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Recent advances in the biology of IL-1 family cytokines and their potential roles in development of sepsis

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ABSTRACT

The IL-1 family comprises two anti-inflammatory cytokines (IL-37, IL-38), two receptor antagonists (IL-1ra, IL-36ra), and seven ligand agonists (IL-1α, IL-1β, IL-33, IL-36α, IL-36β, IL-36γ). The members of this family exert pleiotropic effects on intercellular signaling, leading to pro- or anti-inflammatory responses. They initiate potent inflammatory and immune responses by binding to specific receptors in the IL-1 receptor family, and their activities are repressed by naturally occurring inhibitors. Various immune cells produce and are regulated by these crucial molecules, which appear to be involved in the pathogenesis of diverse diseases including cancer as well as inflammatory and autoimmune disorders. Recent decades have seen substantial progress in understanding how the IL-1 family contributes to the development of sepsis. In this review, we will briefly introduce the IL-1 family and discuss its critical role in inflammatory and immune responses. The potential significance of IL-1 members in sepsis will also be explored, together with the clinical implications for treating this dangerous condition.

1. Introduction

In the mid-1980s, interleukin (IL)-1 was described as the first interleukin [1], but it had already been investigated previously under other names, including hematopoietin 1, endogenous pyrogen, and leukocyte endogenous mediator [2]. IL-1 comprises IL-1α and IL-1β, which share the same receptor IL-1 receptor (IL-1R), including IL-1RAcP and IL-1R1 [3]. Subsequently, IL-1 receptor antagonist (IL-1ra) was discovered, which competitively binds to IL-1R1 without activating the IL-1 pathway [4–6]. In 1989, interferon (IFN)-γ inducing factor was named IL-1γ on the basis of its homology with IL-1 [7], but its name was later changed to IL-18 when it was found to activate IL-18 receptor (IL-18R) rather than IL-1R [8]. In the 2000s, several new members of the IL-1 family were described, including IL-33, IL-36, IL-36 receptor antagonist (IL-36ra), IL-37, and IL-38 [9,10]. Up to now, the IL-1 family has 11 members (Fig. 1).

Some of these family members require inflammasome-dependent processing in order to become active; others are released as a result of cell damage or necrosis. IL-1ra is exceptional in that it is secreted from cells as a result of its leader peptide. IL-1 family cytokines generally exert pro-inflammatory effects by reinforcing innate and adaptive immune responses that serve as the first line of defense against pathogens [11–13]. In this way, IL-1 family cytokines play fundamental roles in cellular homeostasis and host defenses against pathogens, damage, and environmental stresses.

Under certain conditions, IL-1 family cytokines can harm rather than help. For example, severe sepsis and septic shock in response to pathogens invading the bloodstream trigger the release of large amounts of inflammatory mediators such as IL-1, IL-18, and IL-33, ultimately causing rampant inflammation and tissue damage [14,15]. Thus, release of IL-1 family cytokines is considered an early marker of sepsis, and the cytokines can serve as biomarkers whose levels allow identification of septic patients at increased risk of poor prognosis [16,17]. Ironically, innate immune responses mediated by IL-1 family

Abbreviations: IL, interleukin; TIR, Toll/IL-1 receptor; IL-1ra, IL-1 receptor antagonist; IGIF, interferon-γ-inducing factor; IL-1RAcP, IL-1 receptor accessory protein; SIGIRR, single Ig IL-1R-related molecule; TIGGIR-2, three Ig domain-containing IL-1R related-2; MAPKs, mitogen-activated protein kinases; NF-κB, nuclear factor-κB; TRAF6, TNFR-associated factor 6; IRAK4, IL-1R-associated 4; MyD88, myeloid differentiation primary response protein 88; NK, natural killer; DCs, dendritic cells; SLAM, signaling lympocytic activation molecule; Tregs, regulator T cells; iNOS, inducible nitric oxide synthase; COX-2, cyclooxygenase-2; TNF-α, tumor necrosis factor-α; LPS, lipopolysaccharide; TNFRSF11b, TNF superfamily member B11; CLP, cecal ligation and puncture

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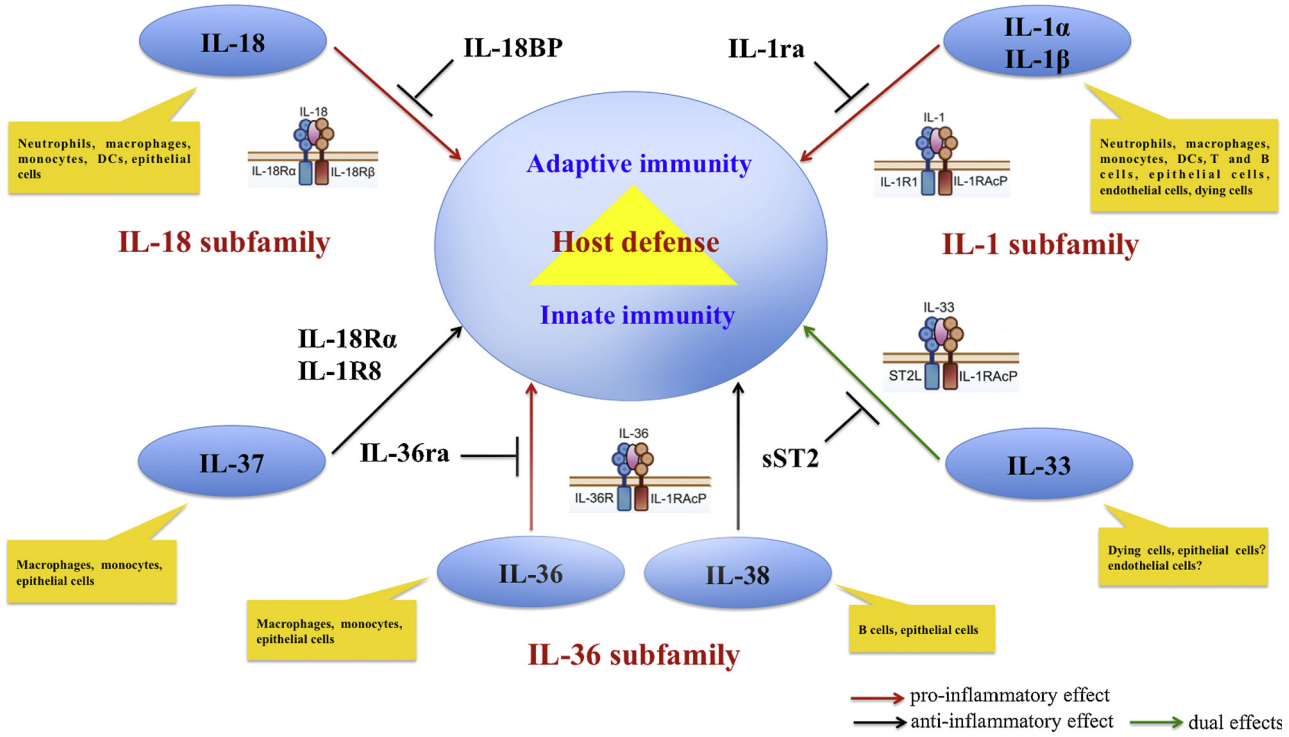

