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HIGHLIGHTS

Clinical

REVIEW

Current perspectives on the interleukin-1 family as targets for inflammatory disease

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Since the first description of interleukin-1 (IL-1) and the genesis of the field of cytokine biology, the understanding of how IL-1 and related cytokines play central orchestrating roles in the inflammatory response has been an area of intense investigation. As a consequence of these endeavours, specific strategies have been developed to target the function of the IL-1 family in human disease realizing significant impacts for patients. While the most significant advances to date have been associated with inhibition of the prototypical family members IL-1α/β, approaches to target more recently identified family members such as IL-18, IL-33 and the IL-36 subfamily are now beginning to come to fruition. This review summarizes current knowledge surrounding the roles of the IL-1 family in human disease and describes the rationale and strategies which have been developed to target these cytokines to inhibit the pathogenesis of a wide range of diseases in which inflammation plays a centrally important role.

Keywords: Canakinumab · Inflammation · Inflammatory disease · Interleukin-1 family · Therapy

Introduction

Since the earliest descriptions of the prototypical cytokine interleukin-1 (IL-1) as a soluble endogenous pyrogen, the investigation of how this cytokine, along with subsequently identified related family members, can play centrally important roles in inflammation continues to expand [1]. While these early discoveries can justifiably be described as having contributed to the genesis of the field of cytokine biology, the IL-1 family of cytokines quickly became recognised as critical regulators of inflammatory processes across a range of human diseases [2]. As a result, there has been significant interest in targeting these cytokines for therapeutic intervention in patients where inflammation contributes to the mechanistic basis of disease [3].

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The IL-1 family consists of seven agonistic ligands (IL-1α, IL-1β, IL-18, IL-33, IL-36α, IL-36β, IL-36γ, IL-37), and three specific receptor antagonists (IL-1Ra, IL-36Ra and IL-38) which mediate their effects through four distinct heterodimeric receptor complexes. These receptors include specific ligand binding chains (IL-1R1, IL-33R (ST2), IL-18Rα and IL-36R), which upon ligand interaction recruit either the IL-1R accessory protein (IL-1RAcP), in the case of IL-1R1, IL-33R and IL-36R, or the IL-18Rβ chain in the case of the IL-18R (Fig. 1) [4]. Once activated, these receptor complexes initiate pro-inflammatory intracellular signalling cascades driven by NF-KB and MAPK dependent pathways and can play instructive roles in driving both innate and adaptive inflammatory responses both systemically and in a tissue specific manner.

The basic mechanisms which define the integral role of the IL-1 family of cytokines in the regulation of inflammation have been recently described in extensive detail elsewhere [5, 6]. In this review, we provide an overview of the rationale and strategies employed to target the activity of individual IL-1 family members

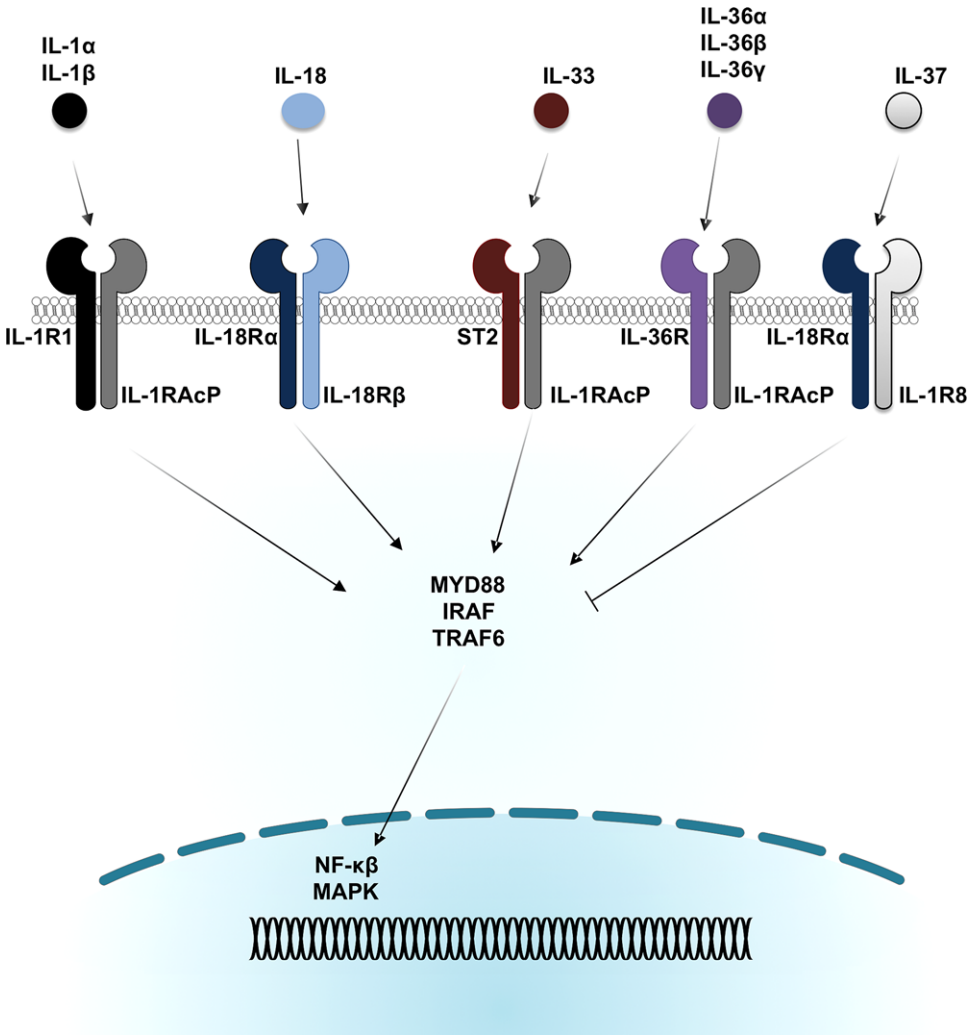

Figure 1. Members of the IL-1 family of cytokines and their cognate receptors. IL-1, IL-33 and IL-36 cytokines initiate signalling by binding to the IL-1R, ST2 and IL-36R respectively, which, upon ligand binding, form heterodimeric receptors with the IL-1RAcP. This results in the activation of MAPK and NFKB signalling, and subsequent pro-inflammatory gene expression, via MyD88, IRAF and TRAF6 dependent signalling mechanisms (as denoted by the arrows). Similarly, IL-18 activates these same pathways through the formation of an IL-18Rα and IL-18Rβ heterodimeric receptor. In contrast, IL-37 initiates an immunosuppressive signalling programme through interacting with IL-18Rα in association with IL-1R8 (SIGIRR).

