NLRC3 in septic immunosuppression: Variation in expression and mechanisms of mediating immune cell dysfunction (Review)

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Abstract. Sepsis is a life-threatening disease caused by a dysregulated host immune response to infection. In the acute phase of sepsis, patients tend to experience a hyperinflammatory state; however, in addition to facilitating the elimination of invading pathogens, this severe hyperinflammatory response can also lead to damage to the host. Thus, to maintain immune system homeostasis, counterregulatory immune responses, referred to as compensatory anti-inflammatory responses (CARs), are initiated. However, in the context of sepsis, the stabilization of the immune system cannot be sustained and protracted CARs can lead to an immunosuppressive state, which makes septic patients highly susceptible to secondary infection and high mortality. Various studies have indicated that the expression of NOD-like receptor (NLR) with a caspase activation and recruitment domain 3 (NLRC3), a member of the NLR family, tends to decrease several hours to days after the onset of infection but afterward increases over time and can mediate the dysfunction of immune effector cells in numerous ways, playing a crucial role in the development of septic immunosuppression. Therefore, this review summarized the expression variation of NLRC3 and the mechanisms through which it mediates immune cell dysfunction in different phases of sepsis, seeking to inspire future immune therapy for modulating septic host immune balance and reversing the immunosuppressive state, with a focus on NLRC3 as a target.

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1. Background

Sepsis and septic immunosuppression. Sepsis, defined as life-threatening organ dysfunction caused by a dysregulated host immune response to infection, is a leading cause of death worldwide, the latest epidemiological data indicates that 166 million cases of sepsis occurred globally in 2021, leading to 21.4 million deaths, which accounted for 31.5% of all-cause mortality in that year. Of all age groups, people aged 70 years and older had the highest number of sepsis-related deaths, at ~9.28 million (1). Sepsis is characterized by a complex pathophysiological process that involves both hyperinflammatory and hypoinflammatory states. In the acute phase of sepsis, to eliminate pathogenic microorganisms and control infections, innate immune cells use pattern recognition receptors to recognize pathogen-associated molecular patterns and damage-associated molecular patterns released from the invading organisms and the host upon injury, respectively. The activation of these pattern recognition receptors can lead to the production of numerous proinflammatory cytokines, such

as TNF-α, IL-2, IL-6 and interferon (IFN)-γ, and increase the inflammatory response to invasive pathogens. An adequate inflammatory response can help the immune system eliminate bacterial and fungal pathogens and restore homeostasis, but excessive activation of the inflammatory response can also result in damage to the host (2,3). Thus, to restrict the extent of inflammation and stabilize the immune system, a counterregulatory, anti-inflammatory state, referred to as compensatory anti-inflammatory responses (CARs), is also initiated (4). However, immune system homeostasis is not well maintained in patients with sepsis. CARs tend to be overactivated in patients with sepsis, leading to numerous changes in immune cells, such as alterations in gene expression patterns and the induction of apoptosis and autophagy, resulting in exhaustion and dampening of cell function and ultimately contributing to immunosuppression (5). Patients with immunosuppression are more susceptible to secondary infection and are unable to eradicate invading pathogens effectively, which results in prolonged hospitalization and increased in-hospital mortality (6,7). Thus, modulating the function of immune cells in septic patients and reversing the immunosuppressive state have increasingly become the focus of sepsis treatment. The divergent immune progression and corresponding clinical outcomes are graphically summarized in Fig. 1.

Structure and anti-inflammatory function of NOD-like receptor (NLR) with a caspase activation and recruitment domain 3 (NLRC3). NLRC3 is a member of the NLR family and was first discovered by Conti *et al* (8) in 2005. Unlike other types of pattern recognition receptors, such as toll-like receptors (TLRs) and C-type lectin receptors, which bind to the cell membrane, NLRs are cytosolic proteins (9). Structurally, NLRs have a typical tripartite architecture, with an effector-binding domain (EBD) at the N-terminus, an intermediate nucleotide-binding oligomerization domain (NBD), and a leucine-rich repeat domain (LRR) in the C-terminus. Compared with the other parts, the EBD is less conserved and can be divided into 4 subfamilies according to the specific type. The NLRA subfamily, A for the activation domain, includes class II major histocompatibility complex transactivator. The NLRB subfamily, B for baculoviral inhibitory repeats, includes NLR family apoptosis inhibitory protein 1-7. The NLRC subfamily, C for the caspase activation and recruitment domain (CARD), includes NLRC1-5. Finally, the NLRP subfamily, P for the pyrin domain, includes NLRP1-14 (10).

Tocker *et al* (11) reported that NLRC3 was highly expressed in immunological tissues in humans, such as the spleen, thymus, liver and leukocytes, and it was indicated to have diagnostic value in pediatric sepsis (12). Numerous animal studies have revealed that NLRC3 is involved in the progression of various infectious diseases. Upregulating or downregulating NLRC3 in septic mice could inhibit/promote the inflammatory response in alveolar epithelial cells (13). The results of Pontigo *et al* (14) also revealed that the expression levels of 6 variations of NLRC3 were elevated from 3 to 42 days in head-kidney samples of Atlantic salmon after infection with *Piscirickettsia salmonis*, indicating that NLRC3 may contribute to immunosuppression in the later period of infectious disease. Consistent with these findings, researchers have reported that the expression level of NLRC3 in the macrophages of septic patients is negatively correlated with the surface expression of human leukocyte antigen (HLA)-DR and the secretory capacity of inflammatory cytokines (15). Currently, comparative evidence derived from humans and other mammalian species remains insufficient. Meanwhile, a phylogenetic distance exists between humans and Atlantic salmon with respect to sepsis pathophysiology. Nonetheless, the evidence mentioned above also demonstrates that NLRC3 expression levels fluctuate throughout the progression of infectious diseases and exert anti-inflammatory effects on the host's immune system.

2. Literature search and study selection

A nonsystematic, narrative literature search focusing on NLRC3 expression variation and its mechanisms in sepsis-induced immunosuppression was performed. The PubMed (pubmed.ncbi.nlm.nih.gov), Embase (www.embase.com), Web of Science (www.webofscience.com) and Cochrane Library (www.cochranelibrary.com) databases were searched for all relevant publications prior to December 2025, prioritizing recent high-quality and classic landmark studies. Mesh terms (including NLRC3, NLR family CARD domain containing 3 protein, NOD3 protein, CLR16.2 protein, sepsis, septicemia, pyemia, immunosuppression) and free-text keywords were combined for retrieval and records were screened by title, abstract and full text. Conference abstracts, letters, case reports, studies not written in English and repetitive reports were excluded.