Fig. 1. Cellular sources of IL-1 family members and their roles in host defense. The common sources of IL-1 family members are epithelial cells, endothelial cells, and some immune cells, such as neutrophils, macrophages, monocytes, DCs, as well as T and B cells. Various stimuli or damage factors can induce the production of these cytokines in cells. IL-1 family cytokines are typically classified into three subfamilies according to the length of the N-terminal pro-piece. The IL-1 subfamily includes IL-1ra, IL-1α, IL-1β, and IL-33; the IL-18 subfamily includes IL-37 and IL-18; and the IL-36 subfamily consists of IL-36, IL-36ra and IL-38. Most IL-1 members exhibit proinflammatory effects, whereas several cytokines (e.g., IL-1ra, IL-36ra, IL-18BP, sST2L, IL-37, and IL-38) attenuate inflammatory responses via a negative feedback loop. The IL-1 members exert their effects through the IL-1 receptor system, which is composed of IL-1R, ST2L, IL-18R, and IL-36R. IL-1 family cytokines include agonists and antagonists of these receptors, allowing various degrees of regulation of downstream signaling pathways. Thus, IL-1 family cytokines can manage a delicate equilibrium between pro-inflammatory and anti-inflammatory responses. The downstream signaling cascades regulate innate and adaptive immunity and are indispensable for host defense against invading pathogens. Imbalance between pro- and anti-inflammatory cytokines exacerbates detrimental inflammation, leading to dysregulated host response and tissue damage.
DCs, dendritic cells; IL-18BP, IL-18-binding protein; sST2L, soluble ST2L.

cytokines are essential for helping the host respond effectively to sepsis. IL-1, IL-18, and IL-33 effectively regulate the activity of innate immune cells such as natural killer (NK) cells, neutrophils, dendritic cells (DCs), and macrophages, which assist adaptive immune response (Fig. 2, Fig. 3). In addition, IL-1, IL-33, and IL-36 act directly on T cells to strengthen adaptive immunity (Fig.2, Fig. 4). IL-37 acts as a negative feedback factor to influence regulatory T cells (Tregs) and thereby dampen lymphocytes (Fig. 3).

Cytokine-based therapies may be a promising strategy for reversing septic process. The extensive involvement of the IL-1 family in sepsis is shown in Table 1–3. Most of these insights have come from experiments in cell culture and small animals; few discoveries have been made in clinical trials. The present review aims to provide an overview of IL-1 family cytokines in sepsis and their significances in early diagnosis as well as therapeutic strategy.

2. Overview of IL-1 family cytokines and their receptors

The IL-1 family cytokines comprise 11 members: IL-1α (IL-1F1), IL-1β (IL-F2), IL-1ra (IL-1F3), IL-18 (IL-1F4), IL-36ra (IL-1F5), IL-36α (IL-1F6), IL-37 (IL-1F7), IL-36β (IL-1F8), IL-36γ (IL-1F9), IL-38 (IL-1F10), and IL-33 (IL-1F11). These members show distinct or complementary activities [9–11]. The genes encoding all members except IL-33 and IL-18 are located in a 400-kb region of human chromosome 2 [12,13]. IL-1 family cytokines are classified into three subfamilies based on the length of the precursor protein and the pro-piece. The IL-1 subfamily comprises IL-1α, IL-1β, IL-1ra, and IL-33; the IL-18 subfamily comprises IL-18 and IL-37; and the IL-36 subfamily comprises IL-36α, IL-36β, IL-36γ, and IL-36ra. IL-38 is likely to be a member of the IL-36 subfamily because it binds to the IL-36 receptor [11–13]. IL-1ra and IL-36ra are natural inhibitors, which behave like receptor antagonists [11]. How IL-1 family cytokines secreted remains unclear. The gene encoding IL-1ra regulates a signal peptide and then facilitates cytokine release via the Golgi apparatus and endoplasmic reticulum [13]. IL-1α, IL-1β, and IL-18 possess a pro-domain at the N-terminus, which is cleaved off by a cysteine protease. The inflammasome can cleave the pro-domain off IL-18 and IL-1β, triggering immune responses [13,14]. The pro-domain of IL-1α is cleaved by the cysteine protease calpain and is not required for IL-1α to exert its effect [18,19]. Other members, including IL-33, IL-36, IL-37, and IL-38, are bioactive as full-length molecules. However, the lack of an integrated N-terminus makes them weaker than processed cytokines.

IL-1 family cytokines exert their effects via members of IL-1R family, which comprises IL-1R accessory protein (IL-1RAcP, also termed ST2), IL-1R1/2, IL-36R, IL-18α/β, single immunoglobulin (Ig) IL-1R-related molecule (SIGIRR), TIGGIR-1 (also namely IL-1RAPL1) and three Ig domain-containing IL-1R-related-2 (TIGGIR-2) [4,5]. SIGIRR features one extracellular Ig region, but the other IL-1R members have three regions. The intracellular receptors feature a Toll/IL-1 receptor (TIR) zone and Ig zone spanning the cell membrane. The IL-1R2 is unique in that it lacks a TIR region [6]. When cytokines bind these receptors, an array of signaling pathways are triggered, such as those involving mitogen-activated protein kinases (MAPKs) and nuclear factor (NF)-κB. The juxtaposition of TIR domains can recruit tumor