across a range of inflammatory disease conditions. Furthermore, we describe how such efforts have also confirmed the previously underappreciated role for inflammation as a contributory mechanism in the pathogenesis of diseases such as atherosclerosis, which had been considered to develop through largely noninflammatory mechanisms. While these approaches have already realized hugely significant impacts in terms of patient care, these benefits will almost certainly expand as we learn more about the mechanisms through which the activity of these cytokines are regulated, as well as their specific roles in mediating the inflammatory response.

Regulation of IL-1 family cytokine activity in homeostasis and inflammation

As IL-1 cytokines play a central role in inflammation a number of distinct mechanisms have evolved to restrict their activity and maintain homeostasis [2]. In providing an endogenous balance against unregulated activity, such mechanisms are a centrally important consideration in efforts to modulate IL-1 family activity to treat disease. In addition, discoveries revealing that several autoinflammatory disease conditions result from monogenic mutations in genes which critically regulate IL-1 family member activity, has added hugely to our understanding of how these cytokines direct inflammation and homeostasis. Such observations have underscored significant, and ongoing, efforts aimed at targeting IL-1 family activity for therapeutic benefit among patients.

As well as the distinct proinflammatory ligands described above, the IL-1 family also consists of endogenous specific receptor antagonists, such as IL-1Ra and IL-36Ra. When these antagonists are present in excess, they preferentially bind to IL-1R1 and IL-36R respectively, thereby inhibiting ligand interaction and appropriate receptor assembly. As well as IL-1Ra, a decoy receptor IL-1R2 has been identified which inhibits the activity of IL-1α

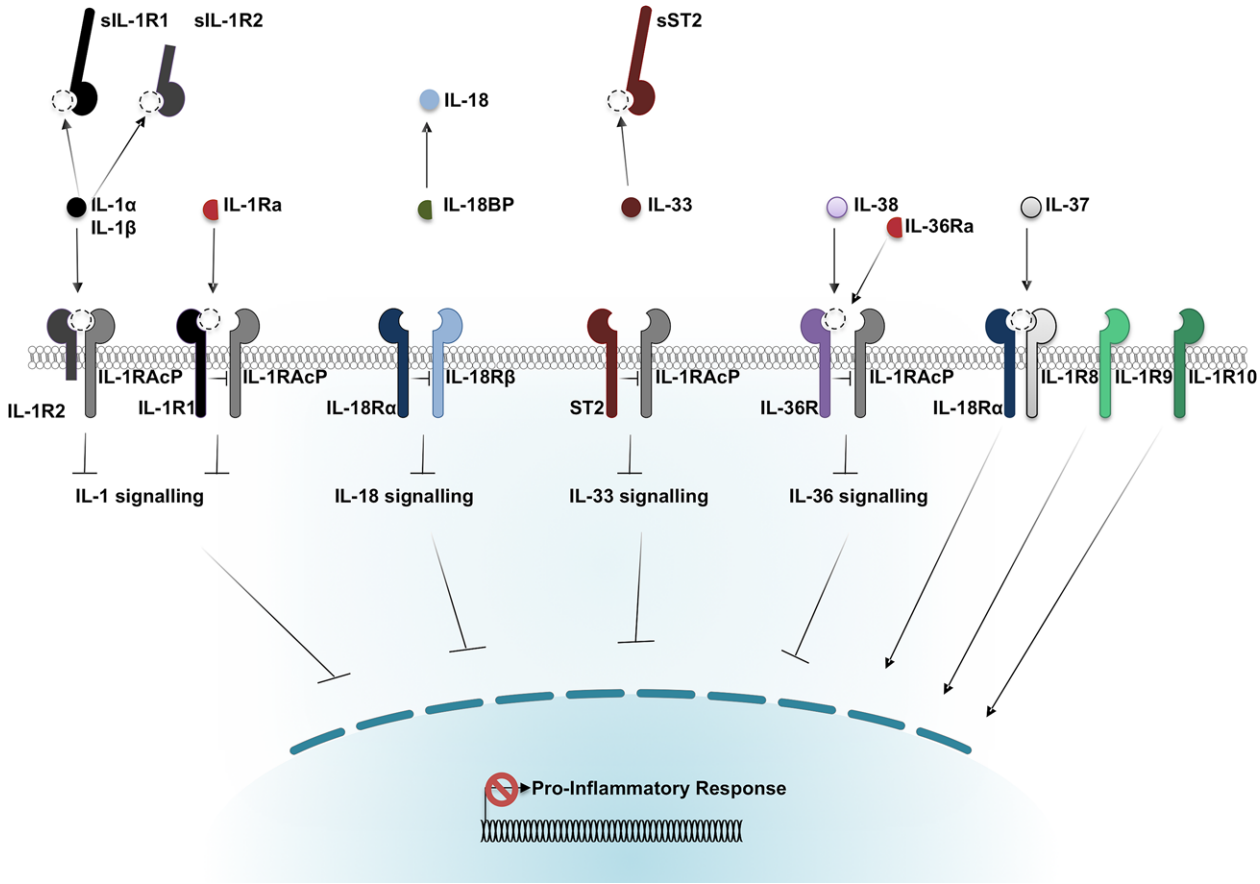

Figure 2. Negative Regulation of IL-1 family signalling. (From left to right) Specific mechanisms have evolved to regulate proinflammatory signalling by IL-1 family cytokines and their receptors. These include inhibition of IL-1α/β through neutralisation with soluble forms of the IL-1R (sIL-1R1/2), specific inhibition of the IL-1R complex through association with cell surface expressed IL-1R2, or direct antagonism through excess IL-1Ra expression. IL-18 activity is regulated through activity of the IL-18 binding protein (IL-18BP) which preferentially binds free IL-18 restricting its ability to interact with the IL-18R. Similarly, IL-33 bioavailability and activity is limited by the expression of the soluble form of its receptor ST2 (sST2). Initiation of IL-36 dependent signalling is regulated through competitive binding to the IL-36R of the specific IL-36Ra and also through the activity of IL-38. Uniquely, IL-37 acts to restrict proinflammatory responses through engagement with the IL-18Rα chain, utilizing IL-1R8 as a coreceptor. IL-1R9 and IL-1R10 are more recently described IL-1 family receptors which are also thought to exert a negative regulatory/ inhibitory function.

