IL-38 could alleviate inflammatory responses in rats probably through up-regulating SIRT1 and down-regulating HIF-1α, TLR4, and NF-κB [62]. Jiang *et al*. suggested that the role of dendritic cells should also be considered when studying IL-38 in the pathogenesis of RA since these cells express high levels of IL-36R and are numerous in synovial tissue and fluid of RA patients [63]. This evidence may support the idea that IL-38 might exert its anti-inflammatory effects through inhibiting the pro-inflammatory function of DCs. In summary, although IL-38 may alleviate the inflammatory condition in RA, further studies in larger populations are required to elucidate the related mechanisms.

Sjogren's syndrome (SS) is categorized into primary and secondary SS based on the combination with other auto-immune diseases, such as RA and SLE [64]. Although IL-1 family cytokines have been proposed to have pathological effects in SS by exacerbating inflammation, IL-37 has an anti-inflammatory role and thereby may act as a therapeutic target for SS [65]. In addition to IL-37, IL-38 may ameliorate SS symptoms mainly through inhibiting Th17-related responses. IL-38 expression was found to be negatively correlated with IL-17 and IL-23 levels in SS. It was suggested that IL-38 significantly suppresses Th17-related responses that are involved in the pathophysiology of SS. Therefore, this could be considered a potential therapeutic target since mice treated with IL-38 indicated lower levels of IL-17 protein [66].

Chronic inflammatory bowel diseases (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), are characterized by inflammation in the gastrointestinal tract leading to digestive disorders [67]. In mice with dextran sodium sulphate (DSS)-induced colitis, IL-36γ, α, and IL-38 levels slightly increased and indicated a positive correlation with IL-17A and IL-1β [11]. Xie *et al*. reported remarkably higher levels of IL-38 in the intestine of IBD patients and DSS-induced colitis mice, while treatment with recombinant IL-38 reduced IBD symptoms of DSS-induced colitis, including colon shortening, weight loss, and disease activity index reduction. Furthermore, LPS-stimulated RAW 264.7 cells and bone marrow-derived macrophages (BMDMs) treated with recombinant IL-38 demonstrated lower levels of pro-inflammatory cytokines, such as IL-1β, IL-6, TNF-α, CCL-7, and CCL-2, similar to the results of previous studies in humans [68]. Double-staining immunohistochemistry (IHC) analysis indicated higher protein expression of IL-36γ, IL-36β, IL-36α, IL-36Ra, and IL-38 in immune and non-immune cells in patients with active IBD compared with non-inflamed controls [69]. In contrast, CD and UC patients demonstrated significantly lower levels of IL-38 protein in serum and IL-38 transcript in the intestinal mucosal tissues compared to healthy controls, as evaluated by ELISA and IHC, respectively. Interestingly, IBD patients showed significantly higher levels of NF-κB and p-STAT3 compared to healthy controls [70]. Overall, it could be suggested that IL-38 plays a protective role in IBD by regulating NF-κB and p-STAT3 signalling pathways, and thereby may be considered as a target for IBD treatment.

The IL-23/IL-17R axis is reported to aggravate the inflammatory condition in thyroid-associated ophthalmopathy (TAO) patients. In order to identify the role of IL-38 in suppressing this inflammatory axis, PBMCs were first treated with anti-CD28 and anti-CD3 antibodies and then pre-treated with different concentrations of IL-38 and stimulated with IL-23 subsequently. The results demonstrated that IL-38 could down-regulate IL-23R expression on CD4+ cells in a dose-dependent manner. IL-38 could also reduce IL-17A secretion from PBMCs induced by IL-23 at low concentrations, although this effect did not continue at higher concentrations [71]. These results were compatible with another study conducted by Shi *et al*. In this study, TAO patients had lower levels of IL-38 in the circulation and orbital connective tissues than healthy controls, which correlated with worse clinical conditions [72]. Overall, clarifying the role of IL-38 in the pathogenesis of thyroid-related diseases may help improve the therapeutic strategies.

