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Review Article

STING1 in sepsis: Mechanisms, functions, and implications

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ABSTRACT

Sepsis is a life-threatening clinical syndrome and one of the most challenging health problems in the world. Pathologically, sepsis and septic shock are caused by a dysregulated host immune response to infection, which can eventually lead to multiple organ failure and even death. As an adaptor transporter between the endoplasmic reticulum and Golgi apparatus, stimulator of interferon response cGAMP interactor 1 (STING1, also known as STING or TMEM173) has been found to play a vital role at the intersection of innate immunity, inflammation, autophagy, and cell death in response to invading microbial pathogens or endogenous host damage. There is ample evidence that impaired STING1, through its immune and non-immune functions, is involved in the pathological process of sepsis. In this review, we discuss the regulation and function of the STING1 pathway in sepsis and highlight it as a suitable drug target for the treatment of lethal infection.

Introduction

Sepsis is a challenging clinical syndrome and the most common reason for admission to an intensive care unit. A major public health concern, sepsis, accounted for 48.9 million cases and 11 million global deaths (19.7% of all) in 2017.[1] An international task force has updated the definition of sepsis, describing it as a life-threatening organ dysfunction caused by a dysregulated host response to bacteria, viruses, or other pathogen infections.[2] Despite its complex pathophysiological mechanism, sepsis is characterized by early excessive inflammation and late immunosuppression, which are related to cell death and various abnormalities in the coagulation response.[2–4] During sepsis, innate immune cells (e.g., macrophages, monocytes, and neutrophils) are activated to trigger inflammation by sensing pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) through multiple pattern-recognizing receptors (PRRs). PAMPs are components or products of microorganisms and include microbial genomes (DNA and RNA) and lipopolysaccharides (LPS, a constituent of the outer membrane components of gram-negative bacteria).[5,6] In contrast, DAMPs are endogenous molecules driven by the host cell and include proteins (such as high-mobility group box 1 [HMGB1]) and nonproteins (such as host DNA and ATP). PAMPs and DAMPs can activate various innate immune pathways and have become important therapeutic targets for sepsis.[7–9]

Stimulator of interferon response cyclic guanosine monophosphate-adenosine monophosphate (cGAMP) interactor 1 (STING1, also known as STING, TMEM173, MITA, or MPYS) was originally identified by multiple groups as a key adaptor protein in producing type I interferons (type I IFNs) in macrophages or monocytes during DNA-induced immune responses.[10–13] Subsequent studies revealed an immune-independent function of STING1 in promoting autophagy[14] and various kinds of cell death (e.g., apoptosis, necroptosis, pyroptosis, ferroptosis, mitotic cell death, and immunogenic cell death) in various cells.[15] As a crucial part of the host immune defense, an aberrated activation of STING1

Abbreviations: STING1, stimulator of interferon response cGAMP interactor 1; PAMPs, pathogen-associated molecular patterns; DAMPs, damage-associated molecular patterns; PRRs, pattern-recognizing receptors; LPS, lipopolysaccharides; HMGB1, high-mobility group box 1; type I IFNs, type I interferons; ER, endoplasmic reticulum; CGAS, cyclic GMP-AMP synthase; mtDNA, mitochondrial DNA; nDNA, nuclear DNA; cGAMP, cyclic guanosine monophosphate-adenosine monophosphate; CDNs, cyclic dinucleotides; EGFR, epidermal growth factor receptor; cfDNA, cell-free DNA; TLR9, toll-like receptor 9; IRF3, interferon regulatory factor 3; ALK, ALK receptor tyrosine kinase; AKT, serine-threonine kinase; CLP, cecal ligation and puncture; AIM2, absent in melanoma 2; caspase, CASP; IFNAR1, interferon alpha and beta receptor subunit 1; CXCL10, C-X-C motif chemokine ligand 10; TBK1, TANK-binding kinase 1; DMXAA, 5,6-dimethylxanthenone-4-acetic acid; TNFα, tumor necrosis factor α; IL, interleukin; CCL2, C-C motif chemokine ligand 2; NF-κB, nuclear factor-κB; SQSTM1, sequestosome 1; RIPK, receptor interacting serine/threonine-protein kinase; MLKL, mixed-lineage kinase domain-like pseudokinase; GSDMD, gasdermin D; GSDMD-N, N-terminal fragment of GSDMD; GPX4, glutathione peroxidase 4; PLCG1, phospholipase C gamma 1.

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might induce an imbalance in the inflammation immune network.[16] Consequently, a hyperactivation of the STING1 signaling pathway plays an indispensable role in the development of various inflammatory diseases, such as Aicardi-Goutieres syndrome, COPA syndrome, and systemic lupus erythematosus.[17] Similarly, preclinical and clinical studies suggest that an excessive activation of STING1 is a pathogenic event of sepsis. In contrast, the pharmacological or genetic inhibition of the STING1 pathway can protect mice from polymicrobial sepsis and lethal endotoxemia.[18–20] In this review, we highlight recent findings revealing how STING1 networks enforce septic response, and discuss the potential of STING1 as a drug target in lethal infection.

STING1 and DNA signals in sepsis

STING1 is an evolutionarily conserved transmembrane protein normally expressed on the endoplasmic reticulum (ER) membrane in immune and non-immune cells.[21] As a key ER-associated adaptor protein, STING1 can be activated by cytoplasmic DNA produced from pathogens or hosts to trigger strong type I IFNs and inflammation responses.[17] Mechanically, cyclic GMP-AMP synthase (CGAS, also known as MB21D1), the upstream PRR of STING1, detects and binds DNA from invading pathogens (e.g., viruses and bacteria) or damaged hosts (including mitochondrial DNA [mtDNA] and nuclear DNA [nDNA]), leading to the production of a second messenger, cGAMP.[21] In addition, bacterial-derived cyclic di-nucleotides (CDNs, such as cyclic-di-GMP and cyclic-di-AMP) can bypass the CGAS-dependent pathway to directly induce STING1 activation.[22] Thus, STING1 can be activated in a CGAS-dependent and -independent manner.