and IL-1β through preferential sequestration of these ligands both intra, as well as extracellularly. As IL-1R2 lacks an intracellular TIR domain, required to initiate signalling pathways, it can act as a molecular sink for IL-1 cytokines. Interestingly, IL-1R2 (and IL-1R1) can also be found in a soluble form where it may exert these neutralizing effects in a cell extrinsic fashion. In a similar way, IL-18 binding protein (IL-18BP) and a soluble form of the IL-33R (sST2) can act to neutralize the activity of their respective cytokines in the extracellular microenvironment (Fig. 2) [7]. Most recently, IL-38 has been shown act in a similar fashion to IL-36Ra, as an inhibitor of IL-36R dependent inflammation [8]. Indeed, upon its initial discovery the IL-38 protein was found to share 41% homology to IL-1Ra and 43% homology to IL-36Ra, which strongly indicated a similar antagonist function. However, unlike IL-36Ra, IL-38 appears to act as a 'non classical' antagonist, with inhibitory effects only observed at lower concentrations, indicating that it acts in a mechanistically distinct fashion from IL-36Ra.

Further negative regulation of IL-1 family signalling is provided by negative regulatory receptors which act to restrict proinflammatory signalling at the cell surface. These include IL-1R8 (also known as TIR8, SIGIRR), IL-1R9 and 10 (also known as TIGIRR2 and TIGIRR1) [4]. IL-1R8 is unique among IL-1 family receptors in that it contains a single extracellular Ig domain as well as specific amino acid substitutions in its intracellular TIR domain. IL-1R8 expression has been found to suppress IL-1 family receptor signalling through blocking the assembly of receptor complexes, and preferential sequestering of intracellular adaptor molecules, such as MyD88, which are required for the initiation of pro-inflammatory signalling [9]. More recently, it has been proposed that IL-1R8, in conjunction with the IL-18Rα chain, can act as a receptor for the immunosuppressive IL-37 and may play a role in mediating its anti-inflammatory activity (Fig. 2) [10]. The activity of IL-1R9 and IL-1R10 are far less extensively characterized, although homology of both receptors with IL-18BP may indicate similar regulatory roles, particularly in tissues of the central

nervous system [4]. Similar to the role of IL-1R8 in mediating IL-37 immunosuppression, it has also been proposed that IL-1R9 may act as a coreceptor for IL-38 and play an important role in mediating its anti-inflammatory effects [11]. Indeed IL-38 has recently been found to ameliorate skin inflammation, possibly through interacting with IL-R9 [12].

Interleukin-1α/β

Unsurprisingly, most progress has been made in our understanding of the respective roles of the initially discovered family members IL-1α and IL-1β. Both cytokines stimulate inflammatory responses through binding to the type 1 IL-1 receptor (IL-1R1) and this interaction can be blocked through preferential binding of the endogenous interleukin-1 receptor antagonist (IL-1Ra). Despite exerting similar pro-inflammatory activity in this way, there are several important distinguishing features between both ligands. IL-1α is largely membrane bound and plays a predominantly local rather than systemic role. By contrast, IL-1β is the primary circulating form of IL-1, involved in a broad spectrum of inflammatory disorders. Although full length IL-1α can exhibit functional activity, it can be further processed by the Ca^{2+} dependent protease calpain, as well as other inflammatory proteases, to potentially enhance its pro-inflammatory activity [13, 14]. Low levels of IL-1α are constitutively expressed in numerous cell types, in particular epithelial cells, vascular endothelium, keratinocytes and platelets, and its expression is increased upon exposure to stress/inflammatory signals. As well as in its membrane-associated form, IL-1α can also be expressed intracellularly in cytosolic and nuclear fractions [15]. While cell surface IL-1α acts locally by activating IL-1R1 signalling in an intra- and paracrine manner, nuclear localized IL-1α is linked to pro-inflammatory activation of transcription [16]. Cytosolic and nuclear IL-1α are also recognised as "alarmins" which can act to initiate sterile inflammation upon release into the microenvironment during the course of cell injury or necrotic cell death [17].

In contrast, the precursor of IL-1β (ProIL-1β) is biologically inactive, with its expression driven by microbe-associated molecular patterns (MAMPs), danger-associated molecular patterns (DAMPs), as well as cytokines such as tumour necrosis factor-α (TNFα), IL-18, IL-1α or IL-1β itself. ProIL-1β cleavage, to its active form, is mediated by inflammasomes, such as NOD-like receptor protein 3 (NLRP3), that activate the cysteine protease caspase-1 [18]. Caspase-1–independent activation of ProIL-1β, mediated by neutrophil-derived serine proteases, has also been described [19–21]. The expression, activation and secretion of IL-1β is mainly associated with innate immune cell subsets including monocytes, macrophages, and dendritic cells and IL-1β is generally considered to be a major pro-inflammatory mediator of the systemic inflammatory response. Ligand binding to IL-1R1 leads to the recruitment of the IL-1 receptor accessory protein (IL-1RAcP), enabling the initiation of pro-inflammatory signalling in a process which is under tight regulation through the distinct mechanisms described above.

