



Cytokine-mediated, organ-specific immune modulation and dysregulation of innate lymphocytes in sepsis

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Abstract

Sepsis is a life-threatening condition that is marked by dysregulated host immune responses that can induce multiorgan dysfunction. Recent evidence suggests that this immunopathology involves tissue-resident innate lymphocytes, including innate-lymphoid cells (ILCs) and innate-like lymphocytes (ILLs). This review elucidates the organ-specific roles of the three ILC groups (ILC1s, ILC2s, and ILC3s) and two ILL types (NKT and $\gamma\delta$ T cells) in sepsis, particularly their cytokine-mediated functions and cell-cell interactions. The literature shows that in the lungs, ILC2-derived IL-9 and IL-13 mitigate pulmonary inflammation and preserve endothelial integrity but dysregulated ILC2 activation may exacerbate injury. In the heart, ILC2s may mediate cardioprotective effects by inducing IL-13-STAT3 signaling and IL-5-mediated eosinophil recruitment. Kidney-resident ILC2s may promote tissue repair in acute-kidney injury (AKI) but their role in sepsis-associated AKI remains underexplored. In the gut and liver, ILC3s protect from sepsis *via* IL-22, which promotes barrier integrity, but they can convert into ILC1s, whose IFN- γ contributes to tissue damage. Circulating NK cells may play pathogenic and beneficial roles at different times after sepsis onset. NKT and $\gamma\delta$ T cells are respectively protective and pathogenic in the gut and liver, likely through their respective production of IFN- γ and IL-17 A. Thus, ILCs and ILLs play key roles in sepsis and could be potential therapeutic targets. Further research is needed to elucidate their precise contributions in each organ and how time since onset and local and systemic conditions affect these contributions.

Keywords Sepsis · Cytokines · Innate lymphoid cells · Innate-like lymphocytes · Innate immunity

Introduction

Sepsis is characterized by an exaggerated immune response to infection that damages the host organs and tissues [1]. The definition of sepsis has evolved over time. Initially, it was defined as a suspected or proven infection accompanied by at least two systemic-inflammatory response syndrome criteria [2]. However, this definition failed to identify one in

eight critically-ill patients with sepsis [2]. Thus, the current definition of sepsis (designated Sepsis-3) is life-threatening organ dysfunction caused by a dysregulated host response to infection [3, 4].

Sepsis is a significant threat to health that places a substantial economic burden on healthcare systems. Although its incidence (1.6%) is lower than that of myocardial infarction (2.6%) and stroke (2.7%), it associates with a 3-fold higher 30-day mortality rate (31.8% *versus* 13.4% and 11.8%, respectively) [5]. Globally, 49 million people develop sepsis each year, resulting in 11 million deaths: this accounts for a fifth of all annual global deaths [6, 7]. The mortality rate is particularly high in septic shock (40–80%) [3, 8], which is defined as persistent sepsis-induced hypotension despite adequate intravenous fluid resuscitation [4, 7, 9]. Consequently, sepsis is a leading cause of death in intensive-care units (ICUs) [2].

The dysregulated immune response that drives sepsis-related organ dysfunction and mortality involves not only hyperinflammation but also immune suppression and failure

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to restore immune homeostasis [3]. The hyperinflammatory state, which emerges early in sepsis, is characterized by the elevation of systemic inflammatory cytokines such as TNF- α , IL-6, and CXCL2 [10–13]. Compensatory immunosuppression, also termed immunoparalysis, subsequently develops [3, 13]. This increases the risk of secondary infections and persistent organ damage, thereby contributing to long-term mortality [3, 13–15].

Innate lymphocytes are distinguished from adaptive lymphocytes (T and B cells) by the absence or restricted expression of antigen-specific receptors. They play critical roles in innate immunity as both effectors and regulators [16]. Most reside in non-lymphoid and mucosal barrier tissues [17, 18]. Some also circulate in the periphery and migrate into these tissues [19]. This, together with their abundance and ability to elicit rapid immune responses, means that they serve as sentinels that provide the first line of defense against pathogen invasion. They also play crucial roles in local immune and tissue homeostasis [19, 20]. Innate lymphocytes can be broadly classified into two major groups: innate-lymphoid cells (ILCs) and innate-like lymphocytes (ILLs) [20] (Fig. 1). ILCs constitute a lymphocyte lineage that lacks rearranged antigen receptors [21]. These cells respond rapidly to cytokine and microbial signals and are potent innate sources of proinflammatory and immunoregulatory

cytokines [21]. Consequently, they help modulate and resolve inflammatory reactions [21]. ILLs include NKT and $\gamma\delta$ T cells. While they express antigen-specific receptors and can mount adaptive immune responses, they lack the ability to generate long-term immune memory. Instead, they can rapidly produce large amounts of cytokines in response to pathogens, which resembles innate-immune responses [20, 22]. These features suggest that ILLs bridge the innate and adaptive immune systems [20]. An increasing body of evidence indicates that both ILCs and ILLs are critically involved in sepsis. In particular, ILCs may play double-edged roles: some may protect the host from sepsis by preventing infection and attenuating damage to key organs such as the lungs and heart [23–25] whereas others may intensify organ injury [24, 26]. Indeed, some ILCs may have both beneficial and pathological effects (Table 1). ILLs may also play protective and pathogenic roles depending on the organ.

However, studies on ILCs and ILLs in sepsis are limited. In this review, we will comprehensively summarize the recent primary literature on the protective and pathogenic roles that these cells play in specific organs in sepsis. We also outline future research directions that may improve our understanding of the diagnostic and therapeutic potential of these cells in sepsis.

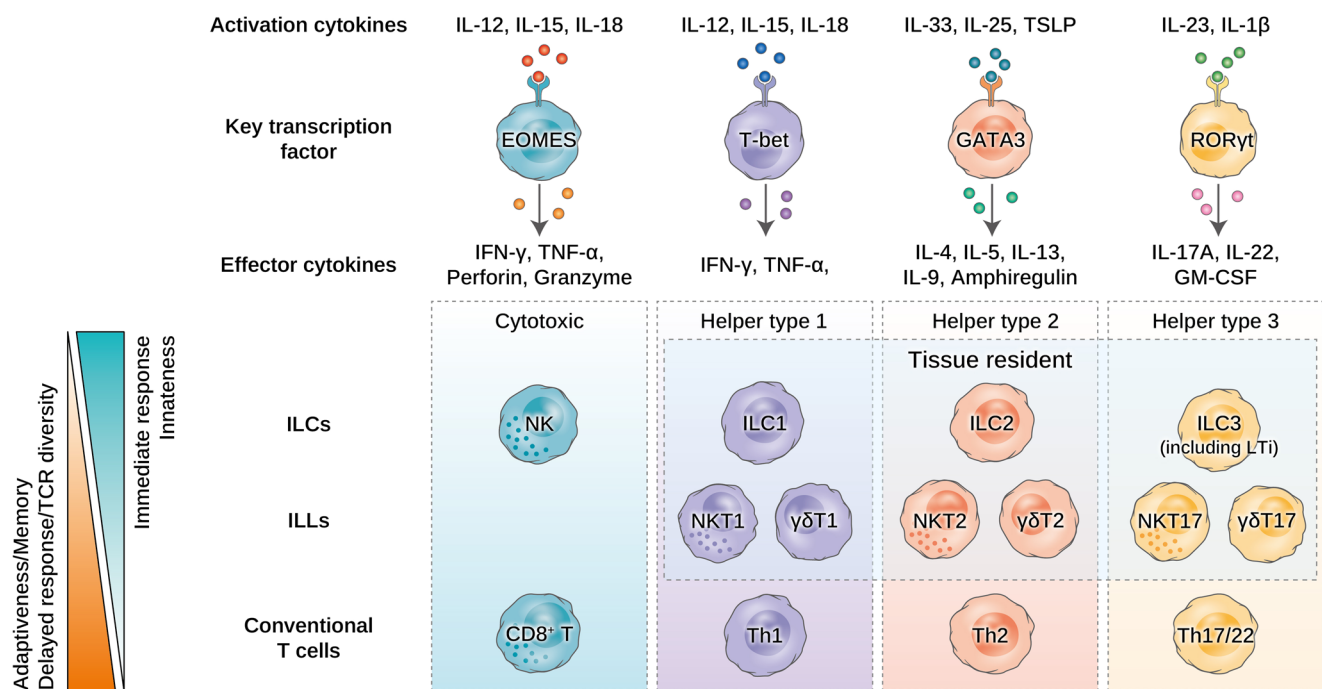


Fig. 1 Cytokines secreted by ILC and ILL. Innate lymphocyte can be divided into four types according to activation cytokine, transcription factor, and effector cytokine. Even if the same cytokine is secreted, it can be classified into two depending on the transcription factor. It is largely divided into cytotoxic lymphocyte, helper type 1, helper type 2, and helper type 3. Even within these four divisions, it is divided in

detail by adaptivity and immediate response information. ILC has a low adaptivity but a fast reaction rate. Conversely, in the case of conventional T cells, there is a TCR and memory capacity, and conversely, the immediate reactivity is low. What lies between this ILC and conventional T cell is the ILL.