3. NLRC3 expression changes and mechanisms of mediating immune cell dysfunction

Macrophages. Macrophages play a pivotal role in the innate immune system, with the ability to eliminate invading pathogens directly by phagocytosis and present antigens to adaptive immune cells to promote more profound microbicidal efficacy. In septic patients, owing to their ubiquitous and comprehensive immune effects, macrophages are deeply involved in changes in septic pathophysiology and their dysfunction contributes prominently to sepsis-induced immunosuppression. In 2017, Guo *et al* (16) reported that within 24 h after *Pseudomonas aeruginosa* (PA) infection, the expression level of NLRC3 in RAW264.7 cells decreased. Another group of researchers confirmed that NLRC3 expression was downregulated in the head-kidney macrophages of Siberian sturgeon after lipopolysaccharide (LPS) treatment (17). Li *et al* (18) reported that the expression level of NLRC3 decreased progressively within 9 h after hypoxia/reoxygenation injury was induced in RAW264.7 cells. All these studies indicated that the expression level of NLRC3 in macrophages tended to decrease in the early phase after infection or stimulation. In addition to this variation, the expression of proinflammatory cytokines such as IL-1β, IL-6 and TNF-α was also upregulated, which could facilitate the eradication of bacterial invasion and repair of tissue damage by the host. Several studies have also investigated the mechanisms by which NLRC3 dampens the immune function of macrophages in the acute phase after sepsis.

In 2012, Schneider *et al* (19) reported that NLRC3 could inhibit the TLR4- MYD88 innate immune signal transduction

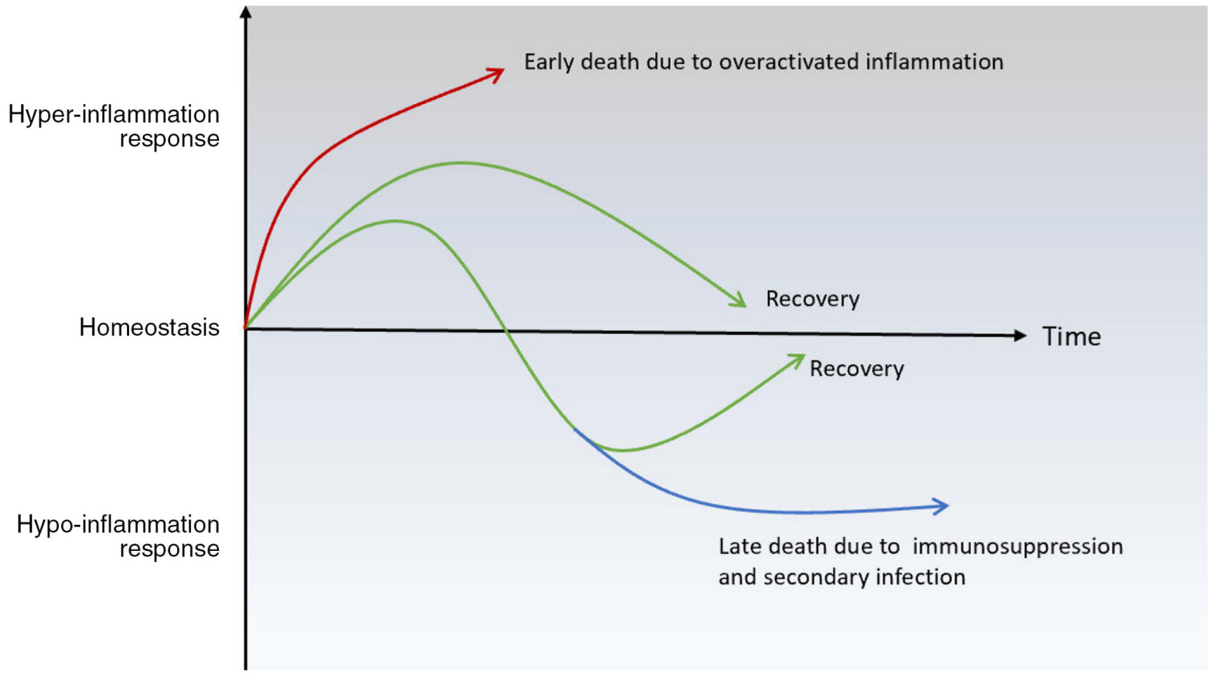

Figure 1. Time course and different outcomes of septic patients. Both the hyperinflammatory response and the compensatory anti-inflammatory response are activated after the onset of sepsis. The early stage is dominated by hyperinflammation, and an overwhelming inflammatory response can lead to multiple organ dysfunction and early death; if the body can rebalance and restore the immune system, the patient will enter the recovery stage. However, immune system homeostasis in septic patients is difficult to orchestrate, and the protracted anti-inflammatory response often leads to an immunosuppressive state and late death due to secondary infection.

adaptor (MyD88)-TNF receptor associated factor 6 (TRAF6) signaling pathway by interfering with the K63-linked ubiquitin on TRAF6, and they also reported that compared with wild-type mice, Nlrc3$^{-/-}$ mice presented an enhanced response to endotoxic shock, manifested as significantly delayed recovery, as measured by their lower body temperature and weight after challenge with a nonlethal dose of LPS. Li *et al* (18) also reported that NLRC3 could attenuate K63-linked ubiquitin on TRAF6 and inhibit the activation of NF-κB to alleviate hypoxia/reoxygenation-induced inflammation in RAW264.7 cells. In 2017, Guo *et al* (16) revealed that NLRC3 could promote the degradation and K48-linked polyubiquitin of interleukin 1 receptor associated kinase 1 (IRAK1) in RAW 264.7 cells after PA infection, attenuating the activation of NF-κB and thus the inflammatory response. However, Schneider *et al* (19) reported that NLRC3 significantly inhibited NF-κB activation in a dose-dependent manner in response to an activating signal from MyD88 and TRAF6 and, to a lesser but not significant extent, through IRAK but not through component of inhibitor of NF-κB kinase complex or p65.

In addition to NF-κB signaling, NLRC3 can regulate the immune function of macrophages through the stimulator of IFN genes (STING)/TANK-binding kinase 1 (TBK-1) pathway in the acute phase after stimulation. In 2017, Zhang *et al* (20) revealed that 6 h after treatment with herpes simplex virus-1 and IFN stimulatory DNA, NLRC3 in bone marrow-derived macrophages (BMDMs) could bind to STING and TBK-1 with its NBD and impede STING trafficking from the endoplasmic reticulum (ER) to the perinuclear and punctated region and colocalize with TBK1, decreasing the activation of IFN regulatory factor 3 (IRF3) and the expression of IFN-β as a result. By yeast two-hybrid screening, Tocker *et al* (11) showed that the scaffolding protein IQ motif containing GTPase activating protein 1 (IQGAP1) could interact with the NBD of NLRC3 via its RasGAP C-terminal domain and disrupt the interaction between NLRC3 and STING. However, interestingly, the knockdown of IQGAP1 in THP-1 and HeLa cells resulted in significantly increased IFN-β production in response to cytosolic nucleic acids, but how the interaction between IQGAP1 and NLRC3 negatively regulates type I IFN production remains largely elusive (11).