Sepsis is related to host DNA damage and subsequent DNA release from multiple sources.[23] Extensive cell death becomes the major source of released DNA during sepsis.[24] Circulating cell-free DNA (cfDNA) released by host cells has been shown to be significantly elevated and causes inflammation and organ failure in septic mice and patients.[7,8,19] Circulating mtDNA is a marker of mortality in intensive care unit patients that is associated with the development and prognosis of sepsis,[25–27] and it initiates inflammation and subsequent immunosuppression, leading to organ dysfunction and lung injury.[28–30] In addition to mtDNA, elevated nDNA levels are also associated with the development of sepsis in patients.[7,31] These findings suggest that elevated cfDNA levels in the early stages of sepsis may represent a candidate biomarker for the severity of sepsis.

At least two DNA sensor or receptor pathways mediate mtDNA activity in sepsis. On the one hand, circulating mtDNA can activate toll-like receptor 9 (TLR9) and inflammasomes, contributing to sepsis.[32,33] On the other hand, STING1 is also required for an mtDNA-induced inflammatory response in sepsis.[20] STING1-deficient mice exhibit a reduced mtDNA-induced inflammatory response and acute lung injury. Additional studies have shown that the function of STING1 in sepsis seems to be parallel to the level of cfDNA. Compared with moderate sepsis, cfDNA in severe sepsis is more elevated. Therefore it is not surprising that STING1 knockout mice are only protected from severe sepsis and not moderate sepsis.[19] Functionally, host genomic DNA can activate interferon regulatory factor 3 (IRF3)-dependent gene transcription in macrophages in a STING1-dependent manner. Considering that nDNA and mtDNA can transfer between cells and activate STING1 through the debris of dying cells or DNA-containing extracellular vesicles,[34,35] it is possible that STING1 senses the cfDNA after having been taken up by cells (Fig. 1). Alternatively, a plasma membrane receptor-dependent pathway can mediate exogenous DNA signals to activate STING1.[18] In particular, CDNs and cGAMP can activate the CGAS/STING1 pathway through transmembrane epidermal growth factor receptor (EGFR) and ALK receptor tyrosine kinase (ALK) in macrophages or monocytes. Although ALK may not be a direct adaptor for cytosolic STING1 due to a lack of direct interaction between ALK and STING1, serine-threonine kinase (AKT) can act as a downstream signal of ALK and promotes STING1 activation through protein phosphorylation (Fig. 1). Pharmacologically inhibiting the ALK-AKT-STING1 pathway by LDK378 protects against cecal ligation and puncture (CLP)-induced sepsis in mice,[36,37] suggesting a potential drug target for treating sepsis.

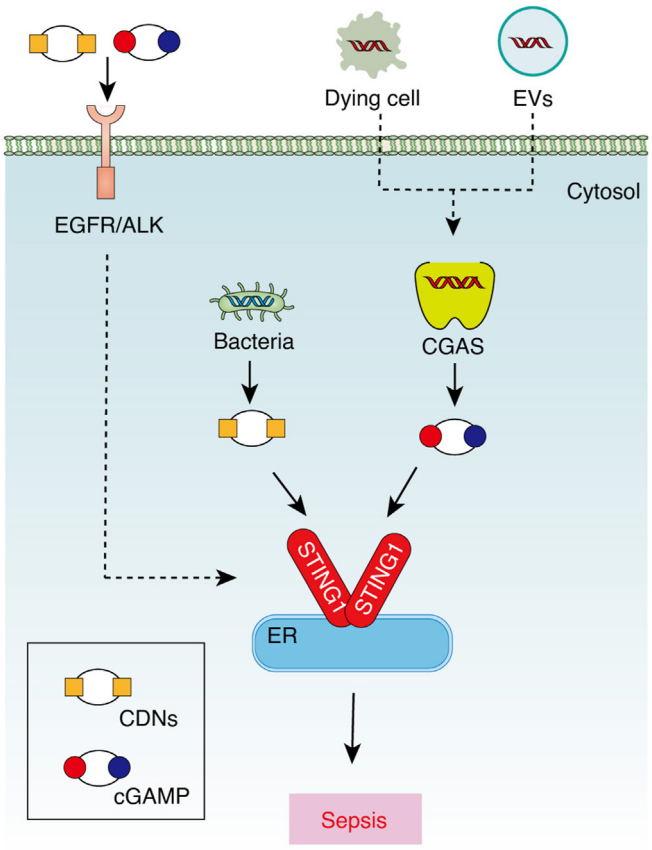

Fig. 1. STING1 senses extracellular DNA signals in sepsis. During sepsis, extracellular DNA may enter cells through the endocytosis of dying cells or DNA-containing EVs, leading to CGAS/STING1 activation, while extracellular DNA signals, including CDNs and cGAMP, may promote STING1 activation through EGFR/ALK-dependent transmembrane receptors.
Abbreviations: ALK: ALK receptor tyrosine kinase; CDNs: cytosolic cyclic dinucleotides; cGAMP: cyclic GMP-AMP; CGAS: cyclic GMP-AMP synthase; EGFR: epidermal growth factor receptor; ER: endoplasmic reticulum; EVs: extracellular vesicles; STING1: stimulator of interferon response cGAMP interactor 1.

Although bacterial infection is the most important cause of sepsis, with immune cell death being attributed to bacterial DNA, the DNA exhibits a less lethal effect in mouse polymicrobial sepsis.[38] Blocking the recognition of bacterial DNA alleviates inflammation, implying that the DNA plays a major role in priming the immune system. Most bacteria release DNA into cells via endocytosis or phagocytosis to bind TLR9,[39,40] whereas some bacteria, such as *Francisella tularensis*, can enter macrophages and release DNA directly into the cytosol to activate the absent in melanoma 2 (AIM2) inflammasome for sepsis.[41] Whether STING1 is involved in sensing bacterial DNA-related TLR9 or AIM2 pathways during sepsis remains to be further clarified.