Table 1 Organ-specific roles of innate lymphocytes in sepsis

Organ	Cell type	Major cytokine	Function	Effect
Lung	ILC2	IL-9	Apoptosis ↓, caspase-1 activation ↓	Protective
		IL-13	Lung injury ↓, tissue repair	Protective
	ILC3	IL-22	Bacterial burden ↓	Protective
		IL-17 A	Bacterial burden ↓, lung damage	Dual role
Heart	ILC2	IL-5	Eosinophil ↑, DC development ↑	Protective
		IL-4	Apoptosis ↓, infection ↓	Protective
		IL-13	M2 polarization ↑, apoptosis ↓	Protective
Kidney	ILC2	IL-5	Eosinophil ↑, neutrophil ↓	Protective
Liver	NK	IFN- γ	Inflammation ↓	Protective
		IL-17 A	Bacterial clearance	Protective
	iNKT	IL-4, IFN- γ	Inflammation ↑	Pathogenic
	ILC1	IL-6	Inflammation ↑, cytotoxic potential ↓	Dual role
Gut	ILC3	IL-22	Apoptosis ↓	Protective
	ILC1	IFN- γ	Apoptosis ↑, IEC death, inflammation ↑	Pathogenic
	iNKT	IL-4, IFN- γ	Apoptosis ↑, IEC death, inflammation ↑	Pathogenic

The table above summarizes at a glance which cell type secretes which cytokines, functions, and ultimately affects the organs. Data compiled from multiple studies

Lung: [24, 27–32]

Heart: [33–37]

Kidney: [38]

Gut: [39–43]

Liver: [44–46]

ILC subtypes and functions

ILCs are lymphocytes that lack rearranged antigen-specific receptors [19], thus distinguishing them from T and B cells [47, 48]. They are enriched at barrier surfaces, namely, the skin, and mucosal tissues [21]. They recognize various environmental and inflammatory signals and respond by secreting cytokines. These cells are thus essential for initiating and regulating immune-defense responses. They also promote the resolution of inflammation and mediate tissue repair processes essential for homeostasis and post-inflammatory recovery. The central immunological role of these cells is evident from their association with diseases such as allergy, autoimmunity and cancer, which often result from excessive, insufficient or dysregulated ILC activity [49–53].

ILCs originate from common lymphoid progenitors (CLPs) and express markers such as the common γ -chain,

IL-7R α (CD127), and Thy1 [21, 47, 54]. Based on their transcription factors, cytokine profiles, and functional characteristics, ILCs are classified into three groups, namely, ILC1s, ILC2s, and ILC3s [54] (Fig. 1). Notably, the ILC1s, ILC2s, and ILC3s respectively share the cytokine profiles of the adaptive Th1, Th2, and Th17 T-cell subsets and thus can be seen as the innate equivalents of these subtypes [47, 54].

ILC1s

The ILC1s are characterized by their ability to produce IFN- γ and comprise cytotoxic natural-killer (NK) cells and non-cytotoxic helper ILC1s [20, 55]. They are primarily activated by IL-12, which induces the expression of the transcription factor T-bet [56] (Fig. 1).

NK cells were first described as large granular lymphocytes that can lyse tumor cells without prior sensitization [20]. The cytotoxic mechanism involves either the engagement of death receptors on target cells or the release of perforin and granzyme, which induce apoptosis [57]. Unlike other ILC groups (including helper ILC1s), which largely reside in tissues, NK cells are primarily circulate in the blood: they will enter tissues as required and subsequently return to the circulation [19]. It should be noted that we refer here to conventional NK (cNK) cells, which are phenotypically defined as CD49a⁺ CD49b⁺ [58]. While nonconventional tissue-resident NK cell subtypes also exist (e.g. liver-resident and thymic NK cells) [59], these subsets are beyond the scope of this review. In general, NK cells potently and directly kill target cells and secrete cytokines that activate other immune cells [44].

By contrast, helper ILC1s, which are defined as CD49a⁺ CD49b⁺, exhibit self-renewal capacity, can be long-lived, and are poorly cytotoxic. Thus, their main function is to secrete cytokines [44, 58, 60]. They are mainly located in the gut and liver [39, 60, 61].

ILC2s

ILC2s express the transcription factor GATA3 and the surface markers ST2 (IL-33 receptor) and CD25 (IL-2R α) [21, 48, 54] (Fig. 1). They reside in healthy lungs, skin, and adipose tissue [21]. They primarily produce type-2 cytokines, namely, IL-5, IL-13, and IL-9, but under certain conditions can also secrete IL-4 and amphiregulin [21, 47, 54]. They are activated by various epithelium-derived cytokines and lipid mediators, including IL-33, IL-25, TSLP [21, 47, 54], prostaglandin-D2, and members of the TNF superfamily (e.g. TL1A) [47]. ILC2s are important for host defense against helminth infection and tissue homeostasis, but they can also be pathogenic depending on the context. For example, abnormal ILC2 activity contributes to inflammatory diseases such as asthma and atopic dermatitis [21, 47, 54].

ILC3s

ILC3s are defined by ROR γ t expression and include natural-cytotoxicity receptor (NCR)-positive ILC3s, NCR-negative ILC3s, and fetal lymphoid-tissue inducer (LTi) cells [21, 54] (Fig. 1). They play crucial roles in repairing damaged tissues of the lungs, liver, and intestines in a way that clears pathogens [21, 60, 62]. They function primarily by producing IL-17 A and IL-22, but they also exhibit cytotoxic activity in some situations, such as in cancer [63]. ILC3-derived IL-22 is particularly important for maintaining the intestinal epithelial barrier, thereby supporting gut homeostasis and limiting inflammation [21, 54]. ILC3s themselves are activated by cytokines such as IL-1 β , IL-6, and IL-23 [21, 47, 54].

Ontogeny, maintenance of cell numbers, and tissue retention of ILCs

NK cells largely circulate in the blood while the other ILCs reside in non-lymphoid tissues. These patterns are established in fetal life. Specifically, all ILCs arise from a bone-marrow-derived common lymphoid progenitor (CLP), which differentiates into intermediate ILC progenitors (ILCps), which then migrate to the peripheral tissues. The local microenvironmental cues cause the ILCps in non-lymphoid tissues to differentiate into mature ILCs [64] while the ILCps in lymphoid tissue become mature NK cells [65]. The tissue ILCs subsequently persist by local self-renewal [66]. However, local ILC numbers can also be replenished by differentiation from bone-marrow-derived progenitors [64]. The latter mechanism also maintains circulating NK cell numbers [67].

The survival of ILCs in non-lymphoid organs is dictated by adventitial stromal cells: ILCs localize in specialized niches inhabited by these cells, which provide essential survival and activation signals such as IL-33 and TSLP [68]. Multipotent stromal cells have also been shown to induce ICAM-1/LFA-1-mediated proliferation in ILC2s in adipose tissue, which sustains their local numbers [69]. ILC retention in tissue is also maintained by specific molecular anchoring mechanisms. For example, ILC migration from tissue is prevented by the tissue expression of CD69, which antagonizes the cell-migration receptor S1PR1 on ILCs, thus preventing their egress [70]. Another example is the ICAM-1/LFA-1 signaling between stromal cells and ILC2s in adipose tissue mentioned above: this signaling also appears to act as an ILC2 retention mechanism [69].