The activation of the NLRP3, a member of the NLR family, is also regulated by NLRC3. Previous studies have shown that NLRC3 can inhibit the activation of the NLRP3 inflammasome through its CARD domain and can inhibit the interaction between apoptosis-associated speck-like protein containing a CARD (ASC) and pro-caspase-1 (21). Zhao *et al* (22) reported that NLRC3 could inhibit the activation of the NLRP3 inflammasome by interfering with NLRP3 inflammasome assembly, promoting the polarization of alveolar macrophages to the M2 type and reducing sepsis-induced acute injury in lung tissue.

In accordance with previous studies, Xu *et al* (15) reported that NLRC3 expression was downregulated in mouse peritoneal macrophages and alveolar macrophages at the beginning after cecal ligation and puncture (CLP), but the expression level of NLRC3 started to increase after 12 h and peaked at 48-72 h. Along with these variations, they reported that the ability of CLP mice to eliminate bacteria from the lungs and blood after PA infection decreased and that mortality significantly increased in CLP mice after 48 h of intratracheal PA challenge (15). These findings proved that NLRC3 was upregulated in the later phase of sepsis and contributed to immunosuppression. Mechanistically, they revealed that

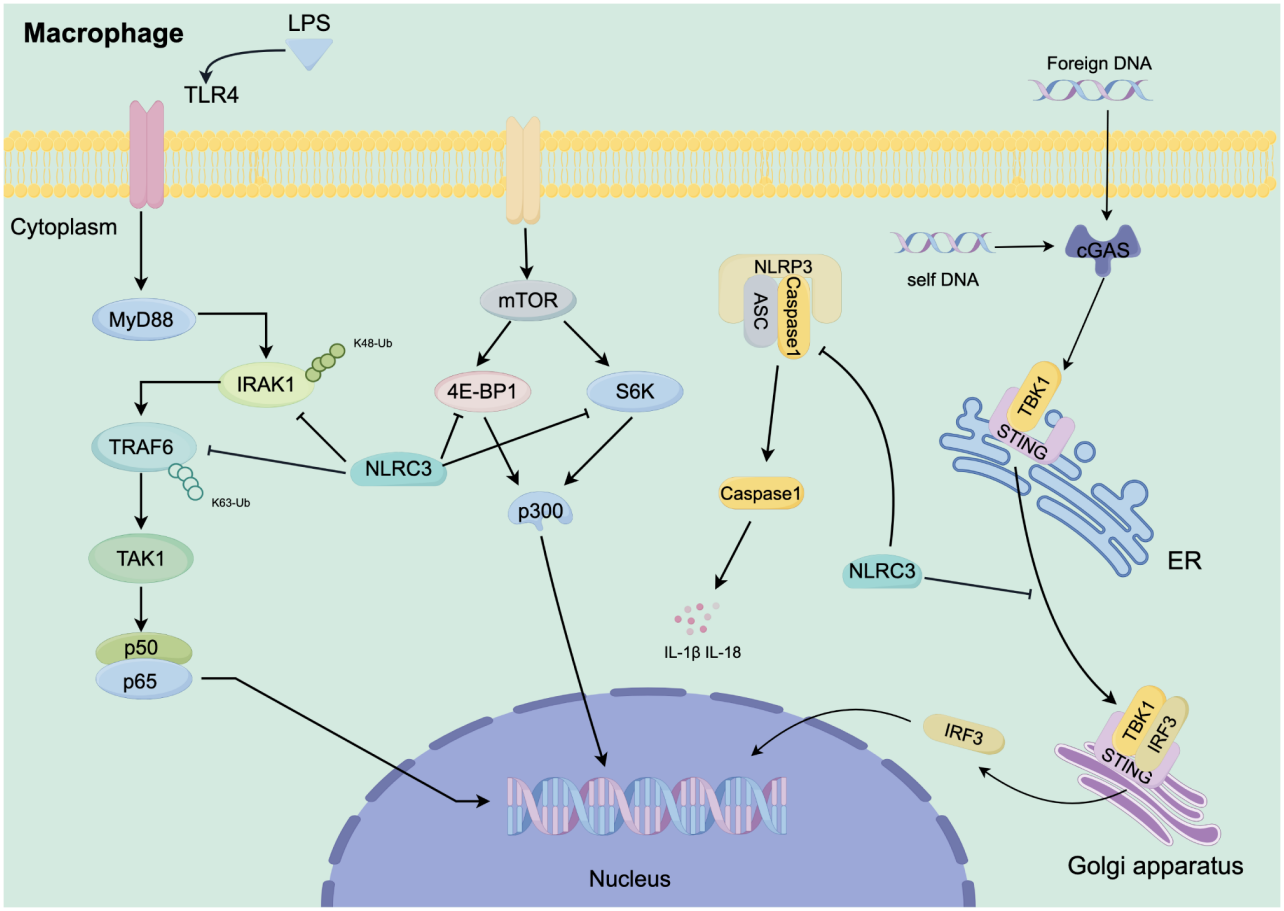

Figure 2. Mechanisms through which NLRC3 mediates macrophage dysfunction in septic patients. This diagram illustrates the core inhibitory mechanisms of NLRC3 in multiple critical signaling cascades of macrophages during sepsis. i) NLRC3 inhibits K48- and K63-linked ubiquitination in IRAK1 and TRAF6, thus dampening the activation of NF-κB signaling. ii) NLRC3 downregulates the phosphorylation of 4E-BP1 and S6K and dampens the activity of p300. iii) NLRC3 inhibits the assembly of the NLRP3 inflammasome by interfering with the interaction between ASC and caspase-1. iv) NLRC3 impedes STING trafficking from the ER to the perinuclear and punctated regions and colocalizes with TBK1, thus downregulating IRF3 activation and IFN-β expression. 4E-BP1, eukaryotic translation initiation factor 4E-binding protein 1; ASC, apoptosis-associated speck-like protein containing a CARD; caspase-1, cysteine-aspartic acid protease 1; cGAS, cyclic GMP-AMP synthase; ER, endoplasmic reticulum; IL-1β, interleukin-1β; IRAK1, interleukin-1 receptor-associated kinase 1; IRF3, interferon regulatory factor 3; LPS, lipopolysaccharide; mTOR, mammalian target of rapamycin; MyD88, myeloid differentiation primary response 88; NLRP3, NOD-like receptor family pyrin domain-containing 3; NLRC3, NOD-like receptor family CARD domain-containing 3; p300, histone acetyltransferase p300; p50, NF-κB p50 subunit; p65, NF-κB p65 subunit; S6K, ribosomal protein S6 kinase; STING, stimulator of interferon genes; TAK1, TGF-β-activated kinase 1; TBK1, TANK-binding kinase 1; TLR4, Toll-like receptor 4; TRAF6, TNF receptor-associated factor 6; K48-Ub, K48-linked ubiquitination; K63-Ub, K63-linked ubiquitination.