Disruption of such regulatory mechanisms has been associated with several rare autoinflammatory disease conditions. These diseases are driven by dysregulated IL-1β activity, and arise due to inherited mutations in genes encoding proteins which regulate IL-1 production and secretion. Such conditions, described to date, include Familial Mediterranean Fever (FMR), Cryopyrin-Associated Periodic Syndrome (CAPS) which includes Familial Cold Autoinflammatory Syndrome (FCAS), Muckle-Wells Syndrome (MWS) and Neonatal-Onset Multisystem Inflammatory Disease (NOMID), as well as others with no known genetic association. These conditions typically present as periodic fever, neutropenia, fatigue, myalgia, elevated CRP levels, and in severe cases with joint deformation and developmental disability [22, 23]. Unsurprisingly, therapeutic intervention with specific therapies targeting IL-1 have been found to dramatically improve patient outcomes in these conditions (Table 1) [24–26].

Targeting IL-1 in human disease

Currently three different therapeutic strategies have been approved to target the activity of IL-1 in an expanding number of systemic inflammatory diseases, with many more in clinical development [27]. Anakinra, a recombinant, non-glycosylated human IL-1Ra, which acts to broadly inhibit inflammation mediated by both IL-1α and IL-1β, was FDA approved in 2001 for the treatment of adult rheumatoid arthritis (RA) and NOMID. Rilonacept, also referred to as IL-1 Trap, is a dimeric fusion protein consisting of portions of IL-1R1 and the IL-1RAcP linked to the Fc portion of immunoglobulin G1. Rilonacept functions as an inhibitor with affinity for IL-1α, IL-1β and IL-1Ra, and is in clinical use for the treatment of CAPS, in adults and children. Canakinumab is an anti-IL-1β monoclonal antibody that binds to human IL-1β and neutralizes its inflammatory activity by blocking its interaction with IL-1 receptors while sparing effects from IL-1α or IL-1Ra. Canakinumab was originally approved in 2009 and indicated to treat FCAS, MWS, as well as systemic juvenile idiopathic arthritis (sJIA) [28]. Administration of canakinumab every 2 weeks offers an advantage over the human IL-1Ra (anakinra) which due to rapid clearance must be injected daily, and is often poorly tolerated by patients for the above indicated conditions [29]. In addition to notable success in treating patients with rare autoinflammatory diseases as described above, targeting IL-1 activity has shown considerable promise in more common disease states considered to have inflammatory IL-1 activity as a key pathogenic mechanism.

Common inflammatory diseases responsive to anti IL-1 therapies

While investigations into inhibiting IL-1 activity across a broad spectrum of human inflammatory disease conditions continue, in certain settings, clear efficacy has been reported. These include rheumatological diseases such as gout and RA, metabolic disorders

Table 1. IL-1 family targeted therapies

IL-1 targeted therapy	Therapeutic strategy	Target	IL-1 associated disease
Anakinra	Recombinant IL-1Ra	IL-1R1	**CAPS** (17), **Rheumatoid Arthritis** (24), **Gout** (21), **Osteoarthritis** (24), **Type 2 Diabetes** (27), **Colorectal Cancer** (41), **Cardiovascular Disease** (35,36)
Rilanocept	IL-1R1 and IL-1RAcp fusion protein	IL-1α IL-1β IL-1Ra	**CAPS** (18), **Gout** (22)
Canakinumab	IL-1β neutralizing antibody	IL-1β	**CAPS** (19), **Stills Disease**, **Gout** (23), **Type 2 Diabetes** (28), **Cardiovascular Disease** (37), **Lung Cancer** (37)
Tadekinig Alfa	Recombinant IL-18 Binding Protein	IL-18	**AOSD** (63, 64)
GSK3772847/ CNTO-7160	ST2 blocking antibody	IL-33R/ST2	**Asthma** (NCT03393806, NCT03207243*), **Atopic Dermatitis** (NCT02345928*)
AMG282/ MSTT1041A/ RG6149	ST2 blocking antibody	IL-33R/ST2	**Asthma** (NCT01928368, NCT02918019*), **Atopic Dermatitis** (NCT03747575*), **COPD** (NCT03615040*), **Chronic rhinosinusitis with nasal polyps** (NCT02170337)
ANB020/ Etokimab	IL-33 neutralizing antibody	IL-33	**Asthma** (NCT03469934*), **Atopic Dermatitis** (NCT03533751*), **peanut allergy** (NCT02920021), **Chronic rhinosinusitis with nasal polyps** (NCT03614923*)
SAR440340/ REGN3500	IL-33 neutralizing antibody	IL-33	**COPD** (NCT03546907*), **Asthma** (NCT02999711, NCT03112577, NCT03387852*), **Atopic Dermatitis** (NCT03738423, NCT03736967*)
BI655130	IL-36R blocking antibody	IL-36R	**Ulcerative Colitis** (NCT0364854*), **Crohns Disease** (NCT03752970*), **Generalized Pustular Psoriasis** (NCT02978690*)
ANBO19	IL-36R blocking antibody	IL-36R	**Generalized Pustular Psoriasis** (NCT03619902*), **Palmoplantar Pustulosis** (NCT03633396*)

*Clinical trial details can be accessed at www.clinicaltrials.gov.

including Type 2 diabetes (T2D) and atherosclerosis and recent developments in the treatment of malignancy (Table 1).

In the instance of gout, swollen and painful joints, resulting from the formation and deposition of pro-inflammatory uric acid crystals, are symptoms of disease pathogenesis. Uric acid crystals, along with TLR stimulation through fatty acid DAMPS, can induce IL-1β secretion in vitro, mimicking the inflammation in the joints of gout patients and prompting the investigation of anti-IL-1 therapies in this setting [30]. Gout patients respond well to anakinra [31], rilonacept [32] and canakinumab [33] with a reduction in clinical severity and prolonged periods without flares compared to conventional steroid treatments. Anakinra has also been effective in many other joint and muscular diseases including osteoarthritis and RA with a reduction in joint destruction observed during the course of disease progression [34]. Despite such observations, a question remains as to whether, particularly among RA patients, anti-IL-1 agents offer any significant improvement over current dominant therapeutics in use such as anti-TNF biologics.