Notably, inflammation can alter tissue numbers of ILCs. For example, the development of intestinal colitis induces the release of inflammasome-derived IL-18 into the blood,

which causes a subset of bone-marrow sinusoid ILCps to downregulate their retention receptors (e.g. integrin- α 4 and CXCR4) and upregulate S1PR1. This facilitates their S1P-dependent egress into the blood and migration to the peripheral tissues [71]. Similarly, IL-33 released by inflamed tissues can promote the egress of bone-marrow ILC2 progenitors and their accumulation in the lung [47]. Moreover, in inflammatory conditions such as asthma and inflammatory bowel disease, ILCs can also convert into other ILC types, which can alter ILC type numbers.

Thus, tissue-resident ILC pools are shaped by local proliferation, replenishment from bone-marrow-derived progenitors, retention, and phenotype plasticity, all of which can be altered by inflammatory cues [17–19, 71].

ILCs in sepsis: organ-specific roles

Our current understanding of the roles of ILCs/ILs in sepsis is almost entirely based on studies on murine sepsis/organ-injury models, namely, the cecal ligation and puncture (CLP), lipopolysaccharide (LPS), and *Pseudomonas* pneumonia infection models. In the CLP model, the cecum is ligated, punctured with a needle, and returned to the abdominal cavity prior to closure [72, 73]. In the LPS model, LPS is injected intravenously or intraperitoneally [74, 75]. In the *Pseudomonas* model, *P. aeruginosa* is injected intratracheally. This prominence of murine studies reflects the fact that sepsis is a critical condition that prevents organ tissue acquisition in living patients, there are no studies on the role of ILCs/ILs in sepsis in humans that do not focus on the blood. Thus, our review below is based almost entirely on the findings in animal models of sepsis. However, human studies will be discussed at the blood level about the role of NK cells, which are circulating ILCs.

Lung

Lung infections are the sepsis source in 46% of cases [76], and nearly half of septic patients develop acute-lung injury (ALI) or its more severe form, acute respiratory-distress syndrome (ARDS) [26, 77–79]. ARDS involves widespread parenchymal injury and disruption of the pulmonary endothelial barrier [26]. Recent outbreaks of infectious diseases such as influenza and COVID-19 have significantly increased the incidence of sepsis-associated ARDS and the sepsis mortality rate [80]. While multiple pathogenic mechanisms drive ARDS, they include inflammatory injury and immune dysregulation [24, 26]. Specifically, the local and systemic infection triggers the release of inflammatory mediators such as IL-1 β , IL-6, and TNF- α , which recruit immune cells, including macrophages and neutrophils into

the lungs [23, 24, 80–82]. These cells then generate an uncontrolled inflammatory cascade that leads to vascular leakage and tissue injury in the lungs [26, 81]. In particular, infection-derived LPS and immune cell-derived TNF- α induce pyroptosis in pulmonary epithelial and endothelial cells [27], which is a caspase-1-dependent form of inflammatory programmed-cell death [27, 81]. This results in the clinical manifestations of ARDS, including pulmonary edema, reduced lung compliance, increased work of breathing, hypoxemia, and impaired gas exchange [83].

With regard to ILCs, most lung sepsis studies have focused on ILC2s. They suggest that the infection- or cytokine-induced injury to the pulmonary epithelial and endothelial cells induces the release of IL-33, an ILC2-activating cytokine, within a few hours after the onset of sepsis [81]. The local IL-33 levels rise rapidly [81] and the cytokine subsequently binds to its receptor ST2 on lung-resident ILC2s [27, 81], leading these cells to expand and accumulate [24, 25]. Subsequently, systemic IL-33/ST2 signaling further expands this ILC2 population and promotes their migration from the bone marrow to the lung [25]. The activated ILC2s then release type-2 cytokines such as IL-5, IL-9, and IL-13 [23, 24, 27]. ILC2s in the lung normally act to ameliorate lung sepsis. While the underlying mechanisms have not yet been fully elucidated, studies suggest

that ILC2-derived cytokines may have multiple protective effects (Fig. 2). First, ILC2-derived IL-9 may bind to IL-9R on endothelial cells, which attenuates caspase-1 activation and reduces their pyroptotic cell death [27]. Second, ILC2-derived IL-13 may drive anti-inflammatory M2 polarization of alveolar macrophages, which is needed for resolving pulmonary inflammation and promoting tissue repair [28]. Third, ILC2-derived IL-9 may reduce the apoptosis of these M2 macrophages [24]. Fourth, ILC2-derived IL-13 may reduce lung neutrophilia [29, 30]: the CLP mouse model showed that neutralizing IL-13 not only worsens survival and worsens lung injury but also increases the production of chemokines that attract neutrophils in the lungs [29, 30]. The blockade also reduced lung levels of TNF- α , which is produced by neutrophils in sepsis [29, 30]. Fifth, ILC2-derived amphiregulin may help remodel the damaged lung tissue [84].

However, if the protective function of ILC2 is suppressed, sepsis may progress further. One potential ILC2 inhibitory mechanism is the early upregulation of programmed cell-death protein-1 (PD-1) on ILC2s [23]. This may reduce ILC2 production of IL-13 and IL-9. This reduction may prevent the beneficial effects of these cytokines described earlier. In particular, it may impair M2-macrophage polarization and survival [23]. This may in turn enhance the polarization

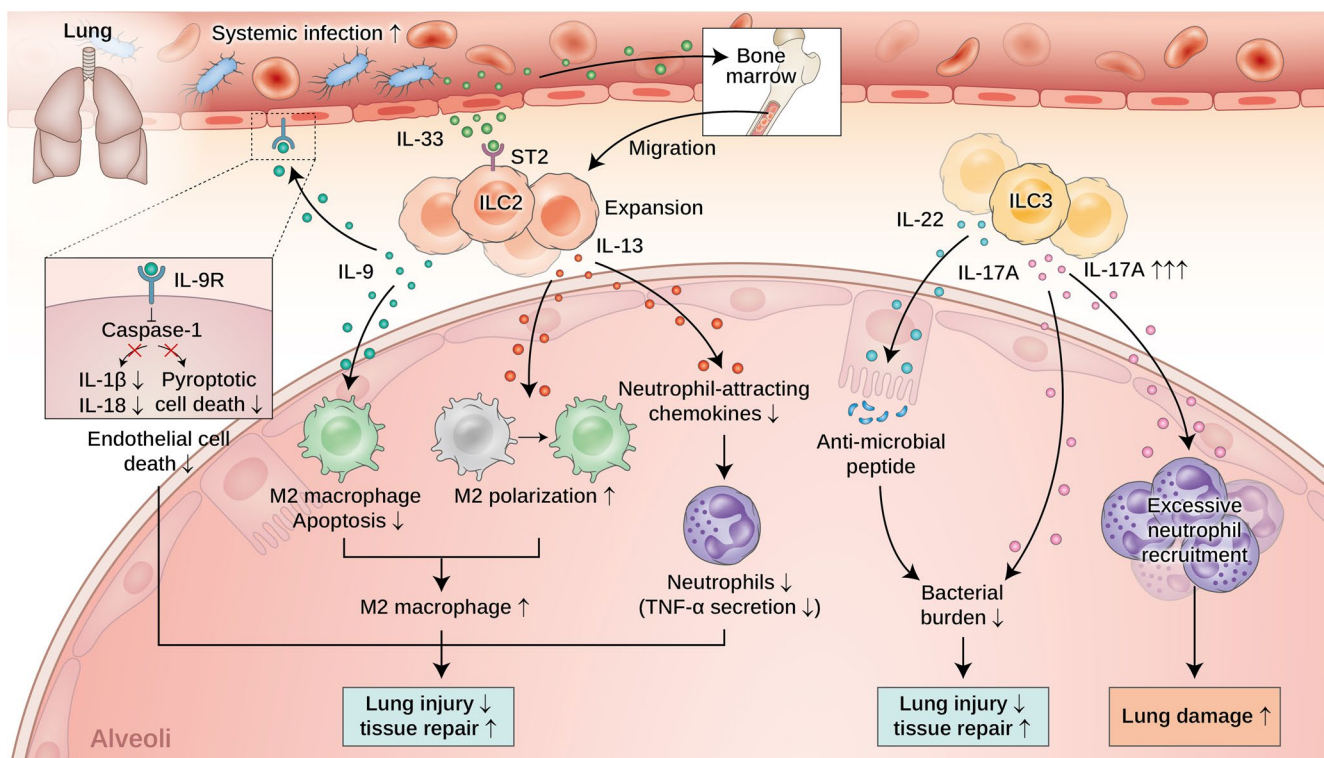


Fig. 2 Cytokine-Innate lymphocyte axis in sepsis-induced lung injury In the lung, ILC2 exerts protective effects by secreting IL-9/IL-13, enhancing M2 polarization and limiting neutrophil recruitment. ILC3

mediates protection via IL-22 and IL-17 A but can drive lung damage when IL-17 A is excessive. In sepsis-induced lung injury, ILC can cause both protective and pathological responses

and expansion of proinflammatory M1 macrophages, which produce large amounts of proinflammatory cytokines [23, 24, 28, 85]. The decreased IL-13 production on the first day of sepsis development suggests that the IL-13 plays an important role in this mechanism [28].