The mtDNA might directly contribute to inflammation through a cytoplasmic signaling pathway during sepsis. Impaired mitochondria produce more cytosolic mtDNA serving as DAMPs, which

activates the NLR family pyrin domain containing 3 (NLRP3) inflammasome and subsequent caspase 1 (CASP1) in macrophages, ultimately releasing cytokines similar to a sepsis condition.[42] Accordingly, the depletion of CGAS inhibits mtDNA-mediated STING1 and NLRP3 activation, thereby protecting against LPS-induced acute lung injury.[43] These findings prove the new connection between the STING1 pathway and NLRP3 inflammasome in causing sepsis.

Taken together, elevated cfDNA signals, including mtDNA and nDNA, could trigger a STING1-dependent inflammatory response during sepsis. The inhibition of DNA sensing by cfDNA scavengers or deoxyribonuclease (DNASE1) can effectively inhibit a severe sepsis-related cytokine storm and organ dysfunction, indicating the novel therapeutics of targeting cfDNA/STING1 in sepsis.[20,44–46]

STING1 and type I IFNs in sepsis

Type I IFNs are essential cytokines in promoting and regulating immune and inflammatory responses as well as for controlling several types of cell death (e.g. apoptosis, necroptosis, and pyroptosis), which are crucial for septic response.[47] Mounting evidence suggests that type I IFNs are essential effectors in LPS- or virus-induced lethal sepsis,[48,49] and their expression is driven by the transcription factor IRF3.[50,51] The pharmacologic or genetic inhibition of type I IFN receptors also ameliorates LPS- and CLP-induced sepsis in mice.[52,53] Neutralizing type I IFN signaling could be a therapeutic option for patients with acute sepsis.[54,55] Mechanically, type I IFNs could induce HMGB1 release, leading to caspase 11 (CASP11)-dependent pyroptosis in macrophages and hepatocytes, thus mediating bacterial infection-induced lethal coagulation.[56,57] Given that sepsis mortality often occurs after a prolonged period of immunosuppression rather than exaggerated inflammation,[58] type I IFNs might play a different role in the later stage of sepsis compared to a role in innate and adaptive immune responses. However, in a low-lethality sepsis model, interferon alpha and beta receptor subunit 1 (IFNAR1)-deficient mice and chimeric mice lacking IFNAR1 in hematopoietic cells display increased mortality after CLP, with elevated peritoneal bacterial counts and reduced C-X-C motif chemokine ligand 10 (CXCL10)-dependent peritoneal neutrophil recruitment and function.[59] These data indicate a host defense role of type I IFNs in sepsis.

STING1 plays a well-known role in driving IRF3-dependent type I IFN production. After binding with cGAMP, STING1 undergoes a change to an active state, thus translocating to the Golgi apparatus and activating the transcription factor IRF3 by recruitment of a phosphokinase, TANK-binding kinase 1 (TBK1).[60] Subsequently, active IRF3 translocate the nucleus to induce transcription of type I IFN genes, which are involved in immune responses in infection and antitumor immunity. As expected, STING1 has been found to contribute to type I IFN-mediated septic response. In human abdominal sepsis, the expression of STING1 in peripheral blood mononuclear cells and intestinal cells is increased, which is associated with intestinal inflammation in patients with sepsis.[20] During lethal sepsis in mice, STING1 is activated by cfDNA to promote IRF3-dependent type I IFN expression.[19,20] STING1-deficient septic mice have reduced inflammation, tissue damage, and bacterial translocation, and STING1 agonist (5,6-dimethylxanthenone-4-acetic acid [DMXAA]) can aggravate CLP-induced intestinal cell apoptosis and systemic inflammation.[20] In addition, the administration of DMXAA causes shock-like symptoms and significant mortality in mice, whereas STING1- or IFNAR1-deficient mice are completely resistant to mortality after DMXAA injection.[61] Considering that the STING1-IRF3 axis is involved in inflammasome activation and cell death as described below,[43,62] the activation of STING1 might contribute to lethal sepsis through type I IFN-dependent inflammation (Fig. 2).

Of note, STING1 might regulate coagulation activation in lethal infections independent of type I IFN signaling. The loss of IFNAR1 and IRF3 in mice only slightly reduces the animals' death but fail to affect the activation of coagulation in CLP-induced sepsis mice.[63] Meanwhile, type I IFNs do not induce the release of coagulation factor III (F3), which is the principal initiator of coagulopathy in sepsis in primary and immortalized monocytes or macrophages. These findings suggest that the involvement of the STING1/IRF3/type I IFN axis may contribute to an earlier step of sepsis by promoting inflammation rather than the coagulation pathway. Nevertheless, type I IFNs play an important role in establishing and regulating the host's defense against microbial infections.

STING1 and cytokine storms in sepsis

The initiation of inflammation is important to eradicate infection and repair tissue damage, whereas an excessive inflammatory response (or cytokine storm) can cause disseminated intravascular coagulation, tissue injury, organ dysfunction, and death in inflammatory diseases, such as severe COVID-19.[64–69] During sepsis, the production of inflammatory cytokines, such as tumor necrosis factor α (TNFα), interleukin 1 (IL1), interleukin 6 (IL6), C-C motif chemokine ligand 2 (CCL2), and CXCL10, are controlled by various transcriptional factors, especially nuclear factor-κB (NF-κB).[58,70,71]

In addition to IRF3, STING1 activation could also recruit transforming growth factor β-activated kinase (TAK) and the inhibitor of NF-κB kinase (IKK) complexes thereby activating NF-κB–mediated