In T2D, obesity can lead to insulin resistance, with a gradual loss of insulin producing beta cells, resulting in hyperglycaemia. Glucose has been shown to directly drive IL-1β expression from beta cells [35] and can increase deposition of amyloid polypeptide which enhances IL-1β expression and contributes to the beta cell loss in diabetic disease [36]. Treatment of T2D with Anakinra or canakinumab have been found to improve insulin production and glycaemic control, while leading to decreased levels of C-reactive protein (CRP) and IL-6 [37, 38]. These studies point to a beneficial effect of anti-IL-1 therapy in T2D, likely through specific blockade of IL-1β. However, a small scale preliminary trial in patients with

T2D using an IL-1α neutralising antibody (MABp1), reduced levels of glycosylated haemoglobin (HbA1c), an indicator of the average blood glucose levels in the previous 2–3 months, suggesting IL-1α blockade may also be beneficial [39]. A possible protective role for canakinumab and anakinra has also been assessed in recent-onset Type 1 diabetes. However, while both agents were found to be safe, they were not effective as single immunomodulatory drugs in improving β-cell function among these patients [40].

IL-1 has also been at the centre of hypotheses linking inflammation with the pathogenesis of atherosclerosis. Cholesterol crystals, an established pathogenic stimulus in cardiovascular disease, can serve as an endogenous danger signal when engulfed by inflammatory monocytes to directly trigger the NLRP3 inflammasome and IL-1β production [41]. Furthermore, in preclinical animal models of atherosclerosis, NLRP3 deficient mice displayed reduced plaque severity and protection from disease, providing a mechanistic link between cholesterol deposition and a systemic pro-inflammatory state in atherosclerosis disease [42]. More recent studies have reported that cholesterol crystals interact with neutrophils to trigger the release of neutrophil extracellular traps (NETs) which prime macrophages to produce the precursor ProIL-1β [43]. IL-1 has also been implicated as mediating pathological events that can occur in the heart following a myocardial infarction, including inflammation and remodelling which act to weaken viable heart muscle tissue contributing to subsequent heart failure [44]. Pilot studies, examining the effects of administration of anakinra for 14 days following myocardial infarction, led to lowering of CRP levels, as well as reduced progression to heart failure [45]. Similarly, anakinra has also been reported to improve clinical scores associated with poor outcomes among ischaemic stroke patients [46]. These studies, alongside the reported beneficial effects of targeting IL-1 in Type 2 diabetic patients with increased risk of atherosclerotic disease, led to the design of The Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS). The CANTOS trial was the first large scale human trial initiated to test the inflammation hypothesis of atherothrombosis, through specifically targeting IL-1β. The primary outcome from the CANTOS trial assessed the incidence of cardiovascular death, myocardial infarction, or stroke and demonstrated that canakinumab was superior to placebo at preventing these adverse cardiac events [47]. This confirmation that targeting IL-1 can benefit patients in an array of cardiovascular disease settings, will likely prompt further investigations, as more information concerning the role of IL-1 in cardiovascular pathology is uncovered.

The significance of IL-1 in tumour development is also currently under investigation. IL-1α and IL-1β have been found to be abundantly expressed in advanced tumours and associated with higher tumour grade and invasiveness [48]. In addition, preclinical studies in mice have demonstrated that blocking IL-1β decreases tumour invasion, growth, and metastases indicating that specifically targeting IL-1β may be beneficial [49]. Anakinra, which neutralizes both IL-1 ligands, has been reported to inhibit colon tumour growth in preclinical studies [50] and has been investigated as a therapy across various malignancies. In metastatic colorectal cancer patients, anakinra administration was reported to provide significant survival benefit and improved quality of life scores, when added to standard-of-care chemotherapy for colorectal cancer [51]. However, in such settings the relative short half-life of anakinra and requirement for continuous administration is problematic and can hinder patient adherence, prompting investigation of anti-IL-1 neutralising antibodies [52, 53]. Along these lines, an IL-1α neutralizing antibody (MABp1) has been demonstrated to improve symptoms in patients with metastatic or unresectable colorectal cancer in a phase 3 study, revealing its potential to be used along with standard of care in the advanced treatment stages of colorectal cancer [54]. As canakinumab had been hypothesized to reduce metastatic disease in part through alteration of adhesion molecule function, incident cancers were tracked in the CANTOS trial. Here canakinumab significantly reduced the incidence of lung cancer and deaths from all cancers [47]. This has subsequently led to the design of a combination trial looking at canakinumab with a programmed cell death protein 1 (PD-1) inhibitor in patients with non-small cell lung cancer [55]. As more trial results are reported greater evidence supporting a role for targeting IL-1 in cancer therapy programs can be assessed more fully.

Interleukin-18

Similar to IL-1β, IL-18 is expressed as an intracellular precursor protein (ProIL-18) which undergoes caspase-1 mediated cleavage into its active form [56]. However, unlike IL-1β, the IL-18 precursor protein is expressed constitutively across a range of different cell types and tissues and exhibits a distinct immunostimulatory profile [57]. Most notably, IL-18 has been described as a potent stimulator of IFNγ expression and was originally identified as IFNγ inducing factor [58]. In this capacity, IL-18 is recognized as a Th1 response inducing factor alongside IL-12, and indeed requires the presence of IL-12 to elicit this function. As well as enhancing IFNγ expression from CD^{4+} T cells, IL-18 can also work in concert with IL-12 to drive NK cell effector function and expression of IFNγ, and induce NK cell expansion through enhanced IL-2 sensitivity [59–61]. IL-18 induces such responses through stimulating a unique heterodimeric receptor consisting of IL-18Rα ligand binding and IL-18Rβ accessory chains. Similar to the IL-1RAcP and other IL-1 family receptors, while the IL-18Rα chain is widely expressed, the IL-18Rβ chain, required to induce intracellular signalling, is usually absent from the cell surface unless its expression is induced by other pro-inflammatory factors such as IL-12 [57].