Among all the cytokines involved in the development of psoriasis, the role of the IL-36 cytokine family is highly significant. These cytokines, mostly IL-36γ and IL-36α, are produced by epidermal keratinocytes, dermal fibroblasts, endothelial cells, dendritic cells, Langerhans cells, and macrophages infiltrating the dermis of psoriatic skin [73]. It was reported that keratinocytes in primary culture with TLR-3 ligand polyI:C or a combination of inflammatory cytokines, such as TNF-α, IL-22, and IL-17A, resulted in enhanced production of IL-36Rα, IL-36γ, β, α and IL-38 by these cells. Among enhanced cytokines, a positive correlation was found between IL-38 and CK10 expression which is considered a marker of keratinocyte differentiation [11]. Another study demonstrated that IL-38 could suppress the production of IL-17 cytokines by γδ T cells through X-linked IL-1 receptor accessory protein-like 1 (IL1RAPL1). Interestingly, elevated levels of IL-17 were found in IL-38 knockout mice with imiquimod (IMQ)-induced psoriasis, and were consequently reduced by administrating γδ T cell-receptor-blocking antibodies or IL-38 [47]. The presence of IL-1β, IL-36α and γ, IL-36Rα, and Th17 cytokines, as well as the lack of IL-38 and IL-37 probably play a key role in the amelioration of skin inflammation and the pathogenesis of psoriasis [51]. However, these reports are somewhat contradictory with Palomo *et al*.'s observation that suggested no IL-36 inhibitory role for endogenous IL-38

in disease development in mice with IMQ-induced skin inflammation [74].

Such contradictions have also been reported in multiple sclerosis (MS). It has been shown that newly diagnosed MS patients had a significantly higher level of IL-38 compared to those who received treatment in the past. This elevation in cytokine levels could result from a feedback loop by IL-38, to ameliorate inflammation in the early stages [75]. In contrast, Huard *et al*. demonstrated that disease severity was reduced in IL-38 knockout mice with experimental autoimmune encephalomyelitis (EAE). This feature was probably due to decreased T cell and macrophage infiltration in the spinal cord. According to this study, IL-38 might unexpectedly promote inflammation in the CNS [76]. As for psoriasis, the precise underlying mechanism for IL-38 in the protection or development of MS remains to be explored.

IL-38 and cancer

There is insufficient information on the role of IL-38 in cancer, and according to our knowledge, it is only restricted to colorectal and lung cancer. IHC analysis in colorectal cancer (CRC) showed a significant association between higher expression of IL-38 and better overall survival, smaller tumour size, and extent of tumour differentiation [77]. Consistently, a more recent study indicated that IL-38 may inhibit cell migration, metastasis and proliferation, and may facilitate apoptosis of colorectal tumour cells by negative regulation of extracellular signal-regulated kinase signalling (ERK) [78]. These two studies suggested that IL-38 may be an important marker to predict the prognosis of CRC.

Besides its beneficial roles in CRC, it has been reported that IL-38 could affect tumour growth by regulating angiogenesis. Angiogenesis plays a significant role in physiological as well as pathological functions. The relation between chronic inflammation and angiogenesis has been demonstrated in recent decades. At the onset of inflammation, a cascade of pro-inflammatory cytokines, such as IL-6, IL-1 β, and TNF-α, start to be secreted [79, 80]. In this regard, the anti-inflammatory property of IL-38 might have a determinable effect to suppress and/or prevent tumours in the initial phase where inflammatory responses may trigger tumour formation and tumour progression [81]. Further to this, IL-38 increases in hyperoxic situations and plays an anti-angiogenic role by decreasing VEGF-induced endothelial cell (EC) proliferation. It has been shown that this effect was eliminated by adding an anti-IL-38 antibody [82]. However, clarifying the exact signalling pathway of IL-38 that inhibits angiogenesis needs more investigation. Given that angiogenesis is a vital phenomenon in cancer progression and IL-38 can inhibit angiogenesis, it can be suggested that IL-38 could inhibit cancer.

In contrast, IHC analysis in lung adenocarcinoma indicated that increased expression of IL-38 was strongly linked with high tumour grades, advanced stages, and the presence of vessel and pleural invasion, as well as reduced overall survival and disease-free survival. In addition to clinical implications, positive cases of PD-L1 presented with higher expression of IL-38 compared to negative cases [83]. Furthermore, *in vivo* injection of Lewis lung carcinoma cells harbouring IL-38-plasmid (LLC-IL-38) was found to be related to lower levels of CD8+ tumour-infiltrating lymphocytes (TILs) [84]. In line with this study, accumulating evidence has shown that IL-36 largely exhibits an anti-tumour activity through Th1 polarizing and CD8 activation. Therefore, it is postulated that IL-38 overexpression, which strongly inhibits IL-36 function, might be involved in carcinogenesis and tumour development through suppressing anti-tumour responses [85, 86]. Accordingly, in lung adenocarcinoma, IL-38 probably influences the components of the tumour microenvironment and/or host immunity and subsequently contributes to disease progression. This data revealed that IL-38 targeting might be a promising strategy to improve disease outcomes in lung cancer.