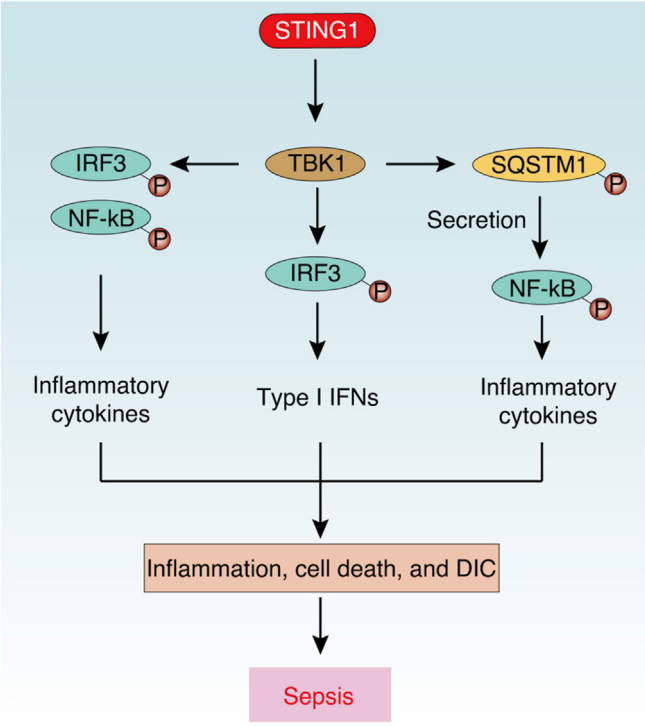

Fig. 2. STING1-mediated type I IFNs and inflammatory cytokines in sepsis. During sepsis, activated STING1 recruits and phosphorylates TBK1, which further activates IRF3- and NF-κB-dependent type I IFN and inflammatory cytokine production. Meanwhile, activated TBK1 could promote phosphorylation and secretion of SQSTM1, which further activates NF-κB.
Abbreviations: DIC: disseminated intravascular coagulation; IRF3: interferon regulatory factor 3; NF-κB: nuclear factor kappa B complex; SQSTM1: sequestosome 1; STING1: stimulator of interferon response cGAMP interactor 1; TBK1: TANK binding kinase 1.

production of inflammatory cytokines such as TNFα, IL6, CXCL10, and CCL5.[60,72] In an acute pancreatitis model, STING1 knockout mice develop less inflammation than control mice, while the STING1 agonist DMXAA increases TNFα expression and worsens acute pancreatitis.[34] Consistent with this, systemic DMXAA administration results in the release of TNFα and IL6 as well as shock-like symptoms in mice, and TNFα is essential for strong necroptosis after the activation of STING1 in macrophages.[61] These data suggest STING1 may act as an enhancer of inflammation by promoting pro-inflammatory cytokine production, leading to a cytokine storm and sepsis.

During human abdominal sepsis, STING1 signaling and STING1-induced inflammatory cytokines (IL1, IL6, and TNFα) are activated in peripheral blood mononuclear cells.[20] DMXAA treatment activates the STING1/IRF3 or NF-κB pathway and increases the levels of serum and intestinal cytokines (IL6 and TNFα) and intestinal epithelial cell apoptosis in CLP-induced septic mice,[20] whereas STING1 deficiency significantly reduces the levels of serum IL6, interleukin 12B, and CCL2 in CLP-induced severe sepsis in mice.[19] These data indicate that STING1 activation contributes to an inflammatory response in polymicrobial sepsis. Moreover, STING1-mediated NLRP3 inflammasome activation triggers the expression of cytokines (interleukin 1 beta [IL1β], TNFα, CCL2, and HMGB1) as well as apoptosis and pyroptosis in mice.[62] ALK-dependent STING1 activation is also required for LPS-induced activation of the IRF3 and NF-κB pathway and the subsequent cytokine storms and systemic coagulation in mice.[36,37] Meanwhile, STING1 deficiency can reduce the expression of ALT and F3 in CLP-induced septic mice.[20,63] Thus, STING1 is an important mediator of polymicrobial sepsis- and endotoxemia-induced inflammation, coagulation, and tissue damage (Fig. 2).

Inflammation is the double-edged sword of infection-related immunity, which depends on the type of signals involved. STING1 has also been suggested to be a negative regulator in some chronic inflammatory diseases, such as inflammatory bowel disease. STING1-deficient mice are prone to intestinal inflammation in response to moderate dextran sulfate sodium stimulation.[73,74] STING1 deficiency impairs the production of interleukin 10 (IL10),[74] which is an anti-inflammatory cytokine regulated by IRF3 and NF-κB.[75] These results suggest a protective effect of STING1-dependent IL10 secretion for gut homeostasis by preventing an excessive inflammatory response. Overall, STING1 signaling may play a paradoxical role in acute and chronic inflammatory response, depending on the induction of anti-inflammatory and pro-inflammatory cytokines.

STING1 and autophagy in sepsis

Autophagy is a lysosome-dependent degradation process and includes three types: macroautophagy, microautophagy, and chaperone-mediated autophagy.[76] Macroautophagy (hereafter referred to as autophagy), the most studied form of autophagy, is closely related to inflammation and immunity.[77] After the onset of sepsis, autophagy is induced by PAMPs, DAMPs, and pro-inflammatory cytokines,[5,78,79] generally conferring protective effects on multiple tissues.[80–83] The pro-survival role of autophagy in sepsis is attributed to the clearance of invasive microbes,[78] the balancing of an anti- and pro-inflammatory response,[80] the maintenance of lipid metabolism,[84] the quality control of mitochondria,[42] and the prevention of cell death.[83,85] Genetically, some autophagy-related (ATG) genes fine-tune these processes.[86] For example, deficiencies in beclin1 (BECN1, also known as ATG6) or microtubule-associated protein 1 light chain 3 alpha (also known as ATG8) result in an exaggerated inflammatory response with the development of organ injury and death.[81,87] PTEN-induced kinase 1 and Parkin RBR E3 ubiquitin protein ligase (PRKN/PARK2)-mediated mitophagy is important for mitochondria integrity and inflammation control in sepsis.[80,88]

Accumulating evidence has demonstrated that STING1 can induce autophagy through a canonical autophagy induction process, which depends on the inactivation of mechanistic target of rapamycin (MTOR) kinase and the activation of BECN1, or through a noncanonical autophagy induction process, which is independent of unc-51–like autophagy activating kinase 1 (ULK1), BECN1, and phosphatidylinositol 3-kinase catalytic subunit type 3 (PIK3C3).[14,89–91] STING1-mediated autophagy is involved in multiple biological processes, including the removal of bacteria and viruses.[89,92] The function of STING1 in autophagy is conserved in invertebrates and vertebrates.[14,92]