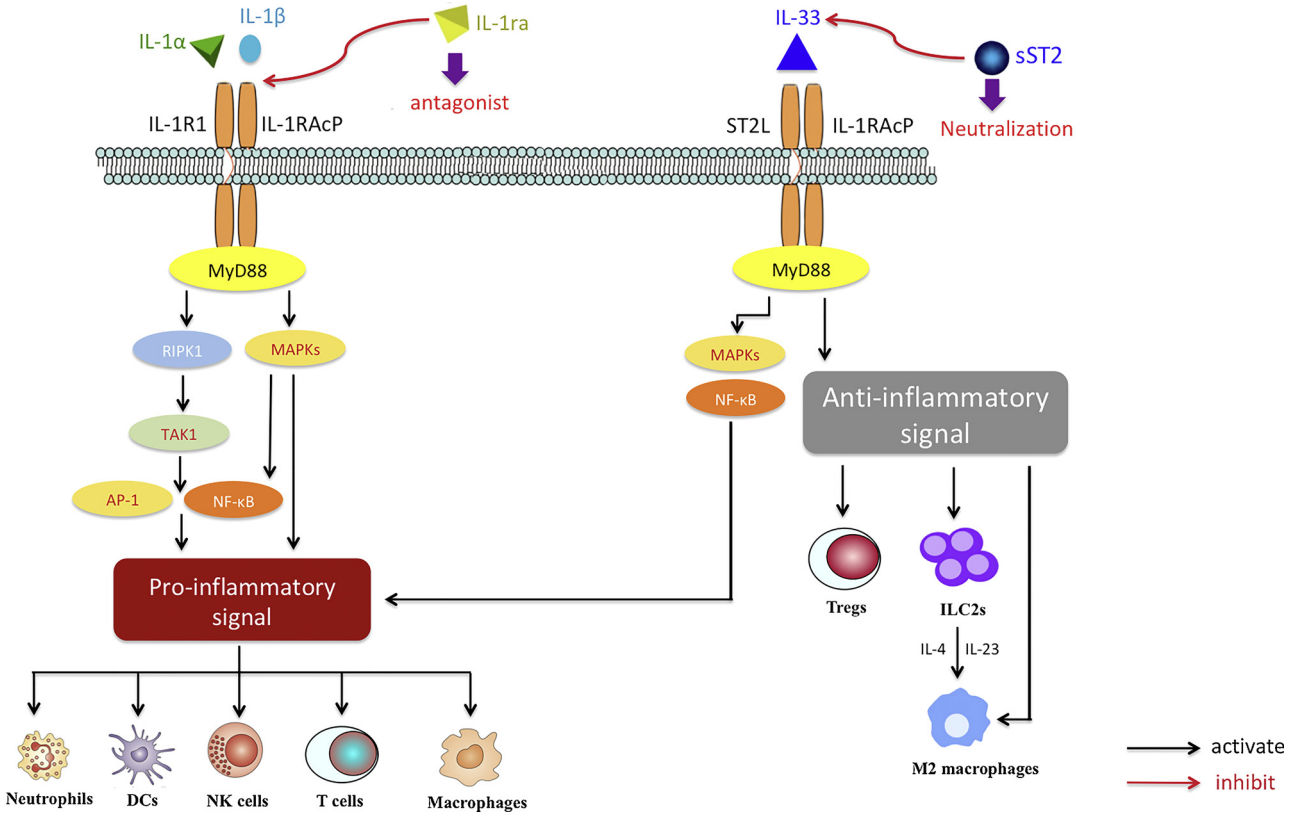

Fig. 2. Balance between IL-1 subfamily agonists and antagonists in inflammation and immunity. The IL-1 subfamily is comprised of IL-1α, IL-1β, IL-1ra and IL-33. The activity of IL-1α/β is regulated by IL-1R1. Its binding resulted in a structural alteration allows the co-receptor with IL-1RAcP, which induces MyD88-dependent intracellular signaling (e.g., MAPKs, RIPK1, TAK1, NF-κB, AP1). The phosphorylation of MyD88 and activation of these kinases engage in a potent pro-inflammatory signal to the nucleus. Also, IL-1α/β is suggested to prime various immune cells (e.g., neutrophils, DCs, NK cells, macrophages, and T cells). IL-1ra acts as the antagonist and competes with IL-1α/β but without recruitment of IL-1RAcP. Thus, IL-1ra does not trigger intracellular signaling. IL-33 binds to ST2L and then recruits to IL-1RAcP, leading to a succession of signaling pathways (e.g., MAPKs, NF-κB). On the one hand, IL-33 exhibits pro-inflammatory abilities and activates a variety of immune cells. On the other hand, IL-33 is effective to expand Tregs, ILC2s and M2 macrophages, thereby attenuating the inflammatory response. In addition, sST2L is expected to a negative regulator of IL-33/ST2L signaling.
IL-1R1, IL-1 receptor 1; IL-1RAcP, IL-1 receptor accessory protein; MyD88, myeloid differentiation factor 88; NF-κB, nuclear factor κB; MAPKs, mitogen-activated protein kinases; RIPK1, receptor-interacting protein kinase 1; TAK1, transforming growth factor-β activated kinase 1; AP1, activation protein 1; DCs, dendritic cells; NK cells, natural killer cells; Tregs, regulatory T cells; ILC2s, type 2 innate lymphoid cells; sST2L, soluble ST2L.

necrosis factor (TNF) receptor-associated factor 6 (TRAF6), IL-1R-associated 4 (IRAK4), and myeloid differentiation primary response protein 88 (MyD88)
(Figs. 2–4) [10–14].

3. Regulation of inflammation and immunity by the IL-1 family

3.1. Regulatory effect on inflammation

Most IL-1 family cytokines exhibit pro-inflammatory responses, with the exception of IL-1ra, IL-36ra, IL-37, and IL-38. These responses can be modulated by naturally occurring factors that inhibit protein processing, receptor synthesis, and receptor activation. The IL-1 system acts as both agonist and antagonist: on the one hand, pro-inflammatory cytokines trigger host responses required to fend off pathogens; on the other hand, excessive formation of pro- over anti-inflammatory cytokines leads to uncontrolled inflammation. In addition, IL-1 family cytokines are potent immune regulators at the crossroads of various pathways involved in pathogen recognition and immune cell activity [25].

3.2. Influence on innate immunity

Most IL-1 family cytokines activate innate immunity to mediate host defenses against invading pathogens. Toll-like receptor (TLR) pathways are involved in release of several IL-1 family cytokines, largely from innate immune cells, in order to relay a danger message to elicit immune responses. The secreted cytokines then influence the immune cells in an autocrine fashion. IL-33 binds its specific receptor ST2 to promote the survival and activity of eosinophils, as well as the production of chemokines. In parallel, IL-33 acts together with IL-5, granulocyte-macrophage colony-stimulating factor (GM-CSF) and IL-3 to accelerate eosinophil-mediated immune response [11]. Silencing of ST2 can reduce eosinophil infiltration during parasite infection in mice. ST2 is expressed at high levels in mast cells, and IL-33 stimulates their activity and promotes their survival [12]. IL-18 and IL-1 also activate mast cells and thereby facilitate the production of TNF-α, IL-13, IL-6, IL-5, and IL-3 [13].

Natural killer (NK) cells produce IFN-γ, which induces helper T cell (Th) 1 response. IL-18 increases the ability of NK cells to lyse target cells and to secrete IFN-γ and IL-12 [15]. IL-33 also stimulates IFN-γ secretion by NK cells. Both IL-33 and IL-18 can accelerate the release of TNF-α, GM-CSF, IL-13, IL-5, and IL-4 by NK T cells [15]. Certain subsets of DCs may generate IL-18 and IL-1 and respond to these cytokines as well as other signals to up-regulate OX40 L (TNFSF4), CD40, IL-12, and signaling lympocytic activation molecule (SLAM) [12]. This up-regulation enhances the efficiency of antigen presentation for the purpose of activating T cells. IL-36 acts via a receptor expressed by DCs and macrophages to activate these innate immune cells [20]. Additionally, IL-37 obviously attenuates macrophage activity [15,21].