Conversely, it is also possible that sepsis induces pulmonary ILC2 overactivation that contributes to ALI. This possibility is suggested by studies on hemorrhagic shock, which causes ALI and shares many immunopathological features with sepsis. In hemorrhagic shock, there is systemic release of the damage-associated molecular pattern (DAMP) molecule called high-mobility group box-1 (HMGB1) [86]. HMGB1 activates lung-resident macrophages and ILC2s. It also promotes ILC2 proliferation and inhibits their apoptosis by binding to RAGE (receptor for advanced glycation end-products) on ILC2s [86]. Initially, the local macrophages bear the M1 phenotype and secrete proinflammatory cytokines such as TNF- α , IL-1 β , IL-6, and IFN- γ [87]. Over time, these macrophages switch to M2 macrophages: together with activated ILC2s, these cells produce type 2 cytokines such as IL-5 and IL-13, leading to eosinophilic infiltration that contributes to acute lung injury [86, 87].

Thus, murine studies show that pulmonary ILC2s normally protect the lung from sepsis by secreting IL-9 and IL-13, promoting anti-inflammatory macrophage responses, and preserving endothelial integrity. However, their dysregulation may promote sepsis. The underlying mechanisms may include inhibition of their IL-13 production early after sepsis onset or conversely, excessive release of type-2 cytokines that exacerbates inflammation and tissue injury. Thus, pulmonary immune homeostasis depends on tight regulation of ILC2 activity, and derangement of this regulation can lead ILC2s to promote sepsis.

Finally, ILC2s predominate in the lung but the remaining ILCs are mainly ILC3s [84, 85, 88]. ILC3s produce IL-22, which induces pulmonary epithelial cells to release antimicrobial peptides [31] (Fig. 2). ILC3s also prevent specific bacterial infections by producing IL-17 A [32]. Moreover, ILC3-derived IL-22 supports lung barrier integrity during bacterial infections [23, 88]. Consequently, ILC3s are key regulators of pulmonary health against bacterial pathogens. Although little is known about the role of ILC3s in sepsis, the prominence of ILC3s in the lungs suggests that dysregulated ILC3s could potentially promote sepsis. For example, excessive ILC3 production of IL-17 A, a potent neutrophil-recruiting cytokine, could potentially exacerbate lung damage by attracting neutrophils to the lung [32].

Heart

Of all the visceral organs, the heart is regarded as being particularly vulnerable to septic injury [89]: up to 40% of

patients with septic shock develop septic cardiomyopathy, a partially reversible form of heart damage [90]. Its presence associates with mortality rates of up to 70% [90, 91].

The mechanisms that lead to septic cardiomyopathy have not been fully elucidated but studies on murine models of sepsis show that innate immune cells, including ILC2s, and their release of TNF- α , IFN- γ , IL-6, and IL-17 A are major contributors to the myocardial damage in sepsis [33]. Thus, recent studies show that the heart contains ILCs [89], and that ILC2s account for ~90% of these cells [89, 92]. Cardiac ILC2s have also been shown to be tissue-resident cells that are minimally replaced by circulating cells [92]. When the heart is injured by sepsis, the local ILC2s expand significantly and quickly: in the CLP mouse model, cardiac ILC2 numbers increased approximately seven-fold within 6 h of sepsis onset, but subsequently declined [33, 89]. This increase appears to be protective since it correlated negatively with serum levels of NT-proBNP, a well-established marker of cardiac dysfunction [89]. The stimulus inducing the heart ILC2s is likely IL-33 [33, 34, 89, 93] because it is markedly upregulated during sepsis. For example, in the LPS-induced mouse model of sepsis, IL-33 mRNA and plasma levels respectively rose by ~108-fold and ~8-fold 6 h after sepsis onset, which coincided with the 6-hour peak in heart ILC2 abundance [89]. Moreover, IL-33 treatment of septic mice improves contractile indices and injury biomarkers, and these benefits coincide with a surge in heart ILC2s [34, 35, 89, 93]. Such beneficial effects of IL-33 treatment are also observed in non-septic mice with myocardial infarction [34, 93].

Subsequent studies showed that local ILC2s may protect the heart by secreting IL-13, IL-5, and IL-4 [33–35, 89] (Fig. 3). Specifically, in the CLP-induced mouse model of sepsis, ILC2-derived IL-13 and IL-5 are both upregulated, again with a peak at 6 h [89]. Moreover, IL-4 levels in the heart are significantly higher 24 h after CLP-induced sepsis, and heart ILC2s are the primary source of this cytokine [33]. Treatment with IL-13 also had cardioprotective effects in LPS-induced sepsis [93]. Notably, knocking out IL-13 also blocked the cardioprotective effect of IL-33 treatment in murine myocardial infarction [34]. Several studies have investigated how these cytokines promote cardioprotection in sepsis. In relation to IL-13, it may serve to reduce cardiomyocyte apoptosis because it specifically activates the STAT3 signaling pathway in these cells [93]. While IL-13 generally signals through both STAT3 and STAT6 pathways [93], the primary involvement of STAT3 in IL-13-mediated cardiomyocyte survival in sepsis is suggested by several observations. First, IL-13R α 1 and STAT3 transcription is upregulated in the heart during murine LPS-induced sepsis [93]. Second, IL-13 treatment of LPS-treated cardiomyocytes *in vitro* suppresses the rise in cleaved caspase-3 while