in addition to inhibiting TRAF6 ubiquitination and NF-κB signaling, mammalian target of rapamycin (mTOR) signaling is involved. NLRC3 can decrease the phosphorylation of eukaryotic translation initiation factor 4E-binding protein 1 (4E-BP1) and ribosomal protein S6 kinase (S6K), which are downstream of mTOR and decrease the activity of p300, thus inhibiting the binding of NF-κB p65 and p300 to the promoter nuclear factor of activated T cells 5 (NFAT5), which controls the expression of glycolysis-related genes such as glucose transporter type 1, phosphofructokinase, hexokinase 2 and lactate dehydrogenase A, restraining the metabolic profile of macrophages reprogramming to glycolysis when they encounter invading bacteria [which is also known as the Warburg effect (23)], impairing their immunological function as a result (15). β-glucans, which are components of fungal cell walls, play a regulatory role in the expression of NLRC3 in macrophages and mediate their immune function. Krishnan *et al* (24) revealed that β-glucans could reverse the upregulation of NLRC3 in seven-band grouper macrophages 72 h after nervous necrosis virus infection, and they reported that hypoxia-inducible factor-1α and AMP-activated protein kinase (AMPK) expression significantly increased. In addition to this change, the metabolism of grouper macrophages is altered because LDH activity and lactate levels increase. As AMPK is the upstream regulatory molecule of mTOR, evidence has also indicated that mTOR signaling and NLRC3 are involved in metabolic alteration and immune function regulation in macrophages after infection. Fig. 2 summarizes the core inhibitory mechanisms of NLRC3 in multiple critical signaling cascades of macrophages during sepsis, and the main conclusions of relevant literature are presented in Table I.

T lymphocytes. As T lymphocytes are adaptive immune cells, immune dysfunction contributes significantly to immunosuppression after sepsis. Studies have indicated that the anergy of T cells, especially $CD4^+$ T cells, plays a vital role and that

Table I. Literature concerning NLRC3 and macrophage dysfunction.

Authors (year)	Mechanism or manner	(Refs.)
Schneider *et al* (2012)	NLRC3 could downregulate the expression level of pro-inflammatory cytokines in macrophages stimulated by LPS through TLR4/MyD88/TRAF6 (K63 linked ubiquitination).	(19)
Zhang *et al* (2014)	NLRC3 combined with STING and the TBK1 with its NBD domain, inhibiting STING and TBK1 interaction and preventing STING trafficking from the ER to a perinuclear/Golgi location and to endoplasmic-associated puncta and colocalizing with TBK1 in these puncta after DNA stimulation.	(20)
Guo *et al* (2017)	NLRC inhibited the K48 linked ubiquitination in IRAK1, preventing the activation of NF-κB, and dampened the inflammatory response of THP-1 after *Pseudomonas aeruginosa* infection.	(16)
Tocker *et al* (2017)	Scaffolding protein IQGAP1 could interact with the NBD domain of NLRC3 with its RGCT domain, interfering the combination between NLRC3 and STING, thus downregulating the expression of interferon.	(11)
Li *et al* (2020)	NLCR3 acted as a deubiquitinase to remove the ubiquitination on the K63 site of the TRAF6, so as to inhibit the activation of NF-κB, and dampened the inflammatory response of RAW264.7 after the stimulation of hypoxia/reoxygenation.	(18)
Zhou *et al* (2021)	α-Rhamnrtin-3-α-rhamnoside could inhibit the production of inflammatory cytokines in RAW264.7, and this effect was achieved by reversing the downregulation of NLRC3 expression and inhibiting the TRAF6/NF-κB signaling pathway.	(33)
Krishnan *et al* (2022)	β-glucan inhibited the activation of NLRC3 and caspase 1, and promoted the expression of HIF-1α, so as to downregulate the production of IL-1β.	(24)
Xu *et al* (2023)	NLRC3 inhibited the K63-linked ubiquitination on TRAF6 and the phosphorylation of 4EBP-1 and S6K, thus dampening the activation of p65 and p300, and the interaction with the NFAT5 promoter region, downregulating the expression of pro-inflammatory cytokines and glycolytic enzyme.	(15)
Zhao *et al* (2024)	NLRC3 inhibited the activation of NLRP3 inflammasome by interfering with the NLRP3 inflammasome assembly and promoted AMs polarizing to the M2 type, thus reducing the sepsis-induced acute injury in lung tissue.	(22)

NLRC3, NOD-like receptor family CARD domain-containing 3; LPS, lipopolysaccharide; TLR4, Toll-like receptor 4; MyD88, myeloid differentiation primary response protein 88; TRAF6, TNF receptor-associated factor 6; STING, stimulator of interferon genes; TBK1, TANK-binding kinase 1; NBD, nucleotide-binding domain; ER, endoplasmic reticulum; IRAK1, interleukin-1 receptor-associated kinase 1; NF-κB, nuclear factor κ-light-chain-enhancer of activated B cells; RAW264.7, mouse macrophage cell line; THP-1, human acute monocytic leukemia cell line; IQGAP1, IQ motif-containing GTPase-activating protein 1; RGCT, A conserved functional domain of IQGAP1; ARR, α-rhamnetin-3-α-rhamnoside; 4EBP-1, eukaryotic translation initiation factor 4E-binding protein 1; S6K, ribosomal protein S6 kinase; p65, NF-κB p65 subunit; p300, histone acetyltransferase p300; NFAT5, nuclear factor of activated T cells 5; NLRP3, NOD-like receptor family pyrin domain-containing 3; AMs, alveolar macrophages; M2, M2-type macrophages; IL-1β, interleukin-1β; HIF-1α, hypoxia-inducible factor 1α; caspase 1, cysteine-aspartic acid protease 1.