Therefore, IL-38 might have a dual role in cancer, and the controversial findings among these studies may result from different types of cancer and components of the tumour microenvironment. All in all, exploring different aspects of this cytokine in cancer may provide an opportunity for new therapies in the future.

IL-38 and infectious diseases

Acute respiratory distress syndrome (ARDS) is a life-threatening form of lung injury that is mainly caused by infectious insults. Pandemic influenza A and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viruses frequently lead to ARDS [87]. The immune components, particularly macrophages and neutrophils, play a profound role in the pathophysiology of ARDS by releasing many pro-inflammatory mediators (*e.g*. IL-1β, TNFα, IL-8, IL-6, and IL-17) and recruiting inflammatory cells (*e.g.* Th17 lymphocytes) [88]. The imbalance of the Treg/Th17 ratio as well as the higher proportion of Th17 cells could exacerbate lung injury in ARD [89, 90]. More importantly, based on *in vitro* studies, AA 3-152 protein, a recombinant form of IL-38, strongly reduced Th17 differentiation and IL-17A production via suppressing p-STAT3 expression. These molecular and cellular processes are the most likely reasons why IL-38 could diminish lung injury and uncontrolled inflammation in ARDC [91]. Anti-inflammatory properties of IL-38 were shown *in vitro* in co-culture of macrophages and human respiratory epithelial cells, and in an animal model based on the establishment of a pneumonia murine model induced by poly (I:C). IL-38, in a dose-dependent manner, was able to mitigate inflammatory responses by suppressing pro-inflammatory mediators (*e.g*. IL-6, TNF-α) through intracellular p38 MAPK, ERK1/2, MEK, STAT1, STAT3, and NF-κB signalling pathways. A similar protective condition was also found in an animal study by up-regulating Tregs and down-regulating NK, NKT, γδ T, Th1, and Th17 lymphocytes. Consequently, the alterations in ratios of the immune cell subsets ameliorated poly (I:C)-induced acute lung injury [92]. These features are in concordance with the specific roles of IL-38 during allergic asthma and sepsis, as explained below [26, 49]. In a clinical setting, however, both circulating IL-36α and IL-38 were found

to be significantly higher in patients with influenza and COVID-19. Importantly, both cytokines strikingly decreased after recovery from acute infection. From this point of view, the results could suggest the prognostic value of IL-38 in respiratory viral infections. Correspondingly, patients with severe COVID-19 demonstrated a lower concentration of IL-38 that was accompanied by higher levels of IL-36α. Interestingly, a negative correlation was found between IL-38 and disease severity. This may clinically support the regulatory and protective roles of IL-38 in response to viral infections, especially for infection with SARS-COV-2 (COVID-19). These data may also provide novel evidence for therapeutic implications of IL-38 in such infections [92]. Notably, it has been reported that IL-36 is considered as a potential marker for severe COVID-19 [93]. Infection with SARS-COV-2 was shown to stimulate the generation of IL-36 from keratinocytes, aggravate skin lesions, and promote leukocyte recruitment [94]. Similar to IL-36Rα, IL-38 acts as an antagonist of IL-36 and inhibits IL-36-mediated hyper inflammation [95]. The levels of IL-6 and CRP were found to be higher in COVID-19 patients, and maximal IL-6 levels, followed by high levels of CRP, could be employed as the strongest predictors of respiratory failure [96-98]. In addition, IL-38 administration appears to exert beneficial effects, at least in part, by suppressing IL-6 produced during infections [99]. The interaction between SARS-COV-2 and Toll-like receptor (TLR) contributes to the release of pro-IL-1β. In addition to IL-6 inhibition, IL-38 was also shown to suppress IL-1β [100, 101]. This may again support the protective roles of IL-38 in COVID-19. In this regard, IL-38 administration might be a promising strategy in the treatment of severe COVID-19, especially for those with reduced levels of IL-38. However, further research is needed to determine the specific role of IL-38 in COVID-19.