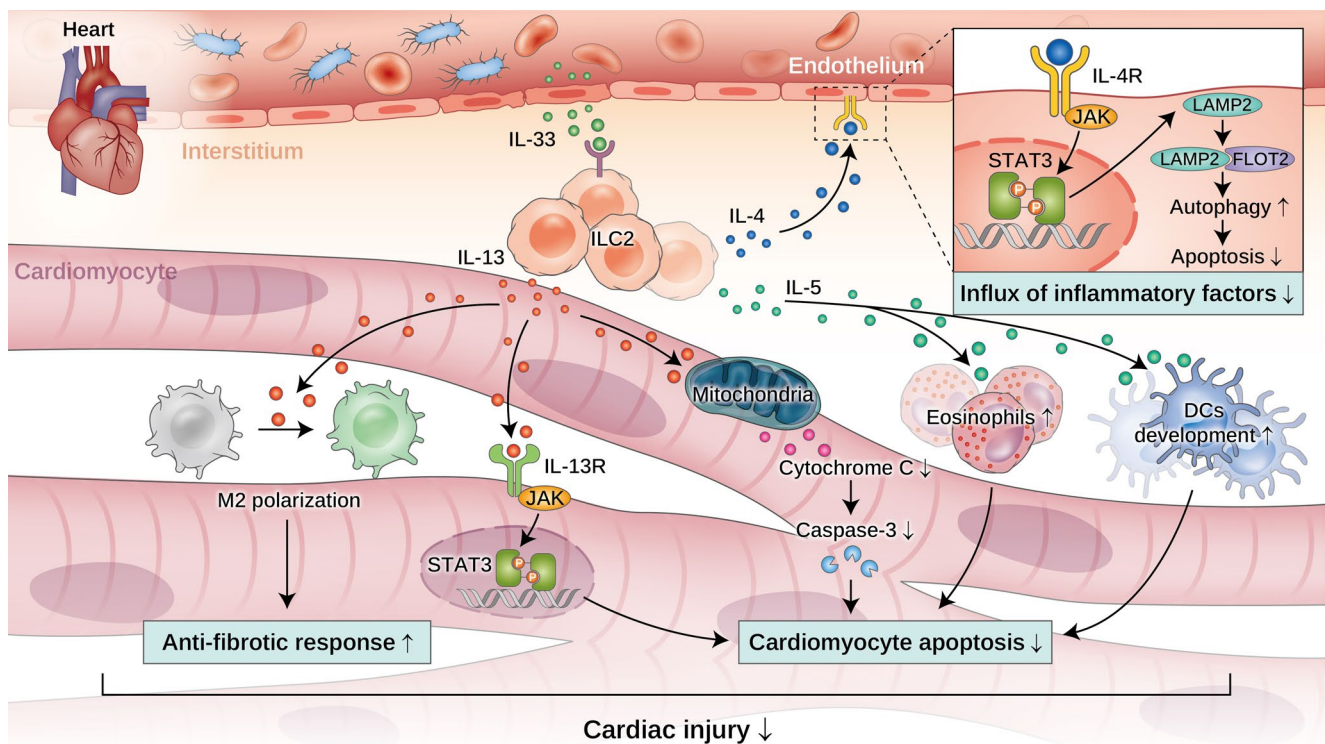


Fig. 3 Cytokine-Innate lymphocyte axis in sepsis-induced heart injury In the heart, ILC2 promotes cardioprotection by secreting IL-5 and IL-13, which reduce apoptosis and enhance tissue repair via eosinophil recruitment and the JAK/STAT3 pathway. IL-4 further contributes by

enhancing STAT3 phosphorylation at both serine-727 and tyrosine-705 [93]. Notably, IL-13 increases serine 727-phosphorylated STAT3 levels in the mitochondria [93], and this associates with reduced cytoplasmic release of cytochrome-C [33, 93]. Thus, IL-13 may prevent cytochrome C-mediated apoptosis of LPS-challenged cardiomyocytes. Notably, this cardioprotective effect of ILC2-derived IL-13 is supported by a study on catecholamine-induced cardiac fibrosis in mice. This study showed that while ILC deficiency worsened myocardial fibrosis cardiac fibrosis, IL-33 administration several days after catecholamine treatment suppressed the fibrosis and that IL-13 knockout reversed this effect [34]. IL-13 is also important for myocardial repair in sepsis: the LPS-induced mouse model of sepsis shows that it promotes the cell-cycle entry of cardiomyocytes, which allows the heart to regenerate after injury [93, 94]. This role of IL-13 was also observed in regenerating hearts in neonatal mice that sustained an ischemic cardiac injury [93, 94].

With regard to heart ILC2-derived IL-5, it also protects cardiomyocytes from cell death. This is shown by the fact that mice lacking IL-5 exhibit increased cardiomyocyte apoptosis and impaired cardiac function in sepsis. The underlying mechanism may involve IL-5-mediated induction of autophagy in cardiomyocytes, which protects them from apoptosis [89]. It is also possible that IL-5 protects

modulating endothelial survival and anti-fibrotic responses. In conclusion, in the heart, ILC2 is mainly involved and functions in a way that protects the heart

the heart from septic cardiomyopathy *via* its key role as a promoter of eosinophil development [36]. This is significant because eosinophils protect cardiomyocytes from apoptosis by producing IL-4 and other molecules that block apoptosis [37]. Thus, local ILC2s may indirectly enhance cardiomyocyte survival in sepsis by expressing IL-5, which recruits and activates eosinophils, which in turn prevent cardiomyocyte death. This is supported by the fact that in murine myocardial infarction, depleting ILC2s reduces eosinophil numbers in the heart and worsens cardiomyocyte apoptosis [35, 36], while administration of IL-5 restores eosinophil numbers and reduces cardiomyocyte apoptosis [36]. Notably, IL-5 also promotes the development of dendritic cells (DCs) in the heart, which are essential for cardiac repair after myocardial infarction and, like eosinophils, suppress cardiomyocyte apoptosis [36]. Thus, ILC2-derived IL-5 may prevent cardiomyocyte death and enhance cardiac repair by increasing local eosinophil and DC numbers.

ILC2-derived IL-4 may also protect cardiomyocytes from apoptosis: while ILC2 depletion amplifies the cardiomyocyte apoptosis and poor cardiac function in septic mice, concomitant injection with IL-4 restores the cardiomyocyte protection provided by ILC2s [33]. Interestingly, another key target of heart ILC2-derived IL-4 appears to be autophagy in the cardiac endothelial cells, which

is impaired in cardiac sepsis [33]. Specifically, IL-4 activates the STAT3-signaling pathway in endothelial cells, which upregulates lysosomal-associated membrane protein-2 (LAMP2), a key regulator of lysosomal function and autophagy [33]. LAMP2 then binds to flotillin-2 (FLOT2) [33]. This STAT3-LAMP2-FLOT2 axis secures lysosomal integrity and permits autophagosome-lysosome fusion, thus preventing endothelial-cell apoptosis [33]. This in turn may maintain tight endothelial junctions, which limits the influx of inflammatory factors into the heart tissue, thus reducing local inflammation, protecting cardiomyocytes, and preventing cardiac dysfunction [33].

In summary, the ILC2 stimulatory cytokine IL-33 drives the expansion of heart ILC2s and their production of IL-13, IL-5, and IL-4, which may protect the heart from sepsis by various mechanisms (Fig. 3). Specifically, they may prevent cardiomyocyte apoptosis (IL-13 *via* STAT3, and IL-5 by promoting cardiomyocyte autophagy); block heart endothelial-cell apoptosis (IL-4 *via* the autophagy-related STAT3-LAMP2-FLOT2 axis) [33]; promote local M2-macrophage polarization (IL-13) [34]; induce cardiomyocyte regeneration (IL-13); and prevent cardiomyocyte apoptosis by recruiting and activating eosinophils and DCs (IL-13) [36]. Thus, these cytokines collectively orchestrate a cardioprotective immune axis that limits cardiac septic injury, supports tissue regeneration, and maintains myocardial homeostasis.

Notably, a recent study reported that LPS-induced septic cardiomyopathy is mediated by HIF-1 α accumulation in cardiomyocytes, which suppresses their mitochondrial respiration *via* iNOS-dependent nitric oxide signaling and induces cytopathic hypoxia [95]. Interestingly, HIF-1 α is also a central immunometabolic regulator of ILC responses in hypoxic and inflammatory conditions: it promotes their glycolytic reprogramming and effector programs, including IL-17/IL-22 production by ILC3s [96]. This suggests that sepsis-induced cardiomyopathy itself can induce pathogenic ILC responses that then potentially worsen the damage to the heart. Further studies on this possibility are needed.

Kidney

When acute kidney injury (AKI) occurs within 7 days of sepsis onset, it is referred to as sepsis-associated (SA)-AKI [97–99]. Recent studies indicate that SA-AKI occurs in 47–50% of patients with sepsis [98] and in 16% of all ICU patients [98, 99]. Australian ICU data suggest SA-AKI is increasing: it was 14% in 2015 and 18% in 2021 [99]. Although most SA-AKI cases are diagnosed on the day of ICU admission or within a day of sepsis diagnosis [98, 99], SA-AKI associates with 1.6-fold higher mortality and

a 3.4-fold greater risk of major adverse kidney events than sepsis or AKI alone [98].

To our knowledge, no studies have directly investigated the role of ILCs in SA-AKI. However, findings in non-infectious AKI settings such as nephrotoxic or sterile injury murine models suggest that IL-33 can induce kidney ILC2s to protect and repair the tissue (Fig. 4). Specifically, it was shown that when mice with adriamycin-induced nephropathy are treated with short-term low-dose IL-33, the kidney-resident ILC2s expand and both renal inflammation and kidney function improve [38, 100]. These beneficial effects may involve ILC2-mediated expansion of regulatory T cells (Tregs) and M2 macrophages in the kidney [101]. Similarly, when nephrotoxic kidney injury models are administered a low dose of IL-233 (a hybrid cytokine containing IL-2 and IL-33), both ILC2s and Tregs are expanded and the kidney is protected from injury [102]. The protective effects of ILC2s may reflect their release of amphiregulin, which induces epithelial repair (including tubular regeneration) and type 2 cytokine-dependent modulation of innate myeloid/granulocyte responses [101]. In relation to the latter effect, the ability of IL-33 to reduce adriamycin-induced glomerulosclerosis was shown to associate with tissue-protective eosinophilia and reduction of tissue-destructive neutrophils [38].