STING1-induced autophagy can also prevent the overactivation of STING1 by sequestosome 1 (SQSTM1/p62), a well-known autophagy selective receptor that induces lysosomal degradation, whereas reduced SQSTM1 expression or pharmacological inhibition of autophagy exaggerates STING1-mediated type I IFN and cytokine production.[72,93] Thus, SQSTM1-mediated autophagic degradation of STING1 may act as a negative controller of the STING1 pathway, protecting the overwhelming inflammatory response. Notably, IFN-dependent C-terminal tail region and IRF3 are not required for STING1-mediated autophagy.[14] Given that IFN-dependent STING1 signaling may originate from the evolution of vertebrates only of which STING1 contains C-terminal tail domain recruiting TBK1 and IRF3,[94] the IFN-independent autophagy induction of STING1 may be a primordial function of the CGAS pathway for antimicrobial infection. Thus, it is possible that STING1-induced autophagy can prevent cytokine storms and sepsis not only through degrading STING1 but also through the clearance of pathogens. Considering that the pharmacological activation of autophagy could prevent sepsis[95,96] and pharmacological inhibition of autophagy worsens septic response,[97] it is recommended that STING1-mediated autophagy be activated to treat sepsis.

In contrast to the intracellular function of SQSTM1 in inflammation, extracellular SQSTM1 was recently found to act as a lethal inflammatory mediator of sepsis after STING1 activation.[98] The activation of STING1 and subsequent TBK1 induces SQSTM1 phosphorylation, expression, and subsequent secretion in macrophages. The extracellular SQSTM1 binding the insulin receptor on plasma membrane activates NF-κB (Fig. 2), causing polarization of pro-inflammatory macrophages, and finally leading to septic death in mice through excessive inflammation and coagulation. These data suggest multifaceted roles for SQSTM1 as an autophagy receptor or pro-inflammatory mediator in sepsis. More efforts should be made to illustrate the contributions of STING1 and SQSTM1-induced inflammatory response and autophagy to sepsis and other diseases.

STING1 and cell death in sepsis

Regulated cell death (RCD) is caused by the activation of one or more signal transduction modules. RCD includes but is not limited to apoptosis, necroptosis, pyroptosis, and ferroptosis.[99,100] Since increased cell death is observed in non-immune and immune cells during sepsis, RCD is considered to play an important role in organ dysfunction and immune dysregulation.[24,101,102] Recent evidence indicates that STING1 mediates various types of RCD and hence contributes to inflammation, immunosuppression, and the coagulation activation of sepsis, as described below.

STING1-mediated apoptosis in sepsis

Apoptosis is generally a form of immune-silent RCD, in which the cellular membranes remain intact and intracellular proteins

and organelles are removed without alarming the immune system. Apoptotic pathways engage mitochondria or death receptor-mediated signal transduction, resulting in the activation of a series of apoptotic effectors, such as caspase 3 (CASP3), caspase 6 (CASP6), and caspase 7 (CASP7), which ultimately leads to nonlytic cell death.[103]

Apoptosis is one of the most well-described mechanisms leading to sepsis-induced organ dysfunction in gut and respiratory epithelial cells, cardiomyocytes, and endothelial cells.[24] Recently, several studies have linked STING1 with non-immune cell apoptosis in sepsis. Increased intestinal permeability after CLP induces intestinal epithelial cell (IEC) apoptosis and is blocked in STING1 knockout mice, while treatment with the STING1 agonist DMXAA aggravates sepsis-induced IEC apoptosis and abdominal sepsis.[20] These findings indicate that STING1-mediated apoptosis favors the pathogenesis of sepsis by damaging the gut barrier. In addition to gut, STING1 also participates in heart tissue apoptosis.[104] During sepsis, LPS-induced STING1 upregulation contributes to apoptosis and subsequent heart injuries in mice, while this process can be inhibited by the administration of selenium, which inactivates the STING1 pathway. In addition, STING1 deficiency significantly reduces the level of apoptotic cardiomyocytes in LPS-treated mice and decreases the activation of CASP3 and reduces the ratio of BCL2-associated X, apoptosis regulator (BAX) to BCL2 apoptosis regulator (BCL2).[62] Given that STING1-mediated apoptosis is often involved in the regulation of ER stress, IRF3, or BAX function in non-immune cells,[15] it is possible the same mechanism is involved in non-immune cell apoptosis during sepsis. Overall, STING1 is directly involved in the apoptosis of non-immune cells and the damage to the intestinal barrier and heart tissue during sepsis (Fig. 3).

The loss of immune cells through apoptosis is one of the known mechanisms responsible for impaired immune defenses in acute critical illness, including septic shock.[105] Extensive apoptosis in lymphocytes and dendritic cells could release a large quantity of DAMPs, including HMGB1, cfDNA, histones, and neutrophil extracellular traps, leading to cytokine storms, immunosuppression, and coagulation activation and finally causing multiple organ failure and death.[106] STING1 activation by agonists has been shown to trigger apoptosis in B cells and T cells,[107–111] indicating that STING1 activation is highly pro-apoptotic in lymphocytes and may contribute to lymphocyte apoptosis in sepsis. Indeed, splenic CD4 T cells experience STING1-mediated apoptosis during sepsis, leading to immunodeficiency in endotoxemia mice.[112] Specifically, LPS-induced cleaved CASP3 is increased in a STING1-dependent manner, which could be blocked by the competitive interaction of the Notch intracellular signaling domain with the CDN-binding domain of STING1, thereby limiting the activation of STING1 by cGAMP and the blockage of STING1-mediated T cell apoptosis (Fig. 3). Interestingly, STING1 activation promotes T cell apoptosis by the regulation of calcium (Ca^{2+}) homeostasis and ER stress independently of IFN signaling.[109] Further research may focus on the pro-apoptotic effect of STING1 in lymphocytes during sepsis, which is independent of IFN.