Sepsis is known as life-threatening organ dysfunction that is mainly caused by an uncontrolled immune response to infectious agents, and often has a high mortality rate [102]. Tregs were shown to naturally potentiate the extent of immunosuppression during the early phase of sepsis to preserve homeostasis [103]. In support of this idea, a recent study identified that CD4+ CD25+ Tregs are essential targets for the IL-38-mediated protective response against sepsis [49]. Preclinical studies have demonstrated that IL-38 and its receptor, IL-36R, were markedly expressed in murine CD4+ CD25+ Tregs, especially after stimulation with LPS. Treatment of CD4+ CD25+ Tregs with IL-38 augmented the immunosuppressive activity through up-regulation of Foxp3 and CTLA-4 and production of anti-inflammatory cytokines, IL-10 and TGF-β. These effects could be amplified by LPS stimulation. Additionally, administration of IL-38 in a CLP model of sepsis led to an increase in Th2 responses and a decrease in the proliferation of effector T cells. These conditions notably improved the survival rate of CLP-induced sepsis and facilitated bacterial clearance [49]. In line with these results, another study indicated that IL-38 administration was clearly linked with reduced levels of various cytokines and chemokines (*e.g.* CXCL1, TNF-α, IL-17, IL-27, IL-6 and CCL2) and less damage to kidney, lung, and liver tissues based on a CLP model of sepsis. Interestingly, anti-IL-38 antibody reversed the beneficial activity of IL-38 [99]. This evidence may introduce IL-38 as a tool for antisepsis therapy or at least as a therapeutic agent to alleviate septic complications in the future.

Hepatitis B is a worldwide life-threatening liver infection caused by hepatitis B virus [104]. The findings of Yuan and colleagues showed an increase in serum levels of different cytokines such as IL-6, TNF-α, IL-17, IL22, IFN-γ, and liver enzymes including ALT and AST in liver injury induced by concanavalin A (Con A) in mice. Accordingly, the expression of exogenous IL-38 caused a significant diminution in circulating pro-inflammatory cytokines and serum levels of AST and ALT but not IL-10, which is an anti-inflammatory cytokine [105]. Such alterations in hepatic toxicity and cytokine level may alleviate the inflammation and may have hepatoprotective properties against Con A-induced liver injury in the murine model. However, in the clinical setting, it has been shown that higher levels of circulating IL-38 in untreated chronic hepatitis B patients may reflect liver injury because a higher IL-38 level at baseline positively correlated with higher AST, an indicator of liver injury [106]. Despite this, higher concentrations of IL-38 before treatment may result in a favourable virological response (VR) to telbivudine (LdT) treatment by facilitating the clearance of HBV infection [106].

IL-38 and allergic asthma

Allergic asthma is closely related to airway hyper-responsiveness (AHR) and the reactivity mediated by type 2 inflammatory responses that strongly result in inflammation-associated tissue injuries; therefore, Tregs may be of therapeutic value by suppressing airway inflammation and preventing the development of allergic asthma [107]. Recently, it has been reported that intraperitoneal injection of murine recombinant IL-38 into HDM-induced mice powerfully ameliorated airway hyper-reactivity by reducing the accumulation of eosinophils, Th2 cells, Th17 cells, and ILC2, but increasing the proportions of Tregs and M2 macrophages [26]. In accordance with these results, significantly decreased levels of CCR3+ eosinophil and human CD4+ CRTH2+ Th2 cells were observed in the humanized murine model of asthma following the administration of human IL-38 [26]. In contrast, another study revealed that the elevated levels of IL-38 were negatively correlated with CD4+ CD25highFoxP3+ and CD4+ CD25highCD127− Treg subsets in asthmatic patients with higher levels of periostin (>40 ng/mL), which is an important biomarker of eosinophilic airway inflammation [108]. In parallel, it has been suggested that IL-38 may promote airway eosinophilic inflammation in asthma, perhaps through IL-5. In support of these data, lower levels of airway eosinophils were observed in an IL-38-knockout C57BL/6 mouse model. However, additional recombinant mouse (rm) IL-38 protein did not significantly increase airway eosinophilia in this mouse model [109]. Some limitations (*e.g.* limitation of the detection kit for murine IL-38) and differences (*e.g.* difference in mouse strains) might be the main reasons for the discrepancies between these studies. Therefore, further studies are

required to more precisely examine IL-38 activity in airway allergic inflammation and/or its applicability as a novel therapeutic approach in the treatment of allergic asthma.