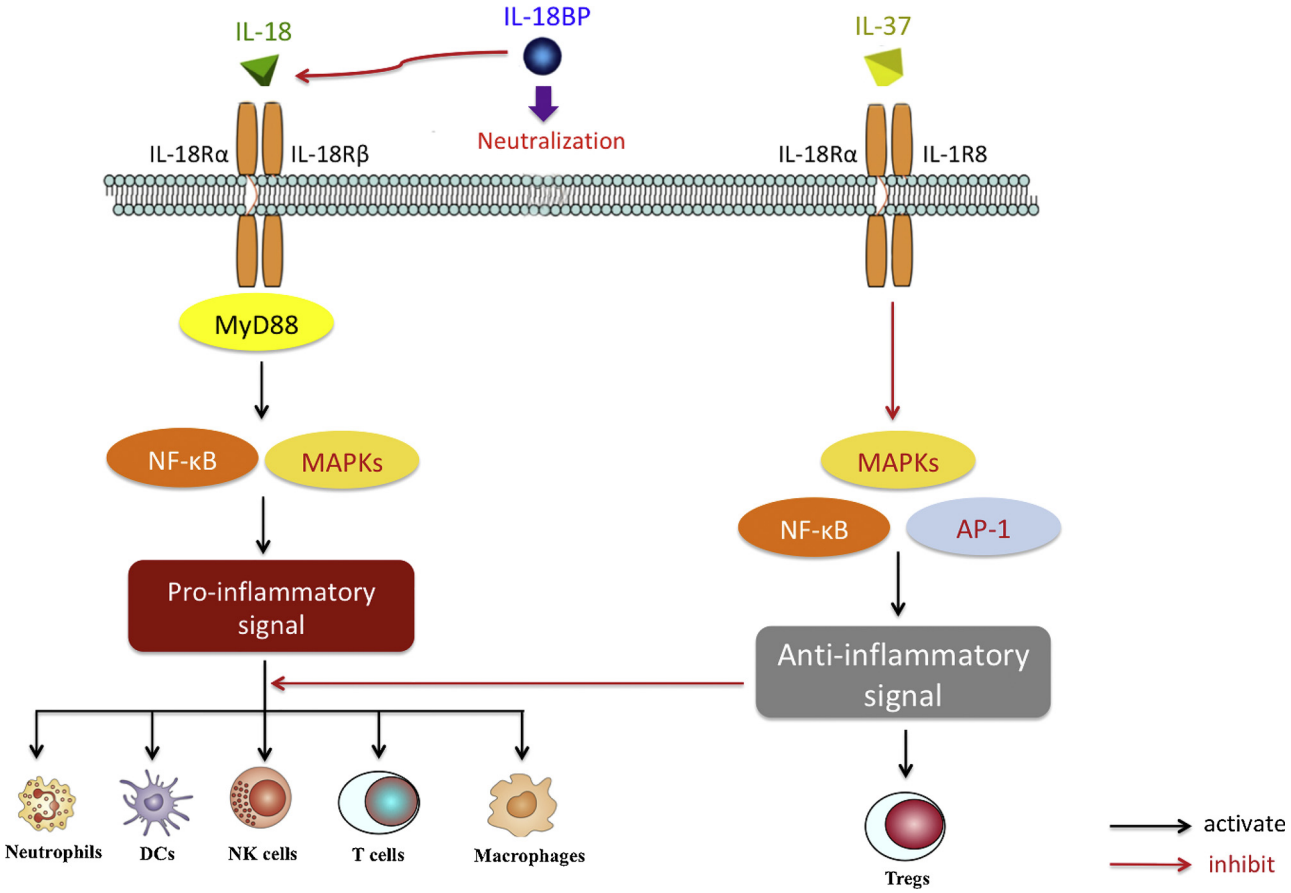

Fig. 3. Balance between IL-18 subfamily agonists and antagonists in inflammation and immunity. The IL-18 system comprises IL-18 and IL-37. IL-18 signaling occurs via IL-18Rα. Binding of IL-18 to IL-18Rα contributes to the recruitment of IL-18Rβ, which is required for initiation of MyD88-dependent pro-inflammatory pathways. IL-18 can drive numerous immune cells including neutrophils, DCs, NK cells, macrophages, and T cells. Furthermore, the biological activities of IL-18 can be inhibited by IL-18BP as the soluble antagonist. IL-37 binds to the ligand receptor IL-18Rα and subsequently triggers the recruitment of IL-1R8, which does not bind MyD88. Typically, IL-37 exerts anti-inflammatory properties and dampens the activities of various immune cells (e.g., neutrophils, DCs, NK cells, macrophages, and T cells). Intriguingly, IL-37 can expand the population of Tregs.
IL-18Rα, IL-18 receptor α; IL-18Rβ, IL-18 receptor β; MyD88, myeloid differentiation factor 88; DCs, dendritic cells; NK cells, natural killer cells; Tregs, regulatory T cells; IL-18BP, IL-18-binding protein; AP1, activation protein 1.

3.3. Effect on adaptive immunity

IL-1 has been known for a long time to enhance the function of B cells in response to mitogenic stimuli [3]. It can also prime T-cell response and is implicated in the differentiation of Th17 cells [14]. IL-1 from antigen-presenting cells can induce proliferation of naive, memory and effector T cells by activating pathways dependent on IL-2R and other mediators, such as phosphoinositide 3-kinase and NF-κB. In this way, IL-1 acts as a T-cell enhancer [4].

IL-1 family cytokines exert different effects on different Th subsets. For instance, IL-18 amplifies Th1-cell response, while IL-33 drives polarization of Th2 cells [22]. In adaptive immunity, IL-18 reinforces effector T cell activity, either directly or through suppression activity of Tregs [23]. Little is known with regard to the potential roles of IL-36, IL-37, or IL-38 in adaptive immunity.

4. Role of the IL-1 family in the development of sepsis

4.1. IL-1α, IL-1β, and IL-1ra

IL-1β is described as the first interleukin, after having been named fever-producing endogenous pyrogen. IL-1α and the subsequently discovered IL-1β bind specifically to receptor IL-1R1 and recruit the receptor subunit IL-RAcP. Following inflammasome activation, caspase-1 cleaves pro-IL-1, generating mature IL-1 [10]. Typically, IL-1α is a cell-associated molecule that is cleaved into two functional domains: the N-terminus is responsible for translocation into the nucleus, while the C-terminus functions as an inflammatory stimulator [11]. IL-1β is a robust activator that stimulates myeloid progenitor cells and increases the number of neutrophils. It up-regulates secretion of pro-inflammatory cytokines and chemokines, and increases expressions of inducible nitric oxide synthase (iNOS) and cyclooxygenase (COX)-2. IL-1 can trigger multiple cascades, such as those involving MAPKs and NF-κB [12,13].

Early studies revealed that IL-1, similar to TNF-α, induced a state similar to septic shock in rabbits, suggesting a major role of IL-1 in the pathogenesis of sepsis [24]. IL-1β is also involved in the modulation of vascular hyporeactivity during lipopolysaccharide (LPS)-induced endotoxemia via up-regulation of Janus kinase (JAK)-signal transducer and activator of transcription (STAT) 3 signaling, vascular calcium sensitivity, and down-regulation of Rho and PKC kinase [25,26]. Surprisingly, IL-1β acts via the FYN/WEK/ERK pathway during sepsis to impair cognitive processes and activate microglia-induced deficits [27–30]. In preterm neonates with sepsis, the combination of elevated IL-1β concentrations in the plasma and cerebrospinal fluid as well as abnormal neuroimaging could accurately predict poor prognosis [31]. Thus, IL-1β may be useful as a potential biomarker to monitor disease progression.

Mice lacking IL-1β (*IL-1β*$^{-/-}$) showed defects in acute-phase inflammation and were resistant to fever development [32]. *IL-1β*$^{-/-}$ mice were protected against the endotoxemia normally induced by low LPS