In summary, STING1-mediated apoptosis can lead to tissue damage induced by non-immune cell death and immunosuppression induced by T cell death. Since many anti-apoptotic strategies have successfully reduced mortality after sepsis,[113,114] it is possible to treat sepsis by inhibiting STING1-mediated apoptosis.

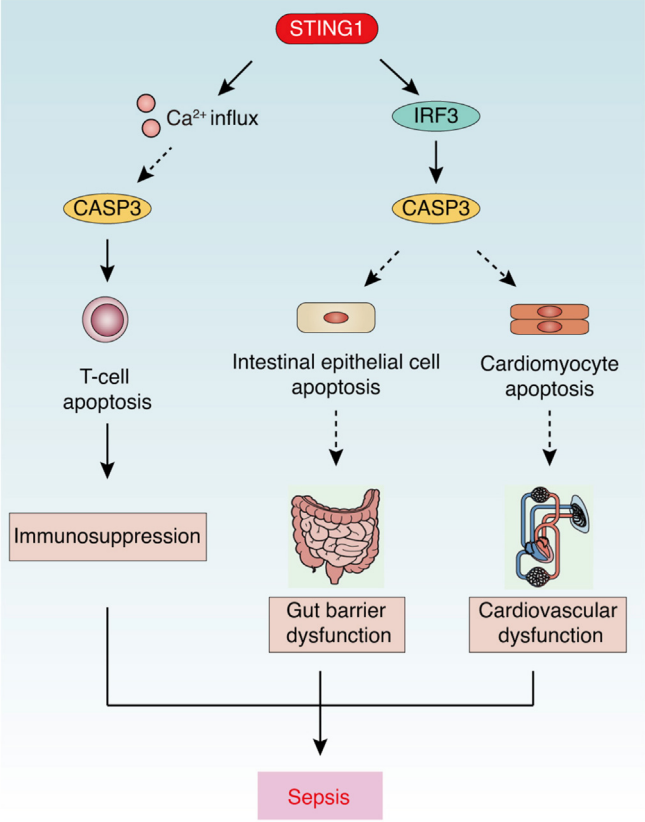

Fig. 3. STING1-mediated apoptosis in sepsis. During sepsis, activated STING1 triggers T cell apoptosis via a Ca^{2+}- and CASP3-dependent pathway, causing immunosuppression or triggering apoptosis in non-immune cells (such as intestinal epithelial cells and cardiomyocytes) via an IRF3-dependent pathway, causing tissue dysfunction (such as gut barrier or cardiovascular dysfunction).
Abbreviations: Ca^{2+}: calcium; CASP: caspase; F3: coagulation factor III; IRF3: interferon regulatory factor 3; STING1: stimulator of interferon response cGAMP interactor 1.

STING1-mediated necroptosis in sepsis

Necroptosis is a programmed form of necrosis, of which the core regulator is composed of three proteins: receptor interacting serine/threonine kinase 1 (RIPK1), receptor interacting serine/threonine kinase 3 (RIPK3), and mixed-lineage kinase domain-like pseudokinase (MLKL). After activation by death receptors or PRRs, RIPK1 phosphorylates MLKL through RIPK3. MLKL then oligomerizes and destroys the plasma membrane, leading to necroptotic cell death.[115] Necroptosis acts as a trigger of inflammation in many diseases.[116,117] Increased necroptosis is also implicated in sepsis through promoting the release or activation of inflammatory effectors, such as HMGB1,[118–120] TNF-related apoptosis-inducing ligand,[121] and gasdermin D (GSDMD).[122] STING1 signals can trigger necroptosis and promote inflammation by initiating MLKL expression or inducing MLKL phosphorylation.[123,124] As expected, TNF and necroptotic signaling is increased in STING1 agonist-induced sterile shock in mice; however, STING1-mediated necroptosis may have a limited role in the production of inflammatory cytokines in blood.[61] The precise role of STING1 in necroptosis during sepsis needs to be further studied.

STING1-mediated pyroptosis in sepsis

Pyroptosis is a form of lytic pro-inflammatory RCD driven by N-terminal fragment of GSDMD (GSDMD-N)- or N-terminal fragment of gasdermin E (GSDME/DFNA5-N)-dependent pore formation, and it occurs in various immune and non-immune cells.[125] The induction of pyroptosis requires the activation of inflammasomes, which are multiprotein intracellular complexes that detect PAMPs and DAMPs.[126,127] Canonical inflammasome complexes, such as NLRP3

and AIM2, activate the CASP1-mediated secretion of IL1 family cytokines (e.g., IL1β and interleukin 18 [IL18]) and cleavage of GSDMD that produces GSDMD-N.[128] Alternatively, cytoplasmic LPS-induced activation of CASP11 (also known as caspase 4 [CASP4] or caspase 5 [CASP5] in humans) triggers noncanonical inflammasome-mediated GSDMD-N production.[129] In contrast, the production of GSDME-N is mediated by CASP3.[130] These findings indicate that the caspase family is involved in apoptosis and non-apoptotic cell death.

Although adequate pyroptosis can protect against bacterial infection, hyperactivated pyroptosis can rupture the plasma membrane, resulting in the release of abundant inflammatory effectors for organ dysfunction in sepsis.[126,131–133] SQSTM1 can also be passively released through GSDMD-dependent pyroptosis, acting as an extracellular mediator of septic death in myeloid cells.[98,134] The chemical inhibition of GSDMD directly is able to reduce the release of inflammatory mediators, including SQSTM1, during sepsis.[98,135] The activation and function of pyroptosis in sepsis is further regulated by STING1. For example, cytosolic DNA signals can activate STING1-mediated pyroptosis by an IRF3-dependent transcriptional upregulation of NLRP3[43] or lysosomal cell death-related potassium efflux to activate NLRP3 inflammasomes.[136] In sepsis, a STING1 deficiency reduces the protein levels of NLRP3 and CASP1 in LPS-treated septic mice, whereas IRF3 activation by STING1 could increase the expression of NLRP3 and CASP1 and subsequent pytoptosis in neonatal rat cardiomyocytes.[62] Thus, an IRF3-dependent pathway downstream of STING1 might be involved in pytoptosis and heart injury during sepsis. Further, type I IFNs could induce HMGB1 release, leading to CASP11-dependent GSDMD activation in macrophages,[56] whereas heparin can inhibit this process to prevent sepsis.[137] These data indicate that STING1-mediated type I IFNs might also contribute to noncanonical inflammasome-mediated GSDMD activation, pyroptosis, and tissue injury (Fig. 4).