IL-38 and metabolic and cardiovascular diseases

Obesity is highly associated with chronic inflammation. In a mouse model with high-fat diet-induced obesity, the transfer of a plasmid DNA encoding IL-38 resulted in decreased adipose tissue, liver fat accumulation, and insulin resistance. IL-38 gene transfer also decreased levels of inflammatory cytokines such as IL-1β, MCP-1, and IL-6 [110]. Recently, it has been shown that IL-38 can suppress the differentiation of adipose cells by increasing the expression of GATA-binding protein-3 (GATA-3) which is considered as an inhibitory marker for adipocyte differentiation. IL-38 was also shown to promote the expression of glucose transporter type 4 (GLUT4) which increases insulin sensitivity in fat cells [111, 112]. Taken together, these studies indicate that IL-38 can be utilized as a promising tool for the treatment of obesity and/or obesity-induced insulin resistance.

Inflammation is tightly associated with the pathogenesis of type 2 diabetes mellitus (T2DM). IL-38 plays an anti-inflammatory role in T2DM to suppress inflammation [113]. Furthermore, IL-38 promotes insulin sensitivity mainly through inhibiting the function of IL-36 since the administration of IL-36 antibody in diabetic mice resulted in downregulation of insulin in plasma and elevated sensitivity to insulin treatment [114].

Hyperlipidaemia, inflammation, and leukocyte accumulation are directly associated with atherosclerosis and cardiovascular diseases (CVD) [115, 116]. The serum levels of IL-38 and IL-38 mRNA expression in PBMCs of hyperlipidaemia patients were found to be elevated, and *in vitro*, it has been shown that this cytokine could inhibit the secretion of IL-6, CRP, and IL-1β in PBMCs of these patients. Although the level of IL-38 increased during the development of hyperlipidaemia based on a mouse model with high-fat diet-induced hyperlipidaemia, IL-38 overexpression using an adeno-associated virus (AAV) suppressed this process. Moreover, IL-38 overexpression using AAV significantly decreased total cholesterol (TC), low-density lipoprotein cholesterol (LDL), and triglyceride (TG). IL-38 also diminished the expression of pro-inflammatory factors, such as IL-1β, IL-6, and CRP. [117]. Therefore, IL-38, by regulating harmful fats and inflammatory mediators, may alleviate atherosclerotic lesions in mice models. Excessive inflammatory responses are known as the hallmarks of atherosclerotic events and CVD [116]. The current evidence indicates that inflammatory cells and/or inflammatory mediators may ultimately exacerbate tissue injury following the MI process [118, 119]. The expression of IL-38 in inflamed cardiomyocytes and CD68+ macrophages was reported to be markedly elevated during acute inflammation of MI in a murine model [50]. Interestingly, IL-38 gene expression and plasma IL-38 levels in circulating PBMCs were at high levels in patients with ST-segment elevation myocardial infarction (STEMI) [120]. Moreover, a recent study introduced IL-38 as a B cell-derived cytokine in healthy individuals which inversely correlated with innate inflammation indicators (*e.g.* CRP, leptin, IL-1Ra, and IL-6). These mediators were found to be associated with an increased risk of CVD in overweight persons [121]. As an inflammatory cytokine, IL-38 may naturally act as an endogenous factor to antagonize inflammatory responses and alleviate cardiac remodelling after the MI process. In addition to endogenous function, a recent study indicated that recombinant IL-38 injection into MI-induced C57BL/6 mice could restore cardiac morphology and function after MI. It was speculated that the interaction of IL-38 with IL-36R on DCs may inhibit DC maturation as characterized by lower expression levels of cell surface molecules (*e.g.* CD40 and CD86) and inflammatory mediators (*e.g.* IFN-γ, TNF-α and IL-23). Such alterations in pro-inflammatory cytokines and co-stimulatory molecules could attenuate inflammatory reactions in post-MI cardiac remodelling. In addition to DC regulation, IL-38 was shown to reduce cardiac complications via inhibiting cardiomyocyte apoptosis in a Bcl2/Bax-dependent manner [50]. Although more studies are required to determine the clinical value, the results may introduce IL-38 as a new target for CVD or MI studies.