Thus, ILC2s could potentially have a protective effect on the kidney in sepsis. However, it should be noted that drug-induced AKI and SA-AKI are thought to be mediated by different mechanisms. Thus, studies that directly examine the roles of ILCs in SA-AKI are needed.

Gut

The gut is often compromised in sepsis and generally recovers slowly [103]. It is both a major originating site of sepsis and a target of septic damage [103]. Specifically, loss of intestinal barrier function can cause bacteria and their products to enter the body and cause sepsis. Conversely, the systemic inflammation in sepsis, regardless of its origin, promotes gut epithelial apoptosis and intestinal permeability, which permits host entry of bacteria and their products. Dysbiosis of the gut microbiome may be a major cause and consequence of sepsis [104].

The normal gut contains all three ILC groups but ILC1s and especially ILC3s predominate [105]. The ILC3s play a particularly important role in normal gut barrier function because they are the primary source of IL-22 in the gut [40–42] and IL-22 causes intestinal-epithelial cells (IECs) (which exclusively express IL-22R) to proliferate and produce antimicrobial peptides and defensins while inhibiting epithelial-cell apoptosis [40, 41] (Fig. 4). Thus, IL-22

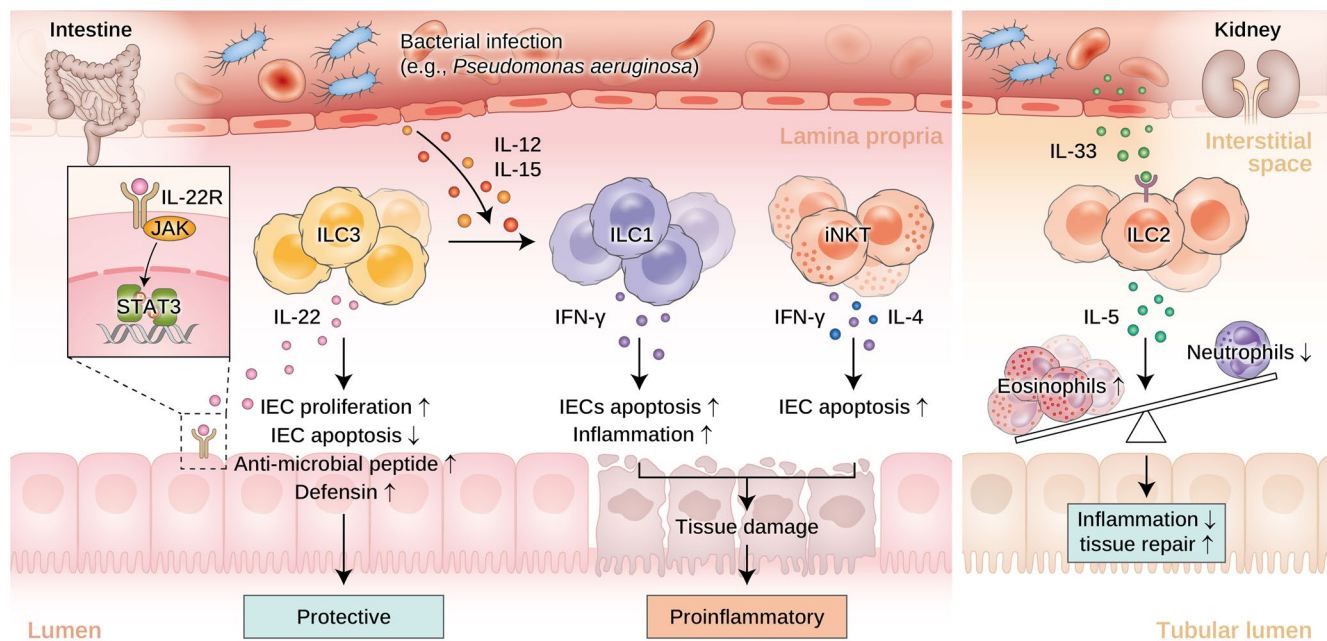


Fig. 4 Cytokine-Innate lymphocyte axis in sepsis-induced intestine injury and kidney injury In the intestine, ILC3-derived IL-22 promotes epithelial recovery, whereas ILC1-derived IFN- γ and iNKT cell-derived IFN- γ , IL-4 induce IEC cell death, highlighting the balance

of protection and damage. ILC3-to-ILC1 plasticity under IL-12/15 signaling exacerbates inflammation. In the kidney, ILC2-derived IL-5 contributes to protection by enhancing eosinophil recruitment and reducing neutrophil infiltration

facilitates IEC integrity, repair, and host defense against pathogens [40–43]. These effects are mediated by the activation of STAT3 signaling in IECs after their IL-22R binds to IL-22 [42]. By contrast, gut ILC1s produce IFN- γ , thereby promoting inflammatory responses [39] (Fig. 4). As intraepithelial lymphocytes, they interact closely with the intestinal epithelium [39], and proinflammatory mediators released by ILC1s can damage IECs. Notably, in vitro studies show that ILC3s can transdifferentiate into IFN- γ -producing ILC1-like cells when they are exposed to cytokines such as IL-12 and IL-15 [39]. These converted ILC1-like cells express the transcription factors T-bet and EOMES, indicating their acquisition of ILC1 and/or NK-cell properties. T-bet drives the IFN- γ production of these ILC1-like cells [39, 106, 107].

In sepsis, the intestinal immune response is primarily mediated by ILC3s and ILC1s, which undergo significant compositional and functional changes during inflammation. Specifically, in the *Pseudomonas* model of sepsis, NCR⁺ ILC3s decrease while helper ILC1s increase. Moreover, the gut, which exhibits increased permeability, demonstrates downregulation of ROR γ t, the master transcription factor of ILC3s, and a concomitant increase in the ILC1 master regulator T-bet (Fig. 4). Thus, in sepsis, the beneficial ILC3s may convert into proinflammatory ILC1s, which disrupts the protective IL-22 pathway in the gut and promotes intestinal permeability [42].

Liver

The liver can exhibit early functional disturbances in sepsis, typically defined as sepsis-associated liver injury when serum bilirubin levels exceed 2 mg/dL [108]. While the liver is often one of the first organs to show biochemical impairment, progression to overt hepatic failure is relatively infrequent compared to renal or respiratory dysfunction: a recent 15-year population-based study showed that hepatic failure occurred in only 1.3% of sepsis cases, which is significantly lower than renal (56.9%) and respiratory failure (15.2%) [109]. However, the development of liver failure in sepsis marks a critical clinical turning point because it is associated with a disproportionately high in-hospital mortality rate (52.0%) and often reflects a state of severe immune dysregulation and systemic metabolic collapse [110].

The liver-resident macrophages called Kupffer cells play a central role in the initial immune response of the liver to sepsis. For example, Kupffer cells showed treatment with sepsis endotoxins greatly increased Kupffer cell production of proinflammatory cytokines such as IL-6 and IL-1 β [110, 111]. These cytokines promote neutrophil and monocyte recruitment [111]. They also inhibit the expression of bile acid transport proteins, which results in bile congestion liver damage [108]. The accumulation of proinflammatory cytokines and bilirubin then promotes systemic toxicity, further worsening the clinical condition of the patient.