Coagulation is characterized as a driver of multiple organ failure in sepsis.[64] GSDMD-N–mediated pore formation could release F3, leading to coagulation, although it may occur in a pyroptosis-dependent and -independent manner.[138–140] STING1-dependent GSDMD activation has been shown to trigger F3 release during sepsis.[63] Global depletion or conditional ablation of STING1 in myeloid cells blocks GSDMD-N production and protects mice against CLP-induced F3 release in the blood, coagulation activation, and finally death. STING1-mediated ER-stress and Ca^{2+} influx are required for CASP activation and subsequent GSDMD-mediated F3 release in macrophages. Moreover, ATPase sarcoplasmic/endoplasmic reticulum Ca^{2+} transporting 2 (ATP2A2) and inositol 1,4,5-trisphosphate receptor type 1 (ITPR1), by controlling Ca^{2+} transport between the ER and cytoplasm, regulate GSDMD-N formation and subsequent F3 release and coagulation activation in sepsis. In contrast, a deficiency of CGAS, IFNAR1, and IRF3 fails to affect CLP-induced coagulation activation in mice, indicating that STING1-mediated GSDMD-dependent coagulation may depend on Ca^{2+} elevation, rather than on the IRF3/type I IFN pathway (Fig. 4). In fact, STING1 has been widely associated with ER homeostasis and Ca^{2+} signals.[89,109,141,142] Since ER-related Ca^{2+} signals play a broad role in various types of cell death,[143] we speculate that Ca^{2+} signals are an important downstream event of STING1 activation, which not only regulates pyrolysis, but also regulates apoptosis and other cell deaths during sepsis.

STING1-mediated ferroptosis in sepsis

Ferroptosis is an iron-dependent oxidative RCD triggered by lipid peroxidation, which is negatively regulated by certain antioxidant systems, especially the solute carrier family 7 member 11

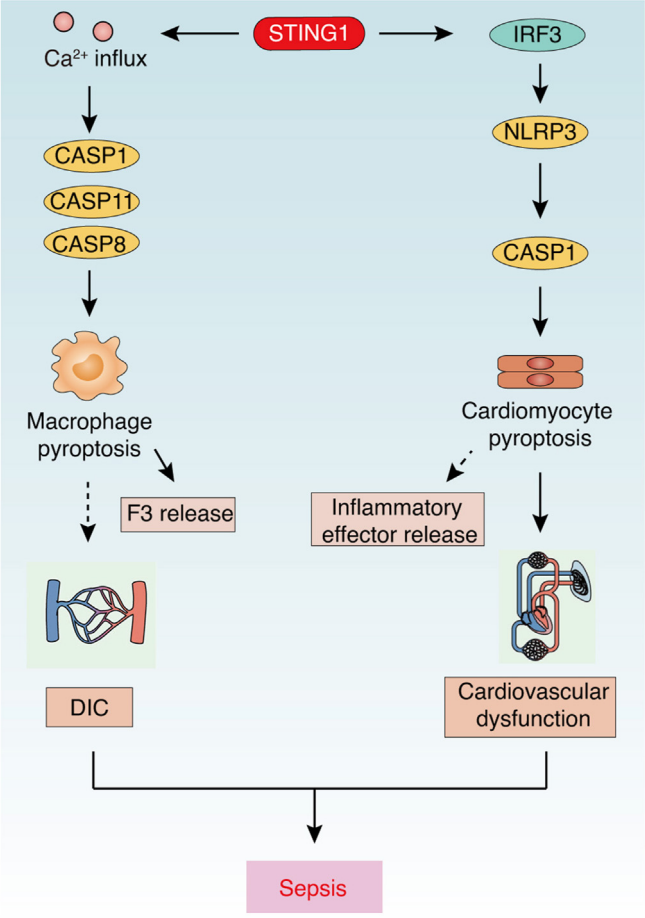

Fig. 4. STING1-mediated pyroptosis in sepsis. During sepsis, activated STING1 triggers Ca^{2+}-mediated pyroptosis in macrophages, leading to F3 release and coagulation. However, STING1 also activates IRF3/NLRP3 axis-mediated CASP1-dependent pyroptosis in cardiomyocytes, leading to cardiovascular dysfunction.
Abbreviations: Ca^{2+}: calcium; CASP: caspase; DIC: disseminated intravascular coagulation; F3: coagulation factor III; IRF3: interferon regulatory factor 3; NLRP3: NLR family pyrin domain containing 3; STING1: stimulator of interferon response cGAMP interactor 1.

(SLC7A11)-glutathione–glutathione peroxidase 4 (GPX4) axis.[144–146] Excessive or defective ferroptotic cell death is associated with a growing list of diseases involving dysregulated inflammation and immune response.[147,148] In sepsis mouse models, the pharmacological inhibition of ferroptosis can protect CLP- or LPS-induced tissue injury via a decreased inflammation response,[149,150] suggesting a role for ferroptosis in sepsis. However, the conditional depletion of GPX4 in myeloid cells increases lipid peroxidation-dependent pyroptosis, rather than ferroptosis, leading to a systemic inflammatory response and multiple organ dysfunctions in polymicrobial sepsis mice.[151] In contrast, a lipid peroxidizing enzyme, arachidonate 5-lipoxygenase (ALOX5), mediates lipid peroxidation that is responsible for CASP11 inflammasome activation and pyroptosis in macrophages, which favors LPS-induced sepsis.[127] This process is further enhanced by the phosphorylation of phospholipase C gamma 1 (PLCG1) activation and Ca^{2+} elevation.[151] Considering the contribution of Ca^{2+} influx in GSDMD activation as we described earlier, we hypothesize that sepsis-induced lipid peroxidation activates the PLCG1/Ca^{2+} pathway and subsequent pyroptosis. In fact, a recent study demonstrated that NADPH oxidase-mediated lipid peroxidation could activate phospholipase C-dependent Ca^{2+} influx, which