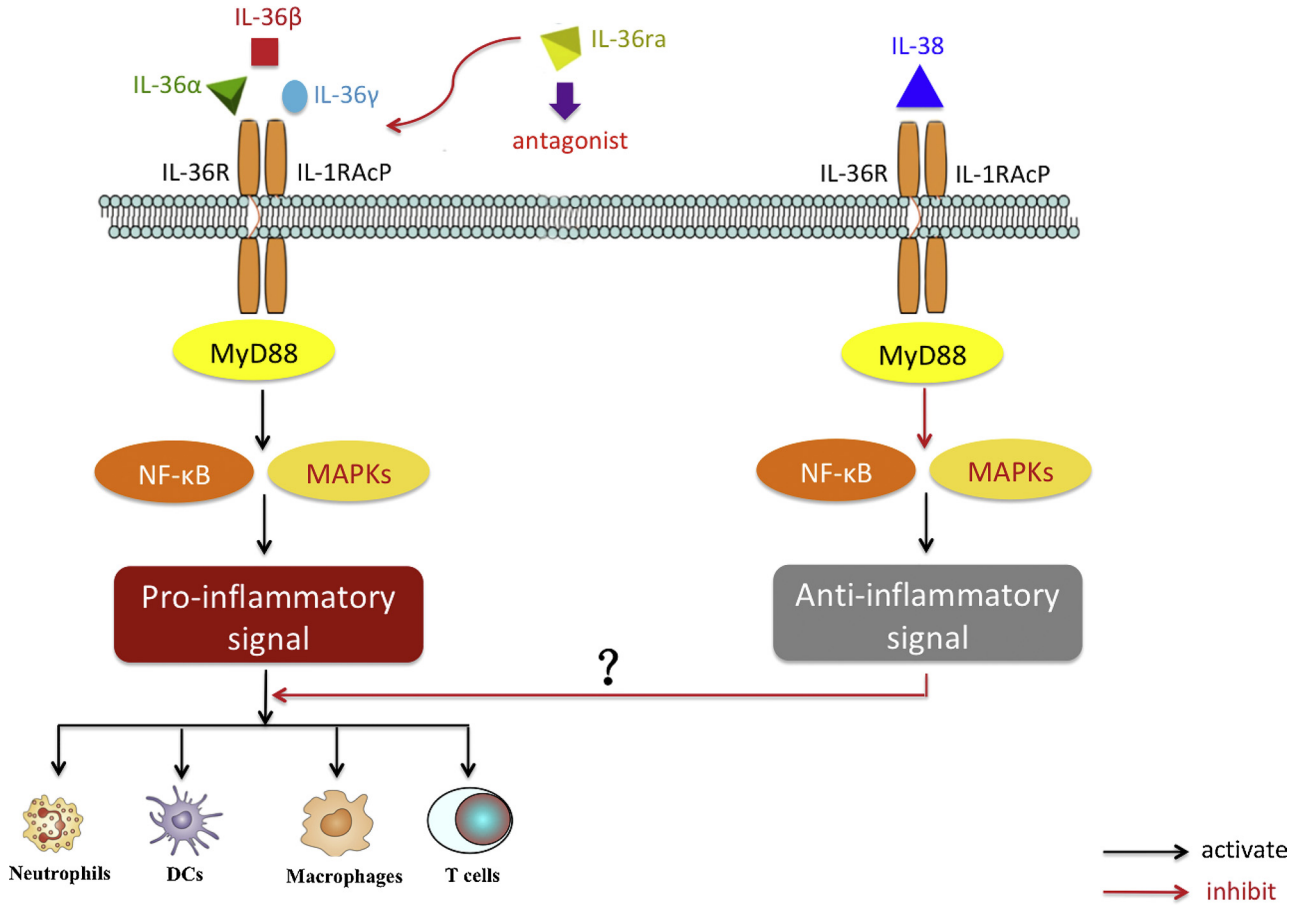

Fig. 4. Balance between IL-36 subfamily agonists and antagonists in inflammation and immunity. The IL-36 system is composed of IL-36, IL-36ra, and IL-38. IL-36α, IL-36β, and IL-36γ bind to IL-36R and recruit their signaling subunits of IL-RAcP, inducing MyD88-dependent signaling pathways such as NF-κB and MAPKs. Then, they can promote production of pro-inflammatory cytokines (e.g., IL-6, IL-8, IL-23) and activate various immune cells, including neutrophils, DCs, macrophages, and T cells. IL-36ra serves as a natural inhibitor which competes with IL-36 for IL-36R binding. However, it binds to IL-36R without initiation of signaling pathway. Similar to IL-36ra, IL-38 is expected to antagonize IL-36R and prevents the recruitment of IL-1RAcP. However, IL-38 displays anti-inflammatory abilities via suppression of NF-κB and MAPKs signaling. Up to now, the effects of IL-38 on immune cells are unclear (*question mark*).
IL-36R, IL-36 receptor; IL-1R, IL-1 receptor; IL-1RAcP, IL-1 receptor accessory protein; NF-κB, nuclear factor κB; MAPKs, mitogen-activated protein kinases; DCs, dendritic cells.

doses [33]. Conversely, silencing IL-1α rendered the animals more susceptible to endotoxemic death and elevated IFN-γ levels. Knockdown of the receptor IL-1R1 rendered animals completely resistant to LPS-induced death, implicating the receptor in sepsis-induced mortality [34]. Consistent with this idea, neutralizing IL-1 reversed LPS-induced mortality in animal models, providing evidence that IL-1 might be a promising therapeutic target against sepsis [35].

Typically, the macrophages, monocytes, neutrophils, and DCs that express IL-1β and IL-1α also usually secrete IL-1ra. IL-1ra is expressed in intracellular isoforms (icIL-1ra1-3) and a secreted isoform (sIL-1ra). It binds to IL-1R and competes with IL-1α and IL-1β without initiating any receptor-mediated signaling pathways [18]. IL-1ra is up-regulated in a broad spectrum of contexts, including sepsis, Crohn's disease, acute respiratory distress syndrome, macrophage activation syndrome, and ulcerative colitis [15].

Silencing of IL-1ra leads to various diseases, such as spontaneous rheumatoid arthritis-like disease and vasculitis [26]. In animals, IL-1ra prevented IL-1β-induced vasodilatory shock [36]. Mice deficient in IL-1ra were more susceptible to endotoxemic death, while administration of IL-1ra markedly improved survival of septic mice. Survival of mice with sepsis depended on the ability of IL-1ra to trigger dimerization of the glucocorticoid receptor [37]. Survival rates might be improved through the ability of IL-1ra to reduce nitric oxide levels in cerebrospinal fluid and promote vasopressin release [38,39]. IL-1ra could protect synaptic function in hippocampus in an animal model of septic encephalopathy [29]. Recombinant human IL-1ra (rhIL-1ra) (generic name, anakinra) has been explored for pharmacotherapy and attenuates numerous rampant inflammatory diseases including sepsis, systemic juvenile rheumatoid arthritis, neonatal-onset multiple inflammatory diseases and Muckle-Wells syndrome [15]. Anakinra infusion, which has been shown to be safe and effective in patients with bacteremia, provided significant survival benefit in animals. Since the 1990s, sepsis trials have examined the therapeutic potential of rhIL-1ra. Three randomized placebo-controlled studies of sepsis have suggested that rhIL-1ra resulted in a 2%–5% absolute reduction in the risk of all-cause 28-day mortality [40–42]. Therefore, it would be a possible therapeutic approach to deal with sepsis [43].

4.2. IL-18

IL-18, initially named IFN-γ-induced factor, was discovered in serum of mice that had been injected with endotoxin [44]. Free IL-18 is biologically active, while IL-18 usually exists in circulation as a complex with IL-18 binding protein (IL-18BP) [45]. Although IL-18 and IL-1β bind to different receptors, they respond to similar stimuli and induce similar downstream signaling pathways. Like IL-1, pro-IL-18 is processed into its bioactive form by IL-1β-converting enzyme (ICE)/caspase-1 [46]. The tertiary structure of IL-18 and the intron-exon

Table 1
Effects of IL-1 and IL-1ra on sepsis.

Cytokine	Authors	Year	Effects	Ref.
IL-1	Xie et al.	2016	In septic neonatal rats, IL-1β acted via FYN/MEK/ERK signaling to inhibit maturation of oligodendrocyte progenitor cells, inducing hypomyelination in the periventricular white matter.	[30]
	Basu et al.	2015	In preterm neonates with early-onset clinical sepsis, elevated levels of IL-1β and TNF-α in plasma and cerebrospinal fluid were associated with increased risk of death or abnormal neuroimaging.	[31]
	Moraes et al.	2015	In septic mice, IL-1β secreted by microglia induced a transient synaptic deficit associated with memory impairment.	[29]
	Liang et al.	2014	In rabbits subjected to LPS-induced endotoxemia, IL-1β acted via the JAK-STAT3 pathway to down-regulate expression of vascular α1 adrenergic receptor.	[25]
	Liang et al.	2013	In endotoxic shock, IL-1β regulated vascular calcium sensitivity and down-regulated PKC and Rho kinase in order to influence vascular hyporeactivity.	[26]
	Mina et al.	2013	IL-1β was involved in cognitive impairment after sepsis in rats.	[27]
	Imamura et al.	2011	IL-1β caused long-term potentiation deficiency in a mouse model of septic encephalopathy.	[28]
	Joosten et al.	2010	IL-1 receptor type I-mediated signals were involved in endotoxemia-induced mortality in mice.	[34]
	Fantuzzi et al.	1996	Treatment with low-dose LPS in IL-1β-deficient mice protected them from LPS-induced mortality.	[33]
	Zheng et al.	1995	IL-1β-deficient mice showed impaired acute-phase inflammatory response to LPS and were completely resistant to fever and anorexia.	[32]
	Okusawa et al.	1988	IL-1 induced a shock-like state in rabbits	[24]
IL-1ra	Meyer et al.	2018	Plasma IL-1ra levels might predict the complex effects of recombinant human IL-1ra on 28-day mortality of sepsis.	[43]
	Wahab et al.	2016	IL-1ra decreased hypothalamic oxidative stress in septic rats.	[38]
	Wahab et al.	2015	IL-1ra decreased nitric oxide levels in cerebrospinal fluid and increased vasopressin secretion in the late phase of septic rats.	[39]
	Kleiman et al.	2012	In sepsis, treatment with recombinant IL-1ra improved survival of mice showing glucocorticoid receptor dimerization in macrophages, as well as survival of mice lacking the glucocorticoid receptor.	[37]
	Opal et al.	1997	In patients with severe sepsis, 72-hour continuous intravenous infusion of rhIL-1α failed to demonstrate a statistically significant reduction in mortality.	[42]
	Fisher et al.	1994	rhIL-1ra might be safe and provide dose-dependent survival advantage to patients with sepsis syndrome.	[41]
	Fisher et al.	1994	Treatment with rhIL-1α resulted in dose-dependent prolongation of survival among septic patients with organ dysfunction and/or ≥24% predicted risk of mortality.	[40]
	Fischer et al.	1992	IL-1ra improved survival and hemodynamic performance in *Escherichia coli* septic shock, but failed to alter host response to sublethal endotoxemia in baboons.	[36]
	Alexander et al.	1991	IL-1 mediated the lethal effects of LPS, and IL-1ra improved survival after lethal endotoxemia in mice.	[35]

boundaries of its gene are similar to those of IL-37. IL-18 precursor constitutively exists in epithelial cells, keratinocytes, and blood monocytes, similar to IL-33 and IL-1α. Membrane IL-18 is also present in macrophages activated by macrophage colony-stimulating factor (M-CSF) [47].