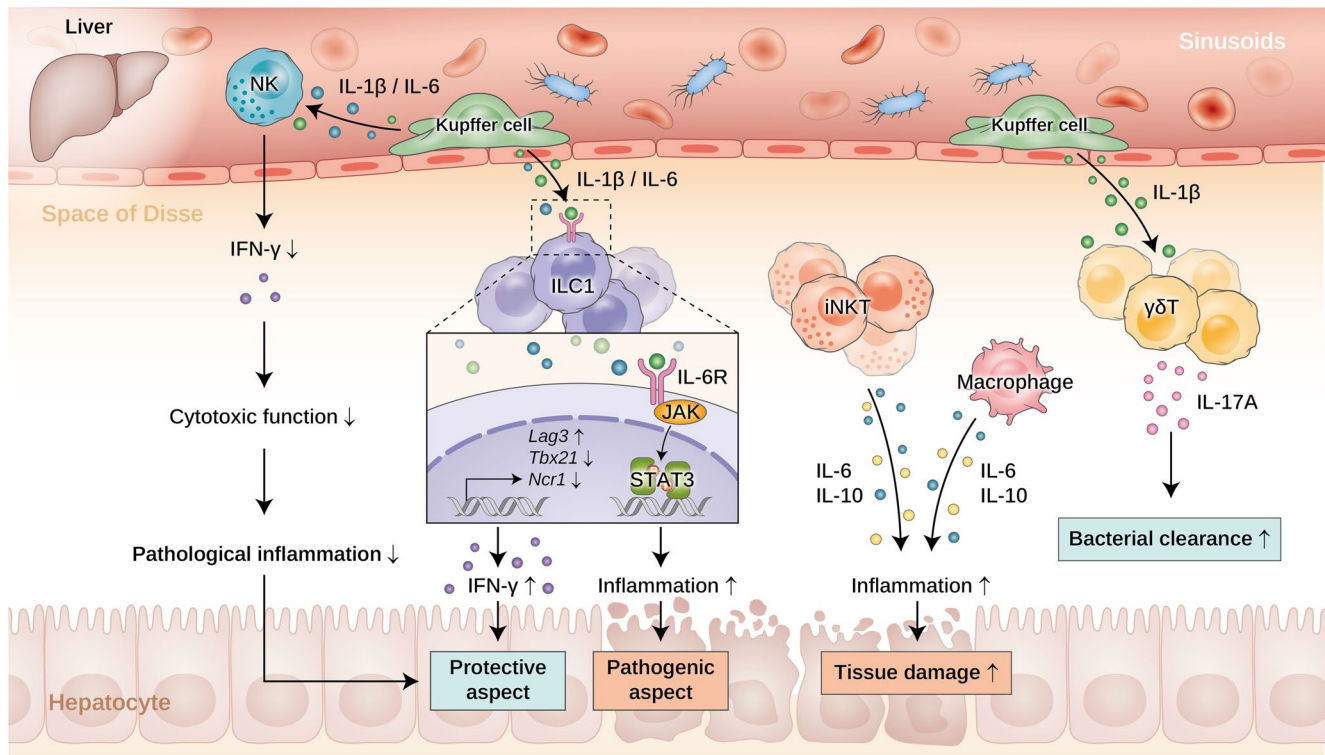


Fig. 5 Cytokine-Innate lymphocyte axis in sepsis-induced liver injury In the liver, ILC1 produces IFN- γ , which results in both protection and inflammation, while IL-6-STAT3 signaling increases pathogenic

inflammation. iNKT cells secrete IFN- γ and IL-4, which amplify tissue damage. In contrast, IL-17 A, which is derived from $\gamma\delta$ T cells, promotes bacterial clearance and contributes to liver protection

With respect to ILCs, the liver mainly contains cNK cells and helper ILC1s [44, 58]. Both liver populations are decreased in CLP-induced sepsis [44] and the remaining NK cells exhibit an immunoparalyzed phenotype that is characterized by reduced cytotoxicity and lower production of IFN- γ [44] (Fig. 5). By contrast, the remaining helper ILC1s have an increased capacity to produce IFN- γ [44] (Fig. 5). Transcriptomic profiling also showed that helper ILC1s from the septic liver expressed higher levels of *Lag3* and lower levels of *Tbx21* and *Ncr1* than their counterparts from sham-operated livers, indicating a shift toward an exhausted phenotype with reduced cytotoxic potential [44]. The IL-6/JAK/STAT3 axis, which associates with inflammatory pathways, was also upregulated in the helper ILC1s [44]. By contrast, the G2/M checkpoint signature was downregulated, which indicates that the proliferative capacity of the ILC1s was curtailed during sepsis [44]. Thus, sepsis may downregulate hepatic cNK cells and impair the proliferation of helper ILC1s while simultaneously reprogramming the ILC1s to produce more IFN- γ . It was proposed that hepatic helper ILC1s could play a dual role in sepsis: while they may aid bacterial clearance early in sepsis, they could also exacerbate the inflammation that induces hepatic and systemic organ injury [44].

Systemic cytokine regulation of cNK-cell function

cNK cells circulate in the blood until they are recruited into tissues by stimuli such as infection or trafficking cytokines [112]. IL-12 activates NK cells and IL-15 are crucial for NK-cell homeostasis and effector function. Sepsis associates with elevated circulating levels of both IL-12 and IL-15 [113, 114], which suggests that circulating cNK cells could be highly activated in sepsis and may shape disease progression. Indeed, several lines of evidence indicate that circulating cNK cells exert both pathogenic and beneficial roles in sepsis.

With regard to the pathological role of cNK cells, high initial NK-cell numbers in the blood is associated with sepsis-related mortality in humans [115]. Similarly, in the CLP sepsis model, early elevation of blood IL-12 correlates positively with biochemical indicators of sepsis severity, and early elevation of IL-15 associates with mortality in severe sepsis. Moreover, IL-15 knockout mice, which have few NK cells, are resistant to CLP- or LPS- induced septic shock, as evidenced by reduced serum levels of pro-inflammatory cytokines and improved survival. This resistance was ablated when the mice were treated with IL-15

superagonist, and this effect in turn was reversed by depleting NK cells [116]. Thus, early expansion and activation of NK cells in the blood may create a positive feedback loop that promotes the cytokine storm in sepsis and results in deleterious outcomes.

However, circulating cNK cells may also be protective. Elevated blood cNK-cell numbers, activation levels, granzyme secretion, and IFN- γ production associate with the survival of sepsis patients [117–119], and an early decrease in circulating cNK cells associates with a greater risk of secondary infection and poor outcomes in some patients [120–122]. Moreover, IL-15 treatment after CLP reduces immune-cell apoptosis and increases murine survival [123]. Thus, blood cNK cells may have beneficial effects in sepsis by killing pathogens and preventing immunoparalysis. They may also have positive effects by secreting the anti-inflammatory cytokine IL-10, since CLP-induced septic mice that specifically lack IL-10 expression in NK cells exhibit increased mortality and prolonged sepsis severity [124]. Notably, this IL-10 expression by NK cells depended on IL-15: treatment with anti-IL-15R antibodies reduced the IL-10-producing NK cells in the spleen [124]. Thus, IL-15 is essential for inducing beneficial regulatory NK-cell functions in sepsis. This finding together with the reports described above that show IL-15 also induces pathological IFN- γ -expressing NK cells [116] suggests that cNK cells may respond to IL-15 in a biphasic manner in sepsis: they first produce IFN- γ and later generate counter-regulatory IL-10 [124]. Thus, circulating cNK cells may have protective effects in sepsis by killing pathogens initially and preventing immunoparalysis and producing anti-inflammatory cytokines later.

ILL subsets and functions

ILLs are unique lymphocytes that straddle the boundary between innate and adaptive immunity [20]. Unlike ILCs, which lack antigen-specific receptors [19], ILLs generally express antigen-specific receptors but possess a more restricted repertoire compared to conventional T cells. Most ILLs do not generate long-term antigen-specific immune memory, although certain subsets can display memory-like features in specific contexts [20]. ILLs can respond rapidly to pathogens with cytokine secretion, similar to innate immune cells, but some ILLs also mediate adaptive-like immune responses [20]. ILLs can be broadly categorized as innate-like B cells and innate-like T cells. The latter, which are of particular interest in sepsis, include natural-killer T (NKT) cells and $\gamma\delta$ T cells (Fig. 1). Notably, while these cells develop in the thymus, they undergo a lineage-specification program that diverges from the conventional T cell pathway, thereby establishing a distinct cellular identity

[125]. This underscores a fundamental ontogenetic distinction from ILCs, which are predominantly derived from bone marrow–origin lymphoid progenitors [64].