ProIL-18 may also be released from dying cells whereupon it can be activated extracellularly, in a caspase-1 independent fashion, by neutrophil or cytotoxic cell derived proteases [62, 63]. In its secreted form, active IL-18 is tightly regulated by the IL-18BP, which exhibits a high affinity for the cytokine and is present in the serum of healthy individuals in significant molar excess over active IL-18 [64, 65]. Disruption of this balanced regulation leads to enhanced IL-18 driven inflammatory responses which can, if unchecked, play important roles in disease.

Targeting IL-18 in human disease

While efforts to target IL-18 in human disease are less advanced compared to IL-1, there has been significant progress in this regard. Similar to IL-1, distinct autoinflammatory conditions have recently been described in which elevated IL-18 activity has been implicated in disease pathogenesis [66]. These include NLRC4 associated autoinflammatory disorders, in which patients with gain of function mutations in the *NLRC4* inflammasome gene, exhibit systemic inflammation, characterised by a macrophage activation syndrome(MAS)-like presentation and severe enterocolitis early in life [67, 68]. Notably, IL-1 blockade (anakinra) as a therapeutic strategy for these patients was found to have mixed results, indicating that alternative mediators may play a more prominent role. Indeed, it was noted that very high levels of 'free' IL-18 were present in patients' serum, offering a potential mechanistic basis for disease and, following these observations, it has recently been shown that treatment with recombinant IL-18BP offers an effective therapeutic approach [69, 70].

MAS is also known as secondary haemophagocytic lymphohistiocytosis (sHLH), and is a life-threatening condition which can arise as a complication of infection, malignancy and rheumatic diseases such as systemic juvenile idiopathic arthritis (sJIA) and adult-onset Still's disease (AOSD). Several reports have demonstrated that levels of 'free' and total IL-18 are elevated in many sHLH patients, while it has recently been reported that levels of 'free' IL-18 are also significantly elevated among patients with sJIA and AOSD [71–75]. These observations provided a sound rationale for an investigation of recombinant IL-18BP as a treatment for AOSD patients in a phase II study, which demonstrated that targeting IL-18 represents an effective therapeutic strategy [76, 77]. Although the studies described above have clearly established a therapeutic benefit of targeting IL-18 activity in human disease, it is as yet unclear whether these effects can completely be ascribed to the inhibition of its IFNγ inducing activity. In this regard, it is notable that preclinical studies indicate that IL-18 can elicit a wide range of both pro-inflammatory, and indeed pro-resolving effects, independent of downstream IFNγ activity, across a range of different tissues [57].

IL-18 activity has also been extensively characterised in the pathogenesis of several other chronic inflammatory disease conditions including Crohn's disease, rheumatoid arthritis, psoriasis, cardiovascular disease and respiratory diseases, such as chronic obstructive pulmonary disease (COPD) and asthma [57]. As such, it seems likely that inhibition of IL-18 may represent a suitable strategy for disease intervention. In particular, targeting IL-18 activity for conditions associated with intestinal inflammation/colitis such as inflammatory bowel diseases may offer significant potential. The rationale for this approach is underscored by the clear pathogenic function of IL-18 in the colon demonstrated in elegant preclinical studies by several groups, as well as the severe colitis evident among NLRC4 associated autoinflammatory disease patients described above [67, 68, 78, 79]. Indeed, both recombinant IL-18BP and an anti-IL-18 neutralising antibody have been investigated as potential therapeutics for Crohn's disease, although to date it remains unclear as to whether this approach has been successful. As our understanding of the role of IL-18 as a mediator of inflammation in the context of human disease continues to expand, its potential as a novel therapeutic target for further conditions is also likely to grow.

Interleukin-33

IL-33 was identified in 2005 through computational analysis of sequence databases, while searching for a ligand for the, until then, orphan receptor ST2, which was originally identified in 1989 [80, 81]. IL-33 is mainly expressed by epithelial cells, endothelial cells and fibroblasts, across various tissues including the lung, skin, stomach and central nervous system [80, 82]. In homeostasis, IL-33 is normally localized in the cell nucleus, and in common with IL-1α, the full-length cytokine is biologically active [83, 84]. Moreover, it has been demonstrated that cleavage of full-length IL-33 by apoptotic caspase-7 or 3 leads to an inactive form of the cytokine. Apoptotic cells release the inactive truncated form of IL-33, while necrotic cells can release the full-length IL-33 which is biologically functional [84, 85]. Thus, IL-33 also acts as an alarmin or DAMP and is secreted in response to necrosis and tissue damage, leading to the recruitment and activation of immune cells. After release, IL-33 can further mature into more bioactive isoforms through processing by neutrophil and mast cell proteases [86, 87].

IL-33 signals through a heterodimeric receptor complex comprised of ST2 and IL-1RAcP, while a soluble form of ST2 (sST2) acts as a decoy receptor, negatively regulating IL-33 signalling. ST2 is expressed in the cell surface of various immune cells, and binding of IL-33 predominantly induces type 2 immune responses, underlining its important role in helminth infection, allergy and asthma. IL-33 signalling promotes cytokine and chemokine production and degranulation of mast cells, basophils, and eosinophils. It is a major activator of type 2 innate lymphoid cells (ILC2) and Th2 cells, and also acts on Treg cells, alternatively activated macrophages, dendritic cells and NK cells. IL-33 promotes the differentiation of macrophages towards an alternatively activated phenotype, and induces eosinophilia and goblet cell hyperplasia by activating ILC2 cells to produce IL-5 and IL-13 [88–90].