NLRC3 is deeply involved in this process. Similar to that in macrophages, the expression level of NLRC3 in T lymphocytes tends to decrease in the early phase after activation. Conti *et al* (8) reported that NLRC3 expression was downregulated 6 h after anti-CD3 and anti-CD28 stimulation of primary T cells. Lim *et al* (25) reported that as early as 1 h after treatment with IL-4 plus TGF-β, the expression of Nlrc3 mRNA decreased in type 9 T-helper (Th9) cells. These two groups of researchers both reported that NLRC3 could mediate immune dysfunction in T cells through the NF-κB signaling pathway. Conti *et al* (8) found that NLRC3 mediated T-cell immune dysfunction by reducing the levels of IL-2 and CD25, which are central to maintaining T-cell activation and preventing T-cell anergy, and that this reduction was accompanied by a delay in IκB degradation. In a study by Lim *et al* (25), a decrease in NLRC3 resulted in the upregulation of K63 ubiquitination of TRAF6 and the subsequent activation of NF-κB signaling. In addition, Ren *et al* (26) reported that NLRC3 in $CD4^+$ T cells could inhibit the accumulation of $TNF\alpha^+$ Th17 cells in the bone marrow and negatively regulate the osteoclastogenesis-promoting functions of Th17 cells by limiting NF-κB activation, thus attenuating osteoporosis. The results of Uchimura *et al* (27) also revealed that 24-48 h after stimulation with anti-CD3 and anti-CD28 antibodies, the Nlrc3 mRNA expression level in $CD4^+$ T cells (Th0, Th1, Th17), but not in $CD8^+$ T cells, decreased. They reported that NLRC3 could attenuate the activation of $CD4^+$ T cells by interfering with aerobic glycolysis by decreasing the ubiquitination of K63 on TRAF6 and the activation of NF-κB signaling. In addition to NF-κB, they reported that NLRC3 could downregulate the

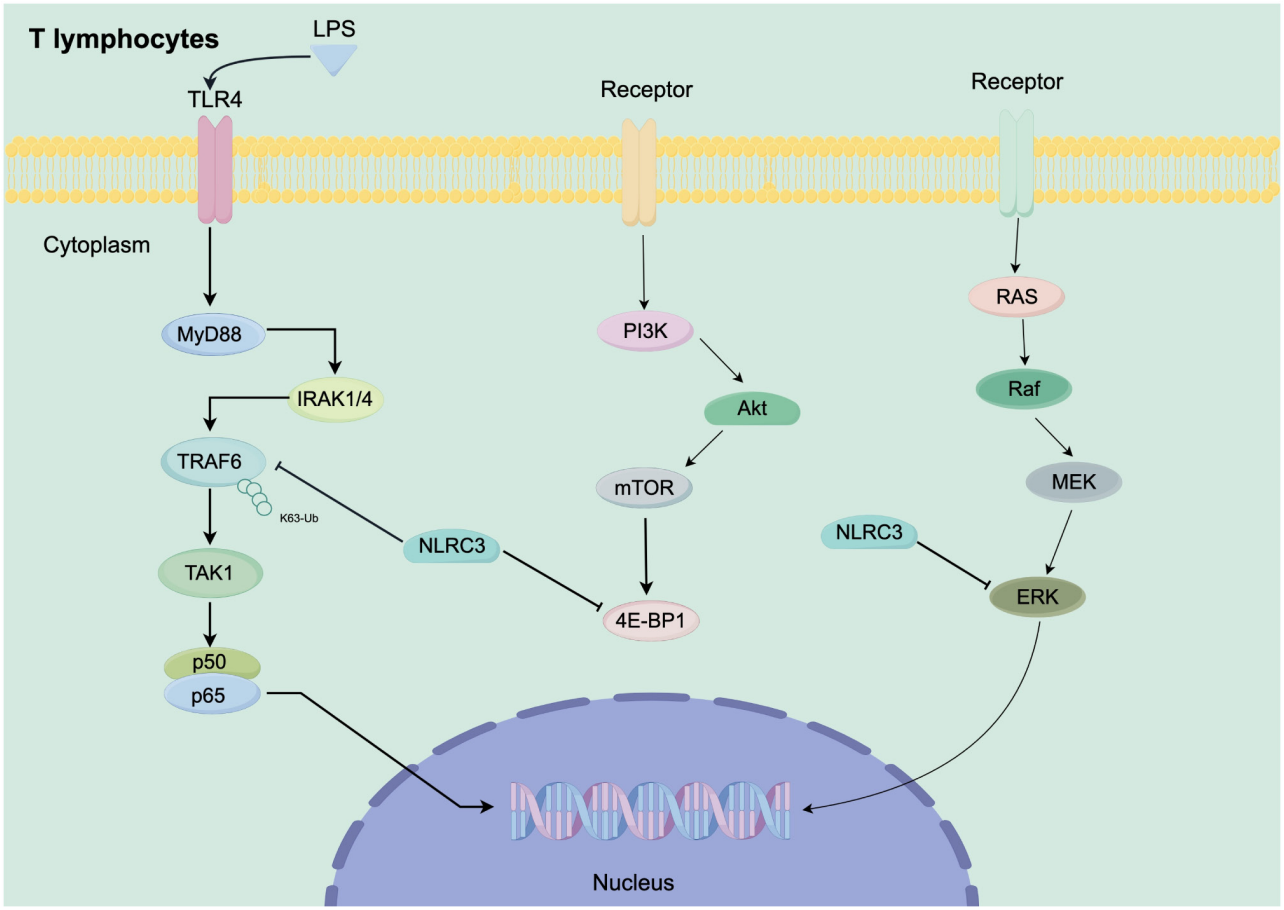

Figure 3. Mechanisms through which NLRC3 mediates T lymphocyte dysfunction in septic patients. This diagram illustrates the multi-pathway inhibitory mechanisms of NLRC3 in T lymphocytes during sepsis. In T lymphocytes, NLRC3 can i) decrease the K63-linked ubiquitination of TRAF6 and the subsequent activation of NF-κB signaling, ii) downregulate the phosphorylation of 4E-BP1, which is downstream of mTOR signaling, and iii) decrease the activation of ERK signaling, thus attenuating the activation and differentiation of T lymphocytes after stimulation. 4E-BP1, eukaryotic translation initiation factor 4E-binding protein 1; Akt, protein kinase B; ERK, extracellular signal-regulated kinase; IRAK1/4, interleukin-1 receptor-associated kinase 1/4; LPS, lipopolysaccharide; MEK, mitogen-activated protein kinase kinase; mTOR, mammalian target of rapamycin; MyD88, myeloid differentiation primary response 88; NLRC3, NOD-like receptor family CARD domain-containing 3; PI3K, phosphoinositide 3-kinase; Raf, rapidly accelerated fibrosarcoma serine/threonine kinase; RAS, rat sarcoma small GTPase; TAK1, TGF-β-activated kinase 1; TLR4, Toll-like receptor 4; TRAF6, TNF receptor-associated factor 6; K63-Ub, K63-linked ubiquitination; p50, NF-κB p50 subunit; p65, NF-κB p65 subunit.

phosphorylation of 4E-BP1 but could not affect the phosphorylation of upstream mTOR and AKT. These findings indicate that mTOR signaling is also involved in NLRC3-mediated CD4$^+$ T-cell anergy (27).