Therapeutic role of IL-38 in different types of diseases

The interleukin-1 superfamily has diverse effects on inflammatory processes. Most members exert pro-inflammatory properties and cause tissue damage, while IL-38 may exert a potent anti-inflammatory activity in systemic and local inflammatory diseases [122]. Recent studies have demonstrated that treatment with IL-38 for respiratory viral infections, CVD, sepsis, allergic asthma, and autoimmune diseases was accompanied by modulated inflammatory responses, possibly by up-regulating Tregs but down-regulating Th17 cells. Moreover, blocking pro-inflammatory cytokines with IL-38 reduced disease severity in patients with respiratory viral infections, and may serve as a new therapeutic target [101]. It has been shown that treatment with anti-IL-17A antibody, secukinumab, exerts a therapeutic effect on psoriatic patients by increasing IL-38 levels and altering IL-36-induced responses [123]. Successful treatment by IL-38 may depend on the type of receptor it binds to, the dose, and the length of the protein [3, 4]; the efficacy of mature (full-length) or N-terminally truncated forms of IL-38 in therapeutic strategies is still a matter of controversy [25, 123]. More clinical trial studies are required to provide new insights into developing therapeutic strategies based on anti-inflammatory molecules (*e.g.* IL-37 and IL-38) in the near future. The therapeutic roles of IL-38 in various types of diseases are summarized in *table 2*.

Conclusion

IL-38 is a newly described cytokine of the IL-1 family. This cytokine acts as a natural inhibitor of inflammation by up-regulating Tregs, down-regulating Th17 cells, and/or suppressing pro-inflammatory cytokines. Regarding the anti-inflammatory activity of IL-38, this may serve as a good therapeutic target for numerous

Table 2.
Therapeutic role of IL-38 in different types of diseases.

Disease	Development stage	Type of intervention	Result(s)	Ref.
Psoriasis	Psoriasis patients and healthy controls who had plastic surgery	Administration of anti-IL-17A antibody (secukinumab)	• Increase of IL-38 in skin of secukinumab-treated patients, and decrease in IL-36γ and IL-36Ra • Increase in IL-38 mRNA levels in skin after 8-week therapy, reduced IL-36Ra and IL-36γ mRNA • Up-regulation of IL-38 serum levels in psoriatic patients following secukinumab	[123]
	BALB/cJ mice	Subcutaneous injection of IL-38 to imiquimod -induced psoriasiform dermatitis mice	• Decrease in CCL20, IL-6, and CXCL8 mRNA expression in the skin of IL-38-treated mice • Decrease in the number of Ly6G+ neutrophils and infiltrating CD3+ T lymphocytes in IL-38-treated mice • Reduced expression of VEGF-A cytokine and number of proliferating Ki67+ keratinocytes	
	BALB/c mice	IL-38 KO mouse model treated with mature recombinant mouse IL-38	• Suppression of IL-17A production by dermal γδ T cells following IL-38 injection • Increase in keratinocyte differentiation markers; in particular, Krt10 expression in IL-38-treated psoriatic animals compared to control animals, indicating recovery of skin regeneration • Reduced skin redness, scaling and stiffness • Reduced protein levels of IL-6 and IL-17A at Day 3 following IL-38 injection • Reduced dermal neutrophil infiltration after 5 consecutive days of IL-38 injection	[47]
	BALB/c mice	IL-38 KO mouse model	• No effect of IL-38 deficiency on the development of IMQ-induced skin inflammation and the local expression of pro-inflammatory mediators in the skin	[74]
Inflammatory bowel disease	C57BL/6 mice	Injection of recombinant IL-38 to mice with DSS-induced colitis	• Improvement of histological damage of colon, weight loss, and disease activity index • Reduced mRNA levels of IL-10, IL-1β, IL-22, TNF-α, and Foxp3	[68]
	Murine macrophage cell line (RAW 264.7) and murine BMDM	Treatment of LPS-stimulated cell lines with recombinant IL-38	• Reduced expression of IL-1β, TNF-α, IL-6, CCL-7, IL-10, and CCL-2 in RAW 264.7 cells • Reduced LPS-induced IL-6, TNF-α, IL-1β, and CCL-7 mRNA expression in BMDM	
SLE	PBMCs derived from healthy volunteers	IL-38 silenced with siRNA in PBMCs	• Increased expression of APRIL, IL-6, and CCL2	[53]
	1. PBMCs derived from SLE patients	PBMCs treated with IL-38	• Reduced expression of inflammatory cytokines (IL-1β, IL-6, IL-23, and TNF-α)	[52]
	2. C57BL/6 mice	Lupus mouse model induced by pristine and then treated with IL-38	• Decrease in proteinuria and improvement in kidney histological examinations • Reduced plasma levels of inflammatory cytokines (IL-1β, IL-23, IL-6, and TNF-α) and glomerular IgG deposition Reduced anti-dsDNA antibody and plasma ANA	
	MRL/lpr mice model of spontaneous lupus-like disease	Intravenous injection of recombinant IL-38	• Alleviation of skin lesions and reduction of proteinuria, leukocyteuria, and nephritis • Suppression of IL-22, IL-17, and pathogenic double-negative T lymphocytes	[54]
Systemic inflammation and arthritis	Male C57BL/6 mice, SCW-induced arthritis, MSU crystal-induced arthritis, systemic endotoxemia, and MSU crystal-induced peritonitis	Mouse model received intraperitoneal recombinant human IL-38	• Reduced inflammation • Reduced SCW and MSU crystal-induced arthritis, joint swelling, inflammatory cell influx, and synovial levels of IL-6, IL-1β, and KC by 50% or more. • Suppressive role of IL-38 was independent of the anti-inflammatory co-receptor IL-1R8 in SCW model • Reduced plasma levels of IL-6 and KC, and peritoneal KC in MSU crystal-induced peritonitis • Systemic reduction of TNFα, IL-6, and KC in the LPS endotoxemia model following IL-38 pre-treatment	[124]
Rheumatoid arthritis	CIA, AIA, K/BxN STIA mice models	Articular injections of AAV 2/8 encoding IL-38	• Reduced inflammation in joints of mice with CIA and STIA but not AIA • Reduced macrophage infiltration • Reduced expression of IL-23, IL-17, TNFα, and IL-22 • No effect on bone and cartilage damage	[59]
	THP-1 monocytic cell line	THP-1 monocyte treated with lentiviral plasmid encoding IL-38	• Reduced levels of IL-6, IL-23 and TNFα • Anti-inflammatory effect of the conditioned media derived from these cells on human primary macrophages and synovial fibroblasts from patients with RA	
	Collagen-induced arthritic (CIA) rats	Intravenous injection of recombinant murine IL-38	• Reduced joint damage • Downregulation of RANK, RANKL, VEGF, VEGFR1, VEGFR2, HIF • Overexpression of OPG in CIA rats	[62]