Targeting IL-33 in human disease

To date, much of the development of strategies to target IL-33 has focused on its role in allergic inflammation. In mouse models of asthma and allergic airway inflammation, blockade of the IL-33/ST2 axis by anti-IL-33 neutralising antibodies or administration of sST2 has been effective in attenuating airway inflammation [91, 92]. Anti-IL-33 treatment has also been effective in allergic rhinitis models, as well as other forms of airway inflammation including cigarette smoke-induced lung inflammation and a fungal induced asthma model in mice [93–95]. IL-33 is also implicated in chronic obstructive pulmonary disease (COPD), where

elevated levels of IL-33 were found in the lungs of patients, and in a mouse model of chronic obstructive lung disease induced by parainfluenza virus infection [96]. In chronic rhinosinusitis with nasal polyps, a type 2 mediated inflammatory disease, epithelial cell derived IL-33 and IL-33-responsive ILC2s producing IL-13, appear to play an important role in disease pathogenesis [97]. Other allergic diseases in which IL-33 appears to play an important role include food allergy and anaphylaxis [98–100], and atopic dermatitis (AD) [101]. In a mouse model of food anaphylaxis, blockade of ST2 or deficiency of ST2 gene expression attenuated disease severity [100]. In both humans and mouse models of AD, IL-33 was elevated in skin keratinocytes [101]. Overexpression of IL-33 in the skin of mice causes an AD-like pathology [102], whereas IL-33 blockade or deficiency in IL-33 or ST2 genes can reduce disease severity in other models [103, 104].

IL-33 has also been implicated in the pathogenesis of other non-allergic inflammatory conditions. Expression of both IL-33 and ST2 were found to be elevated in the synovium and serum of patients with rheumatoid arthritis [105–108], and disease activity was attenuated in a mouse model of collagen induced arthritis, by blocking IL-33 signalling [105, 106]. A possible role for IL-33 in central nervous system (CNS) inflammation was also indicated by increased levels of IL-33 in the serum, peripheral leukocytes and CNS of multiple sclerosis patients [109]. However, studies in the experimental autoimmune encephalomyelitis (EAE) mouse model have shown conflicting results as to whether IL-33 exerts positive or negative effects in disease development. [110–112]. Similarly, IL-33 appears to play dichotomous roles in the gastrointestinal system. IL-33 is elevated in colonic epithelial and lamina propria cells in ulcerative colitis (UC), and its expression correlates with disease activity [113, 114]. However, preclinical studies in mice have resulted in conflicting outcomes, with various studies describing both pathogenic and pro-resolving roles for IL-33 in intestinal inflammation [115–120].

Three distinct strategies for therapeutic targeting of the IL-33/ST2 axis are currently in development: soluble decoy receptors, IL-33 neutralizing antibodies, and anti-ST2 blocking antibodies [121]. Anti-IL-33 and anti-ST2 antibodies are currently under evaluation in clinical trials for a range of allergic conditions including asthma, atopic dermatitis, peanut allergy, chronic rhinosinusitis with nasal polyps, as well as in COPD (Table 1). Decoy receptors, including 'IL-33 Trap', which is a fusion of sST2 and the accessory protein IL-1RAcP, are also under development but have not yet been fully investigated in a clinical setting [122]. Before therapeutic strategies targeting IL-33 can be further explored in non-allergic inflammatory diseases such as inflammatory bowel disease, rheumatoid arthritis and multiple sclerosis, further investigation is required to determine a definitive role of IL-33 in these settings.

Interleukin-36

The IL-36 cytokine subfamily was reclassified from earlier designations in 2010 [123], having also been identified previously based upon sequence homology with other IL-1 family members. The IL-36 subfamily consists of three agonistic ligands, IL-36α, β, γ, and one endogenous antagonist, IL-36Ra [124], all of which bind specifically to the IL-36 receptor, which is a heterodimer of the IL-36R (IL-1Rrp2) subunit and IL-1RAcP. When present in excess, IL-36Ra can bind to the IL-36R and inhibit recruitment of IL-1RAcP and the subsequent activation of downstream signalling pathways [125]. IL-38 has also been described as a possible IL-36 subfamily member, which can act as an antagonist of IL-36R [8]. Similar to other IL-1 family members, IL-36 cytokines also appear to require proteolytic processing to achieve optimal activity, in a process which is thought to be caspase-1 independent, and occurs in the presence of neutrophil derived proteases [126]. Although different cell types have been found to express IL-36 family members, including macrophages, dendritic cells (DCs), neural cells, T cells, keratinocytes, fibroblasts and epithelial cells in various tissues [124], their function is largely associated with epithelial barrier surfaces. Accordingly, much of the focus on investigating the role of the IL-36 cytokines in driving inflammatory diseases has thus far focused on such tissue sites as the skin and gastrointestinal tract [127].

Targeting IL-36 in human disease

In the skin, IL-36 cytokines are of particular relevance in the pathogenesis of a severe form of psoriatic inflammation known as generalized pustular psoriasis (GPP). GPP is a common manifestation among patients with loss-of-function mutations in the *IL36RN* gene, which encodes IL-36Ra, leading to a rare autoinflammatory condition known as Deficiency of Interleukin-36 Receptor Antagonist (DITRA) [128–131]. Several preclinical studies have shed further light on the role of IL-36 regulation of dermal inflammation during psoriasis pathogenesis. Blumberg et al. first demonstrated an important role for these cytokines in promoting dermal inflammation in mice, which shared many characteristics with human psoriasis [132]. These observations were followed by detailed preclinical studies by Tortola et al., demonstrating that IL-36 cytokines can orchestrate psoriasis from inflammation [133]. Using the imiquimod induced model of psoriasis, it was observed that deletion of the *Il1rl2* (IL36R) gene significantly diminished psoriatic inflammation in mice, while disease was severely exacerbated in the absence of *Il36rn,* the IL-36Ra gene. In this setting, IL-36 cytokines were found to direct the infiltration and activation of macrophages, neutrophils and IL-17A expressing γδ T cells to the inflamed skin [133]. Interestingly, bone marrow chimera studies indicated that radioresistant cells are implicated in directing psoriasis-like inflammation in this model, suggesting that non-hematopoietic cell expression of IL-36R is required for psoriasis onset. In support of these observations, it has also been demonstrated that keratinocytes can both express, and respond to, IL-36 family cytokines, which act in concert with IL-17A in an amplification cycle to propagate dermal inflammation [134]. The identification of a monogenic association of the IL-36Ra gene among DITRA

patients has sparked significant interest in targeting the IL-36 family to treat psoriatic inflammation. While it seems intuitive that such a strategy is likely to have significant impact among DITRA patients, a recent clinical study has indicated that this approach will also benefit GPP patients in which the *IL36RN* gene is not mutated, including those with gain of function mutations in the *CARD14* gene, or indeed, no identified genetic association[135]. IL-36 blockade may be a suitable approach, not only for these relatively rare autoinflammatory conditions, but also for more common forms of psoriasis, particularly among patients who are unresponsive to current frontline therapies. Indeed, the use of anti-IL-36R blocking antibodies has been shown extensively to inhibit psoriasis like dermal inflammation in mice providing validation for this approach [136, 137]. In addition, individuals with loss of function mutations in the *IL1RL2* gene, encoding the IL-36R, appear to have normal overall immune function, indicating that IL36R blockade represents a safe therapeutic option in humans [137].