With respect to the duration after infection, NLRC3 can negatively regulate the activation of CD4$^+$ T cells. Three weeks after infection with *Mycobacterium tuberculosis*, compared with CD4$^+$ T cells isolated from wild-type mice, CD4+ T cells isolated from the lungs of Nlrc3$^{-/-}$ mice exhibited more potent expression of intracellular IFN-γ, TNF-α and IL-17A. They also reported that Nlrc3 deficiency resulted in increased phosphorylation of NF-κB p65 and extracellular signal-regulated kinase (ERK) in CD4$^+$ T cells after stimulation with anti-CD3 and anti-CD28 antibodies (28). These findings indicate that NF-κB and the ERK signaling pathway are involved in this process. However, they did not describe the variation trend of NLRC3 expression levels in mice after infection. In Fig. 3 we summarize the multi-pathway inhibitory mechanisms of NLRC3 in T lymphocytes during sepsis, and the main conclusions of relevant literature are presented in Table II.

Dendritic cells (DCs). As bone marrow-derived designated antigen-presenting cells, DCs have the most potent antigen-presenting function among immune cells (29). Once stimulated by an antigen, DCs upregulate the expression of costimulatory molecules on the cell surface and secrete a large number of cytokines to activate naïve T cells and promote their differentiation (9). Previous studies have reported extensive decreases in the number and function of DCs in patients with sepsis and are related to alterations in the immune response (30,31). Fu *et al* (32) reported that after stimulation with LPS, NLRC3 deficiency in DCs led to increased expression of major histocompatibility complex (MHC)-II and costimulatory molecules such as CD40, CD86 and CD80. The expression levels of IL-2, IL-6 and IL-23 also increased, but the expression level of IL-27 decreased, indicating that NLRC3 could impair the immunogenicity of DCs. They also reported that NLRC3 deficiency promoted the ability of DCs to polarize naïve CD4$^+$ T cells into Th1 and Th17 subsets and that the expression of IL-17a and IFN-γ increased in naïve CD4$^+$ T cells cocultured with DCs from NLRC3-deficient mice. Mechanistically, they reported that NLRC3 could decrease

Table II. Literature concerning NLRC3 and T-lymphocyte dysfunction.

Author(s), year	Mechanism or manner	(Refs.)
Conti *et al*, 2005	NLRC3 downregulated the endogenous transcripts of T cells after anti-CD3 and anti-CD28 stimulation, and this reduction was accompanied by the delay of IκB degradation.	(8)
Uchimra *et al*, 2018	NLRC3 inhibited the K63 linked ubiquitination on TRAF6 and the phosphorylation of 4EBP-1 and dampened the secretion of IFN-γ and TNF of CD4+ T cells and the proliferation of Th1/Th17.	(27)
Hu *et al*, 2018	NRLC3 inhibited the activation of CD4+ T cells in mice after infection with *Mycobacterium tuberculosis* through negatively regulating the NF-κB and MEK-ERK signaling pathways. Compared to the wild-type mice, CD4+ T cells derived from NLRC3 knockout mice had a higher costimulatory molecular and INF-γ, TNF-α and IL-17 expression level at 3 weeks after *Mycobacterium tuberculosis* infection.	(28)
Lim *et al*, 2024	Under the costimulation with IL-4 and TGF-β, inhibition of NLRC3 expression in Th9 cells promotes phosphorylation of Smad at Ser213, thereby enhancing K63-linked ubiquitination of TRAF6 and subsequent activation of the NF-κB signaling pathway.	(25)
Ren *et al*, 2024	NLRC3 inhibited the activation of NF-κB signaling, limiting the Th17 accumulating in the bone marrow and related osteoclastogenesis, so as to attenuate osteoporosis.	(26)

NLRC3, NOD-like receptor family CARD domain-containing 3; CD3, cluster of differentiation 3; IκB, NF-κB inhibitor; TRAF6, TNF receptor-associated factor 6; 4EBP-1, eukaryotic translation initiation factor 4E-binding protein 1; IFN-γ, Interferon-gamma; TNF, tumor necrosis factor; $CD4^+$, cluster of differentiation 4 positive; Th1, T helper 1 cells; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; MEK, mitogen-activated protein kinase kinase; ERK, extracellular signal-regulated kinase; TNF-α, tumor necrosis factor α; IL-4, interleukin-4; TGF-β, transforming growth factor β; Smad, Sma- and Mad-related protein; Ser, serine 213.

the phosphorylation of p38 in DCs after stimulation with LPS and that the activation of mitogen- and stress-activated protein kinase 1 and MAPK-activated protein kinase 2, the two crucial target proteins of p38, was also restricted. However, the phosphorylation of p65, AKT, ERK and c-Jun N-terminal kinase (JNK) was not affected. A p38 MAPK inhibitor (SB203580), but not an NF-κB inhibitor (JSH-23), significantly reversed the increased expression of IL-12, IL-6 and IL-23 caused by NLRC3 deficiency in DCs (32). In Fig. 4 we summarize the molecular mechanisms underlying NLRC3-mediated dendritic cell dysfunction during sepsis.

4. NLRC3 in the diagnosis and treatment of septic immunosuppression

NLRC3-related diagnostic biomarkers for sepsis. NLRC3 has the potential to be a diagnostic biomarker for sepsis. High levels of NLRC3 in monocytes/macrophages from patients with sepsis and mice are negatively associated with HLA-DR/MHC-II expression and the secretory capacity of inflammatory cytokines, and the specific deletion of NLRC3 in bone marrow can increase macrophage aerobic glycolysis and immune function and reverse sepsis-induced immunosuppression, suggesting that NLRC3 levels may reflect the host immune impairment status during sepsis (15). Additionally, in acute lung injury (ALI) caused by sepsis, the expression of NLRC3 in the lung tissue of mice is correlated with the inflammatory response (13). Overexpression of NLRC3 by lentiviral transfection significantly reduced the inflammatory response in the lungs of LPS-induced ALI mice, whereas NLRC3 silencing via lentiviral transfection exacerbated the inflammatory response. In contrast to tissue-based assays, peripheral blood mononuclear cell-based detection of NLRC3 expression and immune function is minimally invasive, easily accessible and cost-effective, which renders it a promising routine clinical strategy for monitoring immune function in septic patients. However, the current evidence is hypothesis-generating, and the relationships between NLRC3 expression, immune cell function, and the inflammatory response in sepsis have been elucidated mainly in animal models and in *in vitro* cellular experiments. By contrast, evidence from human studies remains limited, highlighting the necessity of further research in this field. Furthermore, large-scale clinical investigations are urgently needed to determine the diagnostic sensitivity and specificity of NLRC3 for sepsis-induced immunosuppression among different populations (4,5).