Depending on its microenvironment, IL-18 appears to be a dual-function molecule that drives Th1 and Th2 responses by binding receptors IL-18Rα and IL-18Rβ. The complex of IL-18/IL-18R induces pathways involving NF-κB, STAT3 phosphorylation, and p38 MAPK [44]. It is required for host defense against invading pathogens including protozoa, bacteria, virus, and fungi. IL-18, together with IL-15 or IL-12, plays an important role in the production of IFN-γ from NK cells and T-cells in the Th1 paradigm [48]. Without co-inducers, IL-18 does not promote IFN-γ, and it participates in Th2 diseases. High IL-18 levels in septic patients correlated with poor prognosis [49]; septic patients with Gram-positive infections had higher IL-18 levels than those with Gram-negative infections [50]. Elevated concentrations of IL-18, independently of IL-1β levels, were a prognostic indicator of poor outcome in severe sepsis and septic shock [51,52]. Therefore, IL-18 seems to be a novel diagnostic and prognostic biomarker in severe sepsis and septic shock.

Animal studies of endotoxic shock have given conflicting results concerning the effects of IL-18. In an early study by Sakao et al. [53], administering anti-IL-18 antibody to mice in endotoxic shock led to high levels of TNF-α and high mortality. Another study showed that deficiency of IL-18 rendered animals susceptible to septic shock, yet it protected against LPS-induced liver injury [54–56]. In other studies, mice deficient in IL-18 were resistant to LPS-induced sepsis [57–59]. Neutralizing antibodies against IL-18 protected against severe endotoxemia in animal models, and it involved in suppression of IFN-γ

Table 2
Effects of IL-18 and IL-18BP on sepsis.

Cytokine	Authors	Year	Effects	Ref.
IL-18	Wynn et al.	2016	Targeting IL-17A attenuated neonatal mortality of sepsis induced by IL-18 in mice.	[59]
	Eidt et al.	2016	IL-18 was an important predictor of mortality in patients with severe sepsis and septic shock.	[51]
	Vanden Berghe et al.	2014	Anti-IL-18 antibodies and anakinra completely protected mice from endotoxin-induced death.	[55]
	Sekine et al.	2009	IL-18 supplementation prevented against LPS-induced acute lung injury by inhibiting macrophages and stimulating IL-10 production.	[57]
	Zaki et al.	2007	IL-18 levels were elevated in patients with sepsis and correlated with C-reactive protein levels and leukocyte counts.	[49]
	Kinoshita et al.	2004	IL-18 therapy decreased mortality among mice with burn injuries that had subsequently suffered severe infection; unexpectedly, it increased mortality among burned mice with mild infection.	[60]
	Ono et al.	2003	Giving LPS-treated CLP mice antibodies against IL-12 and IL-18 antibody resulted in significantly higher survival rate and less severe liver damage than those in untreated mice.	[56]
	Emmanuilid-is et al.	2002	IL-12 might contribute to protective immune reactions against septic challenge, whereas IL-18 preferentially augmented organ injury and lethal shock in patients.	[52]
	Oberholzer et al.	2001	IL-18 production might discriminate between Gram-positive and -negative sepsis in patients.	[50]
	Hochholzer et al.	2000	IL-18 played an important role in induction of IFN-γ and in LPS-induced death in mice.	[58]
	Netea et al.	2000	Neutralization of IL-18 reduced neutrophil tissue accumulation and protected mice against lethal *Escherichia coli* and *Salmonella typhimurium* endotoxemia.	[53]
	Sakao et al.	1999	IL-18 drove progression of endotoxin-induced liver injury and down-regulated endotoxin-induced TNF-α production in *Propionibacterium acnes*-primed mice.	[54]
IL-18BP	Remick et al.	2003	IL-18BP decreased survival among mice at low risk of death due to sepsis.	[62]
	Novick et al.	2001	IL-18BPa substantially decreased circulating IL-18 levels in septic patients.	[61]

Table 3
Effects of ST2, IL-33, IL-36, IL-37, and IL-38 on sepsis.

Cytokine	Authors	Year	Effects	Ref.
IL-38	Xu et al.	2018	Serum IL-38 levels were significantly increased in adult and pediatric patients with sepsis; IL-38 decreased inflammation, reduced tissue damage, and improved survival in mice with sepsis induced by LPS- and CLP.	[107]
IL-37	Wang et al.	2016	IL-37 enhanced the suppressive activity of regulatory T cells in the presence of LPS and improved the survival rate of CLP mice.	[101]
	Nold-Petry et al.	2015	Mice expressing transgenic IL-37 and intact IL-1R8 were protected from endotoxemia.	[100]
	Li et al.	2015	IL-37 suppressed LPS-induced production of IL-1β, IL-6, and TNF-α in M1 differentiated human blood macrophages.	[98]
	Nold et al.	2010	Mice with transgenic expression of IL-37 were protected from LPS-induced shock, showed markedly improved lung and kidney function, and reduced liver damage after LPS challenge.	[97]
IL-36	Tao et al.	2017	IL-36α production was strongly elevated in the blood, lungs, and peritoneal lavage fluid of CLP mice. IL-36α attenuated sepsis in these mice by enhancing antibacterial activity of macrophages.	[91]
IL-33	Peng et al.	2018	IL-33 down-regulated inflammatory reactions in *Acinetobacter baumannil* pneumonia by suppressing TLR4/NF-κB signaling.	[66]
	Lv et al.	2017	IL-33 up-regulated SOCS3 in CLP mice, which inhibited IL-17 receptor signaling and thereby prevented the development of sepsis.	[68]
	Nascimento et al.	2017	IL-33 contributed to sepsis-induced long-term immunosuppression by expanding the regulatory T cell population in CLP mice.	[70]
	Li et al.	2016	IL-33 prevented apoptosis of T lymphocytes and improved survival in a mouse model of sepsis.	[69]
	Chang et al.	2015	IL-33 level was obviously elevated in septic patients and was related to the severity of sepsis.	[74]
	Alves-Filho et al.	2010	IL-33 attenuated sepsis by enhancing neutrophil influx to the site of infection in CLP mice.	[67]
ST2	Babic et al.	2018	ST2 deficiency down-regulated myeloid precursors as well as inflammatory NK and dendritic cells in CLP mice.	[80]
	Hur et al.	2015	ST2 and PCT in combination might be useful for risk stratification and prognosis prediction of patients with suspected sepsis.	[75]
	Carducci et al.	2014	ST2 level could prove useful for predicting bacterial etiology in children with systemic inflammatory response syndrome.	[76]
	Blok et al.	2013	ST2 augmented rather than inhibited cytokine release by blood leukocytes and splenocytes exposed to *Streptococcus pneumonia* or Klebsiella pneumoniae, but played a limited role in host defense during sepsis caused by these pathogens.	[79]
	Buckley et al.	2011	ST2-deficient mice exhibited an increased susceptibility to polymicrobial infection and showed impaired bacterial clearance, which was associated with defects in phagosome maturation and NOX2-derived production of reactive oxygen species.	[77]
	Hoogerwerf et al.	2010	Sepsis elevated serum ST2 levels in a sustained way, and the levels correlated with disease severity and mortality in patients.	[73]
	Brunner et al.	2004	Serum ST2 was increased in sepsis and trauma patients.	[72]
	Sweet et al.	2001	ST2 treatment of primary bone marrow-derived macrophages inhibited production of LPS-induced pro-inflammatory cytokines, down-regulated TLR-1/4 expression, and induced translocation of NF-κB. ST2 administration significantly reduced LPS-mediated mortality in mice.	[71]

and neutrophil accumulation [53]. In an animal model of burn injury followed by infection, IL-18 improved survival of animals subjected to severe infection but reduced survival of animals with mild infection. In severe infection, IL-18 increased the number of NK cells and restored fallen IFN-γ levels. In mild infections, however, serum IFN-γ concentrations did not fall and IL-18 triggered excessive secretion of IFN-γ [60]. Taken together, IL-18 supplementation might be a potential therapeutic strategy against severe bacteremia or septic shock, but attention should be paid to its deleterious influence. The opposite effects of IL-18 in sepsis may depend on the microenvironment, which should be clarified in future studies.