As well as important drivers of dermal inflammation, several studies have also investigated the role of the IL-36 family in intestinal inflammation. In colon tissues, elevated levels of IL-36α and IL-36γ have been detected in patients with Crohn's disease and ulcerative colitis [138–141]. Similar to related IL-1 family members, the role of IL-36 in the gut is complex. While some studies have demonstrated that IL-36 has a pro-inflammatory role [138, 142], other studies have described its role in promoting the resolution of intestinal inflammation [140, 141]. On the one hand, IL-36 signalling facilitates neutrophil and inflammatory monocyte infiltration to intestinal tissues and can regulate the balance of pro-inflammatory mucosal CD^{4+} T cell subsets [138, 143, 144]. In contrast, IL-36R signalling can also promote the recovery of intestinal damage and accelerate mucosal healing [140, 141]. In addition, a more recent study has demonstrated that IL-36R signalling may promote intestinal fibrosis in both mice and patients with inflammatory bowel disease [145]. Although these data have underscored a current clinical evaluation of anti-IL-36R blocking antibodies among IBD patients, given such contrasting outcomes, further studies are required to determine precisely how IL-36 cytokines can mediate such apparent opposing effects in the gut.

While most studies to date have focused on IL-36 as mediator of inflammatory diseases in the skin and intestine, these cytokines have also been implicated in diseases of other tissues. Patients affected by rheumatoid arthritis, psoriatic arthritis and osteoarthritis all have elevated levels of IL-36 family members [146]. However, *Il1rl2* deficient mice were not found to exhibit any alterations in the pathogenesis of arthritic disease in preclinical models examined to date [147]. IL-36 cytokines may also play a role in the lung, as IL-36γ is highly expressed in asthma patients [148]. However, it is currently unclear as to what the mechanistic significance of these observations are.

Interleukin 37

Uniquely among the IL-1 family, IL-37 appears to act to restrict inflammatory responses in a variety of cells and tissues. Originally identified in 2000, its specific role as a natural immune suppressive cytokine has only recently come to light, sparking significant interest [149, 150]. Requiring proteolytic processing, possibly through caspase-1, for full activity IL-37, can act in both an extracellular and intracellular capacity to suppress inflammation. In its secreted form, IL-37 appears to bind the IL-18Rα chain leading to the subsequent recruitment of IL-1R8 as a coreceptor, resulting in the activation of anti-inflammatory intracellular signalling pathways [10]. The human *IL37* gene encodes 5 transcripts, of which the IL-37b isoform has been the most studied. However, unlike other IL-1 family members, no homologue of IL-37 has been found to exist in mice, arguably hindering the investigation of its unique function. Humanised IL-37 transgenic mice have been helpful in this regard and have revealed that IL-37 can exhibit broad immunosuppressive functions inhibiting both innate and adaptive immune responses [149]. Most notably, these mice exhibit reduced severity across a range of inflammatory disease models including experimental colitis, obesity driven metabolic disease and endotoxic shock among others [10, 151, 152].

A possible role for IL-37 in human disease is also beginning to be uncovered. Perhaps most significantly, several mutations in the *IL37* gene been described to be associated with the severity of rheumatoid arthritis, ankylosing spondylitis and coronary artery disease [153–155]. Expression levels of IL-37 have also been described to be altered in many disease settings with both increased and decreased levels observed [149]. Together these observations raise significant implications for the possibility of harnessing IL-37 activity to treat inflammatory disease in humans. In this regard it is particularly noteworthy that administration of recombinant IL-37 has also proven effective in treating preclinical models of inflammatory diseases including obesity dependent metabolic disease, asthma, endotoxaemia and rheumatoid arthritis [156–159]. Such observations hold considerable promise for the future translation of these effects to patients.

Conclusion

While unquestionable progress has been made in advancing therapeutic targeting of the IL-1 family in inflammatory disease over recent decades (Table 1), new discoveries continue to expand possibilities and reveal novel indications where such approaches may be of benefit [160]. Recent discoveries surrounding the mechanisms which regulate the expression and activation of IL-1 family members are also opening possibilities for novel approaches to target these pathways e.g. through NLRP3, protease and gasdermin D/pyroptosis inhibitors [161–163]. While a greater understanding of the specific, and often unique, roles each family member plays in driving systemic and tissue specific inflammatory responses will expedite these endeavours, some significant gaps in our knowledge still remain. In particular, the importance of more recently identified anti-inflammatory family members such as IL-37 and IL-38 in human disease have yet to be clarified. Similarly, uncovering the respective roles of intrinsic negative regulatory receptors such as IL-1R8, in homeostasis and disease, will likely represent critical

steps forward. As the field develops, it is probable that the number of strategies to target the IL-1 family will continue to expand across a broader range of inflammatory disease indications.

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Abbreviations: **CAP**: Cryopyrin-associated periodic syndrome · **DAMPs**: Danger-associated molecular patterns · **DITRA**: Deficiency of interleukin-36 receptor antagonist · **FCAS**: familial cold autoinflammatory syndrome · **FMR**: familial mediterranean fever · **IL-1**: Interleukin-1 · **IL-1Ra**: Interleukin-1 receptor antagonist · **IL-1RAcP**: IL-1 receptor accessory protein · **ILC2**: innate lymphoid cells · **MAMPs**: Microbe-associated molecular patterns · **MWS**: Muckle-Wells syndrome · **NOMID**: neonatal-onset multisystem inflammatory disease

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