Potential therapeutic targets related to NLRC3. Targeting NLRC3 may be a potential strategy for treating sepsis. Given its role in attenuating the activity of multiple proinflammatory signaling pathways, such as the NF-κB, phosphoinositide-3 kinase (PI3K)-mTOR and STING pathways, modulating the expression or activity of NLRC3 may help restore immune balance and prevent excessive inflammation and tissue damage. For instance, in ALI induced by sepsis, overexpression of NLRC3 can reduce lung inflammation (13). Furthermore, since NLRC3 is involved in the regulation of immune cell dysfunction during sepsis, targeting NLRC3 may reverse the immunosuppressive state. In macrophages, genetic suppression of NLRC3 can disrupt the NLRC3-mTOR-p300 complex, enhancing the binding of NF-κB to the NFAT5 promoter and thereby improving macrophage glycolysis and host immune defense (15), indicating that NLRC3 inhibition may be appropriate in the late immunosuppressive phase after sepsis. Thus, timing is essential for NLRC3-targeted intervention, while inappropriate intervention can aggravate inflammation,

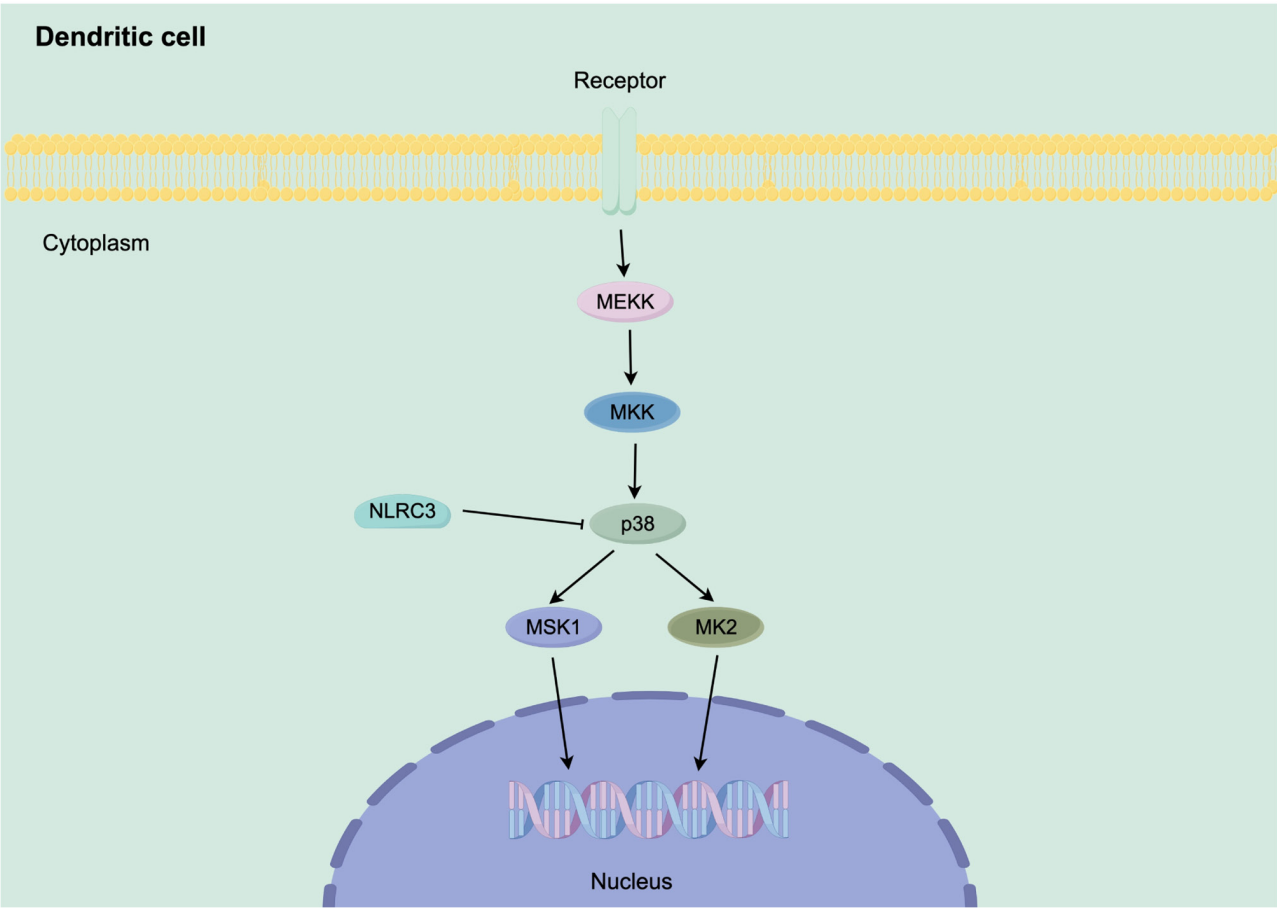

Figure 4. Mechanisms through which NLRC3 mediates dendritic cell dysfunction in septic patients. In DCs, NLRC3 can restrict the activation of p38 MAPK signaling and decrease the activation and antigen-presenting capacity of DCs after stimulation. MEKK, MAPK kinase kinase; MKK, MAPK kinase; MK2, MAPK-activated protein kinase 2; MSK1, mitogen- and stress-activated kinase 1; NLRC3, NOD-like receptor family CARD domain-containing 3; p38, p38 MAPK.

compromise immune function, facilitate disease deterioration and lead to poorer patient prognoses (9,15).

At present, the therapeutic potential of NLRC3 against sepsis-induced immunosuppression is merely speculative and based on available research findings, which are largely restricted to preclinical mechanistic investigations and limited experimental models. Accordingly, future studies are warranted to further delineate the complex regulatory networks associated with NLRC3 in humans, ensure that relevant interventions have no unintended adverse effects on other immune functions and develop specific and efficacious NLRC3-targeted therapeutic strategies.