Lung carcinoma	LLC	Transfected with IL-38-expressing plasmid	• Reduced tumour cell proliferation of LLC-IL-38 cells	[84]
	Female C57BL/6J mice	Injection of LLC-IL-38 subcutaneously	• Reduced number of CD3+ and CD8+ TILs in the tumour microenvironment • Suppression of IFN-γ, IL-17A, and TNF-α in the tumour microenvironment	
Sepsis	Male BALB/c	Septic mice induced by CLP, intraperitoneally injected with recombinant murine IL-38	• Improvement of survival rate • Increase in immunosuppressive activity of CD4+ CD25+ Tregs • Amplification of Th2 response • Reduced effector T cell proliferation	[49]
Asthma	Two types of mice with allergic asthma:1. HDM-induced allergic asthmatic mice; 2. humanized HDM-induced allergic asthmatic mice	Intraperitoneal injection of IL-38	• Reduced airway hyper-reactivity via reducing the accumulation of eosinophils in the lungs and suppressing the expression of Th2-related cytokines (e.g. IL-4, IL-5, and IL-13) in the bronchoalveolar lavage fluid (BALF) and lung homogenates • Reduced frequency of Th2 cells but increased the number of Tregs in HDM-induced allergic asthmatic mice • Reduced population of CCR3+ eosinophils in the BALF and lungs • Reduced frequency of human CD4+ CRTH2+ Th2 cells in the lungs and mediastinal lymph nodes	[26]
Myocardial infarction	BMDCs	DCs treated with IL-38	• Decreased release of IL-23, TNF-α, and IFN-γ from IL-38-DCs	[50]
	MI-induced C57BL/6 mice	Injection of recombinant IL-38 in mice	• Amelioration of ventricular remodelling after MI • Improvement of cardiac function • Reduced post-MI mortality • Inhibition of cardiomyocyte apoptosis and decrease in myocardial fibrosis	
Hyperlipidaemia	ApoE-deficient C57Bl/6J mice with HCD (high-cholesterol diet)	Injection of an AAV expressing IL-38	• Suppression of development of hyperlipidaemia • Inhibition of inflammatory mediators (CRP, IL-6, and IL-1β) and the atherosclerosis process	[117]
Obesity	Adipose precursor 3T3-L1 cells	Treated with IL-38	• Reduced number of lipid droplets in 3T3-L1 cells • Increase in GLUT4 and GATA-3 mRNA expression • Inhibition the secretion of IL-1β, MCP-1, and IL-6 by 3T3-L1 cells • Suppression of human adipocyte differentiation	[112]
	Mice with high-fat diet-induced obesity	Treated with plasmid encoding IL-38	• Reduced insulin resistance caused by obesity, body mass, and liver fat content • Suppression of IL-6, MCP-1, and IL-1β production	[110]
Type 2 diabetes	C57BL/6	Plasmid AAV expressing IL-38	• Inhibition of IL-36 function • Inhibition of T2DM development	[114]
Retinopathy	Cultured HRECs and HUVECs	Supplementation of IL-38 in cell culture	• Reduced VEGF-induced EC proliferation, migration and tube formation	[82]
	Mice with oxygen-induced retinopathy (OIR)	Intraperitoneal injection of IL-38	• Suppression of neovascularization in the mouse model of OIR • Reduced retinal angiogenesis	
Autism spectrum disorder	Human microglia cells stimulated with neurotensin	Treated with recombinant IL-38	• Inhibition of CXCL8 and IL-1β secretion by about 30%	[125]
Pulmonary fibrosis	Mice with pulmonary fibrosis induced by bleomycin	Injection of lentivirus expressing IL-38 into the nasal cavity of mice	• Reduced IL-1β, IL-17A, TNFα, IL-6, and MCP-1 levels • Increase in anti-inflammatory cytokines (IL-1Ra) • Reduced body weight loss and improvement in survival of mice induced by bleomycin • Reduced pulmonary inflammation and fibrotic damage induced by bleomycin	[126]
Pneumonia	Human bronchial epithelial cell line, BEAS-2B cells, A549 cells, human BEAS-2B/A549 cells and HMDMs	Treated with human recombinant IL-38	• Suppression of the production of main cytokines and chemokines (e.g. IL-6, viral infection-related Th1 chemokine [CXCL10], and TNF-α) • Amelioration of inflammatory responses in co-cultured human respiratory epithelial cells with macrophages following stimulation by viral poly (I:C) in a dose-dependent manner	[92]
	Viral-related TLR3 ligand poly(I:C)-induced mouse model of pneumonia	Intraperitoneal injection of recombinant murine IL-38	• Elevation of IL-38 in response to poly (I: C) stimulation • Alleviation of lung tissue damage	