NKT cells

NKT cells are unconventional innate-like T cells. Instead of recognizing peptide–MHC complexes, they respond to glycolipid antigens presented by the non-polymorphic molecule CD1d [20, 126]. Based on their T-cell receptor (TCR) repertoire, they are classified as invariant NKT (iNKT) cells, which express a semi-invariant TCR (V α 14-J α 18 in mice; V α 24-J α 18 in humans) [127], and type 2 NKT cells, which have more heterogeneous TCRs [128]. iNKT and type 2 NKT cells are tissue-resident cells that respond to both foreign and self lipid antigens [129, 130]. Their residence in tissue means that they are among the first immune cells to respond to pathogens. Both NKT cell types also produce proinflammatory and anti-inflammatory cytokines and thus regulate the activity of various innate, innate-like, and adaptive immune cells, including Tregs [45, 131]. They not only play critical roles in the early phase of infection and inflammation, they have also been implicated in the pathogenesis of various autoimmune and inflammatory diseases [132].

$\gamma\delta$ T cells

$\gamma\delta$ T cells are also unconventional innate-like T cells that bear TCRs composed of specific γ and δ chains. They do not rely on classical MHC molecules for antigen presentation and can thus recognize a broad spectrum of structurally diverse antigens [133–135]. They are abundantly distributed in barrier tissues, particularly the intestinal epithelium [135]. In addition to TCR-mediated activation, they can also be stimulated by cytokines such as IL-12 and IL-18 [136]. They release cytotoxic molecules such as perforin and granzyme and produce cytokines such as IFN- γ , IL-17, and IL-22 that recruit and activate other immune cells [137]. These activities and their tissue residence mean that $\gamma\delta$ T cells play important protective roles against pathogens and tumors [134]. However, $\gamma\delta$ T cells have also been implicated in autoimmune and inflammatory diseases [133].

ILLs in sepsis: organ-specific roles

Liver

Both NKT and $\gamma\delta$ T cells are relatively abundant in the liver since they respectively constitute more than 10% of total

liver T cells [45] and 3–5% of the liver-resident lymphocytes [46]. Thus, both may play crucial roles in the hepatic immune system (Fig. 5). In CLP-induced sepsis, hepatic iNKT cells exhibit marked activation and rapidly produce high levels of IFN- γ and IL-4 in a CD1d-dependent manner. These responses may be pathogenic because blocking CD1d in the CLP model decreased Kupffer cell production of IL-6 while increasing their IL-10 secretion, and this associated with altered systemic cytokine levels and improved survival. Moreover, iNKT cell deficiency protected mice from sepsis-induced mortality [45]. Thus, liver NKT cells may play pathogenic roles in sepsis.

By contrast, $\gamma\delta$ T-cell deficiency in CLP-induced sepsis increased the bacterial load in the bloodstream, liver damage, and mortality [134]. Moreover, CLP increased the frequencies of IL-17 A-expressing $\gamma\delta$ T cells in the liver from 0% to 30% of $\gamma\delta$ T cells, and specific deletion of IL-17 A-producing $\gamma\delta$ T cells raised sepsis mortality from 70% at 7 days to 100% at 3 days in conjunction with greater bacterial load and liver injury. Significantly, adoptive transfer of V γ 4⁺ $\gamma\delta$ T cells, which accounted for the majority of IL-17 A-expressing $\gamma\delta$ T cells in the liver of post-CLP mice, ameliorated the CLP-induced liver injury in mice lacking IL-17 A-producing $\gamma\delta$ T cells [46]. Thus, liver $\gamma\delta$ T cells, especially those that express IL-17 A, may promote bacterial clearance and mitigate sepsis-induced injury of the liver (Fig. 5).

In summary, hepatic NKT cells promote sepsis-induced liver damage whereas hepatic $\gamma\delta$ T cells prevent it.

Gut

NKT cells are abundant in the intestinal tract [40]. These intestinal NKT cells exhibit basal activation even under steady-state conditions. Notably, their gene-expression profiles differ from those of lymphoid tissue-resident NKT cells, suggesting that intestinal NKT cells have adapted to the unique microenvironment of the intestinal barrier. Specifically, intestinal NKT cells demonstrate inflammatory-pathway activation and high expression of cytokines such as IFN- γ and IL-4. These NKT cell-derived cytokines are particularly crucial for IEC survival. However, during infection or inflammation, excessive activation of intestinal NKT cells can directly induce IEC apoptosis in an IFN- γ -dependent manner (Fig. 4). Lack of NKT cells also increases IEC turnover [40]. Thus, intestinal NKT cells are vital for IEC homeostasis. Intestinal NKT cells may also influence gut homeostasis by regulating the function and recruitment of other intestinal immune cells such as B cells, Tregs, and ILCs [40].

These functions of intestinal NKT cells promote CLP-induced sepsis. Specifically, in the *Pseudomonas* pneumonia-induced sepsis model, IFN- γ released by activated

intestinal NKT cells can directly induce IEC death [40] (Fig. 4). Moreover, since (i) intestinal NKT cells can regulate ILC3 production of IL-22 (which induces IEC integrity, repair, and defense against pathogens; see Section Liver), (ii) intestinal NKT cells can regulate ILC1 secretion of IFN- γ (which induces IEC apoptosis; see Section Liver) and (iii) pulmonary *P. aeruginosa*-induced sepsis reduces IL-22-expressing ILC3s while increasing IFN- γ -expressing ILC1s in the intestinal mucosa [42], it is possible that NKT cells can alter gut barrier function during sepsis by modulating ILC1 and ILC3 activity [40] (Fig. 4). However, further work is needed to test this notion.

With regard to $\gamma\delta$ T cells in the gut, mice that lack these cells not only demonstrate more mortality after CLP-induced sepsis, they also exhibit increased intestinal damage and permeability.

Thus, intestinal NKT and $\gamma\delta$ T cells may respectively promote and reduce intestinal damage in sepsis.

Conclusions

Sepsis is a particularly challenging conundrum in terms of finding immunotherapeutics because it is a systemic disease that can affect multiple visceral organs, and it simultaneously involves hyperinflammation and immunosuppression. Both ILCs and ILLs appear to be crucial players in the development and progression of sepsis, likely due to their tissue residency, rapid and abundant cytokine production, and high immunoregulatory capacity. ILC2s generally demonstrate protective functions in the lungs, heart, and kidney during sepsis. This protection appears to be mediated by ILC2-derived IL-9, IL-13, IL-4, IL-5, and amphiregulin, which help resolve the inflammation and induce tissue repair. However, there is also potential for ILC2s to be pathogenic if they become overactivated in sepsis, as shown by the hemorrhagic-shock model. By contrast, ILC1s and NKT cells appear to drive IFN- γ -mediated inflammation in sepsis that may intensify liver and gut injury. ILC3s, which are abundant in the gut, protect the gut and its barrier function in sepsis by releasing IL-22, but can be converted into IFN- γ -expressing ILC1-like cells that damage the intestinal epithelium and increase its permeability. This plasticity of ILC3s under septic stress emphasizes the complexity of ILCs and how they can swivel from protective to pathogenic depending on local and systemic conditions. This is also demonstrated by circulating NK cells, which promote sepsis in some studies but reduce it in others. This may reflect the fact that the IFN- γ released by these cells can simultaneously induce organ damage and amplify the cytokine storm while also killing the pathogen. Notably, IFN- γ -producing NK cells may eventually be replaced with IL-10-producing

NK cells, which may help calm the cytokine storm. In terms of ILLs, NKT cells may promote sepsis-induced liver and gut damage *via* their IFN- γ production while $\gamma\delta$ T cells protect these organs, possibly *via* their secretion of IL-17 A. Thus, the ILCs and ILLs are not merely bystanders, they are active regulators of organ-specific immunity and damage during sepsis. This indicates their potential as therapeutic targets in sepsis. However, the fact that they can play both protective and pathogenic roles depending on the organ, the local and systemic conditions, and time since sepsis onset means that more work is needed to unravel the roles of these cells in sepsis.

A major limitation of the current literature is that the studies on humans with sepsis are almost entirely limited to studies on the blood [138]; to our knowledge, no studies have assessed the role of ILCs in organs in human sepsis due to limited access to these organs in these critically ill patients. Thus, it remains unclear whether the findings in animal models of sepsis, which are the primary focus of this review, can be extrapolated to the human setting. Further studies in humans are needed.

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Data availability This review article does not involve any new data generation; therefore, data sharing is not applicable.

Declarations

Competing interests The authors declare no competing interests.

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