5. Summary and prospects

The proper function of immune cells is the basis of the host's immune defense ability. An appropriate inflammatory response can facilitate immune cell immune recognition and elimination. However, when the inflammatory response is overly intense, excessive inflammation can cause very similar damage to the host. Thus, maintaining the balance between pro- and anti-inflammatory responses is essential for sustaining host immune function.

As mentioned above, in the acute stage after pathogen invasion, the expression level of NLRC3 in immune cells tends to decrease to promote the inflammatory response and facilitate immune defense against microorganisms. However, over time, NLRC3 expression increased continuously, dampened immune cell function in many ways and contributed to the development of immunosuppression states.

The expression level of NLRC3 in macrophages tends to decrease in the early phase following inflammatory challenge and pathogenic insult. Nevertheless, the evidence also indicates that NLRC3 can exert immunosuppressive effects and attenuate the immune function of macrophages through the following mechanisms. First, relevant studies have demonstrated that NLRC3 can inhibit the ubiquitination of IRAK1 and TRAF6 to downregulate the activation of NF-κB signaling. Researchers have also reported that some substances can regulate the activation of NF-κB through NLRC3, α-rhamnrtin-3-α-rhamnoside, a principal compound extracted from *Loranthus tanakae* Franch. & Sav., reversing the downregulation of NLRC3 in RAW 264.7 cells 24 h after treatment with LPS and dampening the activation of TRAF6 and downstream NF-κB p65 signaling molecules (33). Acacetin (5,7-dihydroxy-40-methoxyflavone), a flavonoid derived from *Agastache rugosa*, can also upregulate the expression of NLRC3 and inhibit the activation of NF-κB both *in vivo and in vitro*, thus alleviating sepsis-induced acute lung injury (34). Second, other studies have confirmed that NLCR3 interferes

with cyclic GMP-AMP synthase (cGAS)-STING signaling by restraining the cotranslocation of STING and TBK1 from the ER to perinuclear and punctated regions. A similar mechanism has been described for tumors. Heath *et al* (35) reported that saturated fatty acids could inhibit STING by inducing NLRC3 in head and neck squamous cell carcinomas (HNSCCs) and BMDMs, thus dampening the immunogenicity of HNSCCs and the surveillance of immune cells. In the context of tumor immunity, the cGAS-STING pathway also plays a significant role. Preclinical studies have demonstrated that activating cGAS-STING signaling can enhance a patient's response to immune therapy and that the administration of a cGAS agonist can promote the maturation and function of antigen-presenting cells and increase the activity of effector T cells, thus amplifying immune activity within the tumor microenvironment (36,37). Cutting-edge gene editing technology, CRISPR-Cas9, and NLRC3 inhibitors have also been employed to knock out or silence NLRC3 to increase the ability of the immune system to recognize and eliminate tumor cells (38). In the late phase of infection and the inflammatory response, NLRC3 expression in macrophages tends to increase. NLRC3 exerts immunosuppressive effects by inhibiting the K63-linked ubiquitination of TRAF6 and phosphorylation of 4E-BP1 and S6K in the NF-κB and mTOR signaling pathways, thereby suppressing the activation and nuclear translocation of downstream p65 and p300 proteins and ultimately downregulating the expression of genes encoding glycolytic enzymes and proinflammatory factors.

Studies have also demonstrated that NLRC3 expression is temporally expressed in T lymphocytes following infection and inflammatory challenge. During the early phase, similar to macrophages, NLRC3 exerts immunosuppressive effects by inhibiting the activation of the NF-κB and mTOR signaling pathways. According to Guo *et al* (39), NLRC3 inhibits the inflammatory response in rabbits infected by *Pasteurella multocida* through interactions with TRAF4 and TRAF6, indicating that NBD-LRR is the functional domain that regulates the NF-κB pathway. Zha *et al* (40,41) reported that NLRC3 can attenuate the activation of the PI3K-mTOR pathway and inhibit the monocrotaline- and platelet-derived growth factor-induced proliferation of pulmonary arterial smooth muscle cells, and green walnut husks (QLY), a traditional Chinese medicine, promoted tumor apoptosis through the NLRC3/PI3K/AKT/mTOR/pathway (42). These findings indicate that NLRC3 can also regulate upstream mTOR signaling, but this has not yet been reported in immune cells. After infection, NLRC3 has been confirmed to exert immunosuppressive effects by regulating the NF-κB and MAPK-ERK signaling pathways in lymphocytes. However, in DCs, NLRC3 inhibited the phosphorylation of p38, whereas ERK and JNK were not affected. These findings indicate that in different immune cells, specific MAPK signaling is regulated by NLRC3. However, to date, no studies have verified the expression pattern of NLRC3 in DCs under infectious and inflammatory conditions.

In both macrophages and T lymphocytes, NLRC3 exerts immunosuppressive effects by inhibiting the activation of the NF-κB and mTOR signaling pathways. In DCs and T lymphocytes, NLRC3 mediates immunosuppression through the MAPK-ERK and p38-MAPK pathways, respectively. It may be proposed that the shared and distinct immunoregulatory mechanisms of NLRC3 in different immune cell subsets may stem from their unique immune functions. Under inflammatory and infectious conditions, the expression of immune functional proteins is controlled by cell-specific signaling cascades through which NLRC3 exerts its immunosuppressive effects.

In conclusion, NLRC3 can mediate immune cell anergy through multiple mechanisms in septic patients, thereby driving the development of immunosuppression after sepsis. However, to date, only macrophages and T lymphocytes have attracted widespread research attention, with the most relevant studies being limited to *in vitro* cell experiments and animal models, whereas other immune cells, such as B lymphocytes, DCs, natural killer cells and myeloid-derived suppressor cells, have remained largely uncharacterized. Furthermore, clinical research and applications based on NLRC3 are still in the nascent phase. Thus, future studies are warranted to further explore the immune regulatory role of NLRC3 in other immune cell subsets to validate its diagnostic performance as a candidate biomarker for sepsis-induced immunosuppression and to develop NLRC3-targeted molecular agents or drugs to reverse persistent immunosuppression following sepsis.

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Authors' contributions

ZP and SP performed the literature search and study selection, wrote the original draft and revised the manuscript. TL assisted in the literature screening process and manuscript revision and acquired the funding. XQ sorted the references, extracted literature data, was responsible for visualisation and table layout and assisted in drafting the manuscript. GZ acquired funding and assisted in drafting the manuscript. YS and ZZ formulated the research framework, supervised the study and reviewed and edited the manuscript. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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