Intervertebral disc degeneration	HNPCs stimulated with TNF-α	Treated with IL-38	• Decrease in TNF-α-induced mediators, such as MMP-13, IL-1β, COX-2, IL-6, and ADAMTS-5 secretion • Increase in the production of type II collagen and aggrecan in the TNF-α-induced HNPC-based model of inflammation • Suppression of NF-κB signalling pathway	[25]

KO: knockout; DSS: dextran sulphate sodium; BMDM: bone marrow-derived macrophages; LPS: lipopolysaccharide; MRL: Murphy Roths Large; SCW: streptococcal cell wall; MSU: monosodium urate; AVV: adeno-associated virus; CIA: collagen-induced arthritis; AIA: antigen-induced arthritis; STIA: serum transfer-induced arthritis; SD: Sprague–Dawley; OPG: osteoprotegerin; CLP: cecal ligation and puncture; BMDCs: bone marrow-derived dendritic cells; DCs: dendritic cells; HDM: house dust mite; HRECs: human retinal endothelial cells; HUVECCs: human umbilical vein endothelial cells; poly (I:C): polyinosinic:polycytidylic acid; LLC: Lewis lung carcinoma cells; HNPCs: human nucleus pulposus cells; EC: endothelial cell.

types of diseases, especially respiratory viral infections, sepsis, autoimmunity, allergic asthma, metabolic disorders, and CVD. In respiratory viral infections (*e.g.* COVID-19), IL-38 reduces disease severity and may thus be used to develop a new therapeutic tool. The studies in cancer are limited and controversial, and investigating the biology and function of IL-38 in cancer requires extensive studies. The potential role of IL-38 and IL-38-related cytokines is still an interesting open issue, and further investigations are required to shed light on the role of IL-38 in the treatment of immune and non-immune-related disorders.

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