The soluble protein IL-18BP was identified in human urine and was highly abundant in the serum of healthy individuals [45,46]. IL-18BP is produced primarily by skin-resident cells, monocytes/macrophages, and endothelial cells following inflammatory stimuli. It binds with high affinity, and thereby inhibits, mature IL-18 through negative feedback signaling. When IL-18BP binds to IL-18, it attenuates Th1 and Th2 responses. IL-18BP can bind to IL-37 and thereby weaken the latter anti-inflammatory ability [47,48], while increasing the ability of IL-18 to reduce IFN-γ production. Administering IL-18BP to mice with sepsis, particularly those at low risk of death, showed large survival benefit [61,62], suggesting a potential therapeutic target in sepsis.

4.3. IL-33

The nuclear localization sequence of IL-33, like that of IL-1α, is located in the N-terminal domain. Severe injury or necrosis stimulates production of IL-33, which operates as an alarmin or endogenous danger signal [63]. It can activate a variety of immune cells, including neutrophils, mast cells, basophils, and eosinophils [64]. IL-33 exerts its effect by binding to a heterodimeric receptor of IL-1RAcP and ST2, which recruits IRAK1, IRAK4, TRAF6 and MyD88 [65]. This can trigger signaling pathways involving NF-κB, MAPKs, extracelluar signal-regulated kinase (ERK), p38 and c-jun amino-terminal kinase (JNK), ultimately leading to cell proliferation and cytokine formation [63]. It has been documented that IL-33 can reduce production of IL-6, IL-10, IFN-γ, and TNF-α, and enhance secretion of IL-17, IL-10, IL-4, and IL-5. In addition, IL-33 stimulates mast cells, inducing anaphylaxis and expanding Th2 cells, which ultimately aggravates the pathogenesis of asthma [65].

IL-33 plays an anti-infective role in type 2 immune response to infection. In mice with *Acinetobacter baumannil* pneumia, IL-33 reduced systemic inflammatory reactions by inhibiting the TLR4/NF-κB pathway [66], and it attenuated polymicrobial-induced sepsis in mice by accelerating bacterial clearance and neutrophil infiltration [64]. Likely, IL-33 markedly decreased the sequestration of neutrophils in the lung, a feature of severe sepsis, and it lowered the levels of chemokines and proinflammatory cytokines following the onset of sepsis [65]. In the process of sepsis, pathogen-produced LPS and high mobility group box-1 protein (HMBG1) activate the G protein-coupled receptor kinase-2 (GRK2), which down-regulates expression of the CXCR2 chemokine receptor that recruits neutrophils to infection sites. IL-33 can up-regulate CXCR2 expression and down-regulate GRK2 via the TLR pathway [67], and it also mitigates sepsis by up-regulating suppressor of cytokine signaling (SOCS) 3, which inhibits IL-17 receptor signaling [68]. In septic mice, IL-33 negatively regulated apoptosis of lymphocytes, which was a key determinant of sepsis-induced immunosuppression, and it decreased mortality rate [69]. Therefore, IL-33 plays a protective role in sepsis via multiple immune signaling pathways.

It has been demonstrated that IL-33 may be a major driver of long-term sepsis-induced immunosuppression. For example, IL-33 promoted expansion of M2 macrophages and monocytic myeloid-derived suppressor cells, as well as strengthened the activity of Tregs [70]. In parallel, IL-33/ST2 signaling contributed to expansion of $Fox3^+$ Tregs [70]. Blocking IL-33-mediated signaling appeared to be a target for preventing sepsis-triggered immune response. In these ways, IL-33 acts pleiotropically to drive sepsis through multiple mechanisms, which should be further investigated in future work.

ST2, which occurs as various splice variants in a soluble form (sST2) and a membrane-bound form, exerts its effect inside the nucleus and outside the cell [65]. sST2 acts as an IL-33 receptor without inducing signaling. It is unclear that which kind of cells produce ST2, and elevated sST2 levels in circulation occur in infection, inflammation, and other diseases [71,72]. In the clinical settings, sepsis was associated with increased levels of sST2 and IL-33, and levels correlated with septic severity [73–76]. ST2 knockdown markedly reduced the

microbicidal capacity of granulocytes and NK cells [77], and deletion of the corresponding gene enhanced susceptibility to sepsis and sepsis-related mortality in mice. Deletion of the ST2gene in cecal ligation and puncture (CLP) mice resulted in a substantial decrease in the numbers of eosinophils, neutrophils, and mast cells in the peritoneal cavity [78,79], as well as the numbers of precursors of myeloid cells, NK cells, and DCs in the spleen [80]. Hence, the IL-33/ST2 axis may provide new insights that link sepsis-induced immune depression with poor prognosis beyond other immune and inflammatory markers.

4.4. IL-36 and IL-36ra

Similar to IL-18 and IL-1β, IL-36 must be processed at the N-terminus to be bioactive [81]. IL-36 is typically categorized into four members: IL-36α, IL-36β, IL-36γ, and receptor antagonist IL-36ra [82]. It is extensively expressed in the immune cells, skin, and other tissues [83,84]. IL-36R and IL-36 are predominantly expressed in murine $CD4^+$ T lymphocytes and bone marrow-derived DCs [85]. In bronchial epithelial cells, inflammatory stimuli induced IL-36 expression. In THP-1 cells, LPS challenge elevated the level of IL-36γ but not of IL-36β or IL-36γ [81]. It has been indicated that IL-36 stimulates the production of pro-inflammatory cytokines such as IFN-γ, IL-4, and IL-17, and it also favors Th1 polarization of effector T cells [82]. Moreover, IL-36β was reported to up-regulate markers of bone marrow-derived DCs, which amplified Th1 response in T cells. Stimulating human keratinocytes with IL-1β or TNF-α remarkably enhanced expression of IL-36α and IL-36γ [86].

The IL-36 signaling pathway participates in host defenses against *Candida albicans*, *Aspergillus fumigatus* or *Mycobacteria* [87,88]. In lung fibroblasts, IL-36γ stimulated the secretion of the Th17 chemokine CCL20 and IL-8, and it induced airway hyperresponsiveness, indicating that IL-36 was involved in neutrophilic airway inflammation as a lung host defense [89]. Consistent with this view, challenging mice with influenza virus up-regulated IL-36α expression by alveolar epithelial cells [90]. IL-36 levels were increased in chronic kidney disease and human rheumatoid synovial tissues, suggesting that IL-36 played a potent role in inflammatory disorders [81,82]. In the CLP mice, IL-36α levels were strongly elevated in the blood, lungs, and peritoneal lavage fluid. Giving these animals recombinant mouse IL-36α protected them against sepsis by boosting macrophage function [91]. Thus, IL-36α may serve as a prognostic biomarker and potential therapeutic target in sepsis.

IL-36ra shows 44% amino acid homology with IL-1ra. It binds IL-36R to behave as an antagonist and blocks IL-36-mediated response. This antagonism depends on removal of the N-terminal methionine [92,93]. IL-36ra weakens fungus-triggered Th17 immunity and inhibits IL-36γ-mediated activation of NF-κB [94].

IL-36/IL-36ra signaling regulates innate and adaptive immune responses to contribute to the pathophysiology of inflammatory diseases. Genetic knockdown of IL-36ra exacerbated skin inflammation in a mouse model of psoriasis [93]. IL-36ra was up-regulated in a cellular model of brain micromotion subjected to low-magnitude cyclical strain. Treatment with IL-36ra in primary cortical neurons dramatically down-regulated TNF superfamily member B11 (TNFRSF11b) and up-regulated pro-apoptotic genes, implicating that IL-36ra modulated apoptotic signaling and anti-inflammatory effects in neuroinflammation [95]. Whether IL-36ra participates in other inflammatory diseases remains unclear. The antagonistic activity of IL-36ra implies that it may be associated with IL-36-related diseases, including inflammatory lung diseases, rheumatoid arthritis, sepsis, obesity, chronic glomerulonephritis, and bile duct occlusion disorder [81,82].

4.5. IL-37

IL-37 comprises five splice variants (IL-1Fa, b, c, d, and e), whose functions are poorly understood. It is induced in thymus, testis, uterus, DCs, and peripheral blood mononuclear cells [96]. In contrast to other IL-1 family members, a mouse homologue of IL-37 has yet to be found [97]. Similar to IL-18 and IL-1β, IL-37 requires cleavage by caspase-1 to become active. After this processing, IL-37 travels to the nucleus, where it acts as a transcription factor [98]. IL-37 has different effects on immunosuppressive cytokines: it increases TGF-β1 levels but decreases IL-10 and IL-13 levels. Stimulating activated DCs with IL-37 reduced levels of M-CSF and GM-CSF [99].

Most IL-1 family ligands elicit pro-inflammatory properties. Exceptionally, IL-37 can attenuate inflammatory and immune reactions by suppressing the binding of agonist receptor ligands [99]. It strongly diminishes inflammation caused by activated macrophages: it decreases the pro-inflammatory cytokines including TNF-α, IL-1α, IL-6, and IL-8 in human monocytic cells stimulated with LPS or IL-1β [97]. The genes encoding IL-37 and IL-18 are likely to be related based on similar intron-exon borders and structure form. Existed evidence suggests that IL-18Rα rather than IL-18Rβ is the IL-37 receptor. Deficiency of IL-18Rα aggravated inflammation in mice [98]. IL-37 could bind to IL-1R8, previously termed SIGIRR. The IL-37/IL-1R8/IL-18rα complex obviously inhibited signaling of c-Jun and phosphorylation of p38 MAPK, thereby promoting IL-1 release [99]. The complex also induced the STAT3 cascade, inhibited NF-κB and thereby reduced production of IFN-γ. However, IL-37 does not seem to function as a classical receptor antagonist of IL-18. Low IL-37 concentration could weaken IL-18-triggered IFN-γ release [97]. IL-37 acts via SMAD3, which is phosphorylated by TGF-β receptor, to exert strong anti-inflammatory activity [99].

In animal experiments, IL-37 limited tissue injury by down-regulating excessive inflammation during infection [96]. IL-37 appears to play a role in transplantation and autoimmune diseases, and it down-regulates the LPS-induced pro-inflammatory cytokines including IL-1β, IL-6, and TNF-α in M1 differentiated human blood macrophages as well as monocytic and epithelial cells [98]. It was reported that LPS challenge of transgenic mice expressing IL-37 significantly down-regulated expression of MHC-II and CD86, key DC biomarkers, suggesting the anti-inflammatory effects of IL-37. Expressing IL-37 in transgenic mice effectively prevented LPS-induced septic shock and mitigated damage to kidney, lung, and liver [97]. In the CLP mice, IL-37 preferentially strengthened the suppressive activity of murine Tregs in the presence of LPS, protecting against sepsis [101]. In this way, Tregs might be of importance in mediating the immunoregulatory effects of IL-37 in the setting of sepsis.

4.6. IL-38

IL-38 is the IL-1 family cytokine most recently identified, and it is expressed mainly in tonsil, spleen, skin, thymus, liver, salivary glands, and fetal tissue [102]. IL-38 shows 41% sequence homology with IL-36ra and 43% homology with IL-1ra [103]. Like IL-36ra, IL-38 serves as a typical receptor antagonist to inhibit immune response and curb pro-inflammatory mediators, probably by recruiting inhibitory co-receptors [104]. For example, IL-38 reduces production of IL-22 and IL-17 in Th17 cells, indicating that IL-38 is associated with autoimmune and inflammatory diseases [30,105]. These effects are similar to those obtained by blocking IL-36R and IL-1R signaling. In the presence of LPS, IL-38 further promoted IL-6 release from DCs [106], but relatively few studies investigated the role of IL-38 in inflammatory disorders in details. IL-38 levels were elevated in clinical and experimental sepsis, and treatment with IL-38 to CLP mice could mitigate organ damage, inflammation, and mortality [107]. Up to now, the underlying regulatory mechanism with regard to IL-38 in sepsis is poorly understood.

5. Summary and perspectives

Recent advances in understanding the potential role of IL-1 family cytokines in host immunity have revealed their extensive range of

biological functions. These cytokines and their receptors have emerged as endogenous innate immune signals in the host, while the TLR system supplies exogenous innate immune signals. Both systems enhance the adaptive response. During the process of inflammation, various molecules appear to be participated in a negative feedback loop, such as IL-1ra, IL-36ra, IL-37, and IL-38. In the development of sepsis, IL-1α, IL-1β, IL-33, and IL-18 exert certain effects on various immune cells (Figs. 2–4). Little is known regarding the significances of IL-36, IL-37, and IL-38 in the innate as well as adaptive immune responses associated with sepsis.

Sepsis remains major challenging in critically illness, reflecting its multiple pathophysiologic processes and complex immunological characteristics. The intricate networks of inflammatory and immune responses seem to be correlated with severity and outcome of septic complications. IL-1 family cytokines are increasingly being viewed as key mediators in sepsis, offering new opportunities for understanding and treating this dangerous condition. The levels of various IL-1 family cytokines (IL-1β, IL-18, IL-33, ST2, IL-36α, and IL-38) may provide diagnostic and prognostic value as clinical biomarkers. They also drive immune response during the acute phase and thereby trigger immune defenses against pathogens. At the same time, some IL-1 family cytokines contribute to sepsis-induced immune dysfunction.

Future treatments against sepsis may target certain cytokines (IL-1ra, IL-18, IL-18BP, IL-33, IL-36α, and IL-38), for which studies in humans are needed, since most studies of IL-1 family cytokines except IL-1ra have been carried out in cell culture and small animals. Clinical trials using rhIL-1α (anakinra) to block IL-1 have shown some ability to reduce mortality without increasing risk of opportunistic infections. In contrast, neutralization of TNF-α activity is associated with high risk of such infections, including recurrence of *Mycobacterium tuberculosis* infection. Much work remains to evaluate the actions of IL-1 family cytokines in sepsis.

Future work should clarify the sometimes paradoxical activity of IL-1 family cytokines in the pathogenesis sepsis. For example, IL-33 has been revealed to attenuate sepsis by inhibiting the inflammatory response, the IL-17 receptor pathway, and apoptosis of T lymphocytes, while increasing neutrophil influx. On the other hand, IL-33 can aggravate sepsis-induced immunosuppression by expanding Tregs. Studies should aim to clarify these opposing effects and examine how they depend on the immune milieu and signaling microenvironment.

Author contributions statement

YG and MH conducted the literature review and drafted the manuscript, which Y-MY conceptualized, supervised, and revised. All authors read approved the final manuscript.

Conflict of interest statement

The authors have declared that no competing interests exist.

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