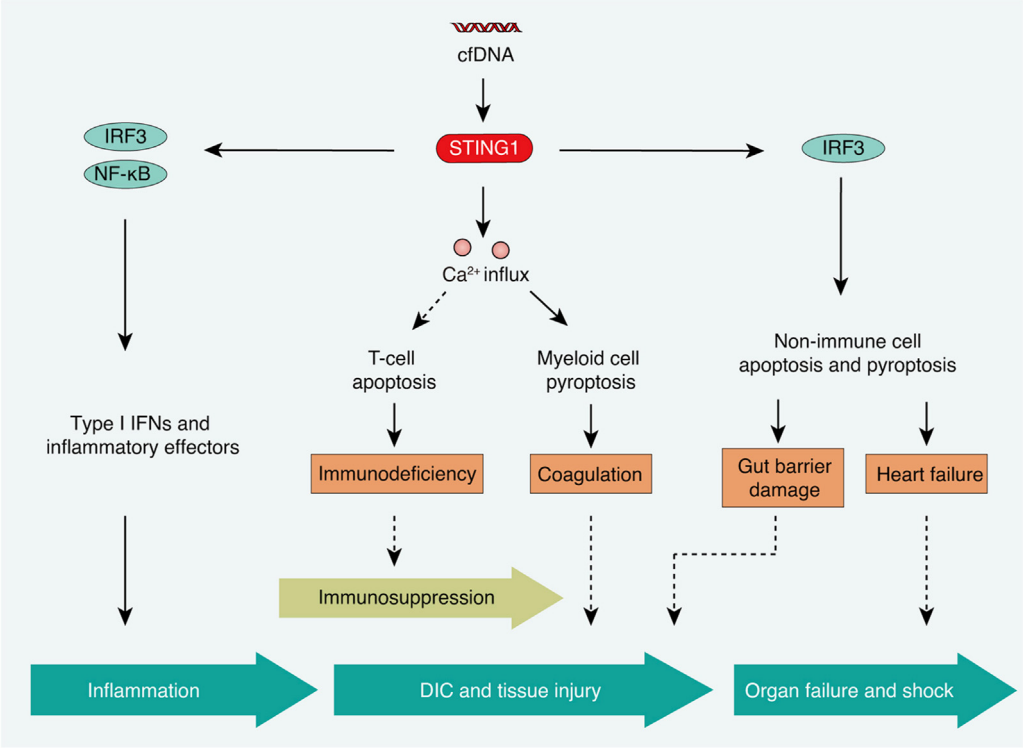

Fig. 5. The network of STING1 in the pathological process of sepsis. Activated STING1 triggers the production of type I IFNs and inflammatory cytokines, apoptosis, and pyroptosis, contributing to different stages in the pathological process of sepsis, such as inflammation, immunosuppression, DIC and tissue injury, organ failure, and shock.
Abbreviations: Ca^{2+}: calcium; cfDNA: circulating cell-free DNA; DIC: disseminated intravascular coagulation; IRF3: interferon regulatory factor 3; NF-κB: nuclear factor kappa B complex; STING1: stimulator of interferon response cGAMP interactor 1.

further promotes NLRP3 inflammasome and CASP1 activation via reactive oxygen species in mitochondria, leading to GSDMD-mediated pyroptosis.[152] These data indicate a crosstalk effect of lipid peroxidation between ferroptosis and pyrolysis during sepsis. STING1 activation can induce lipid peroxidation and ferroptosis in pancreatic cancer cells through STING1-dependent autophagic degradation of GPX4.[153,154] Moreover, STING1-mediated lipid peroxidation contributes to intestinal ischemia-reperfusion injury, which is a systemic inflammatory response syndrome.[155] STING1 deficiency can reduce the levels of lipid peroxidation biomarkers in macrophages and intestinal tissues, and a lipid peroxidation inhibitor, liproxstatin-1, can reverse the lung and liver cell death induced by STING1 activation. In contrast, GPX4 depletion increases lipid peroxidation in macrophages and limits STING1 activation by lipid product 4-hydroxynonenal-mediated carbonylation, indicating a dual regulation between STING1 and lipid peroxidation.[156] Further study of the relationship between STING1 and lipid peroxidation may expand the role of STING1-mediated ferroptosis in sepsis.

Conclusions and prospects

In this review, we summarize the multiple functions of STING1 in the pathogenesis of sepsis (Fig. 5). In the early stages of sepsis, STING1 activation initiates the production and secretion of type I IFNs or inflammatory cytokines and effectors, leading to an overwhelming inflammatory response. In the later stage of sepsis, STING1 activation induces Ca^{2+}-dependent apoptosis in T cells, GSDMD-dependent pyroptosis in myeloid cells, and IRF3-dependent apoptosis and pyroptosis in non-immune cells, which leads to immunosuppression, coagulation, and tissue injury. Several questions remain to be answered: Can STING1-dependent autophagy play the role of a negative regulatory loop in sepsis? Is STING1-mediated necroptosis, ferroptosis, and other types of cell death related to sepsis? Is there any direct link between STING1 and lipid peroxidation in sepsis? How does STING1 activation regulate Ca^{2+} signaling during sepsis?

The multifunctional role of STING1 in sepsis suggests that the chemical inhibition of STING1 might be a novel therapeutic strategy for treating sepsis. Although STING1 agonists have been used as drugs for the clinical treatment of cancer and as antiviral therapy in recent years, few STING1 inhibitors have been developed so far. Future work may focus on the development of new antagonists that directly target the processes of STING1 activation, including DNA sensing, ER transport to the Golgi apparatus, and the recruitment of downstream proteins, such as IRF3, NF-κB, and NLRP3. STING1 activation is tightly controlled by posttranslational modification, such as palmitoylation, which has been proved to be effectively targeted by covalent small molecules that inhibit STING1-induced immune response and T cell death.[110,157] Therefore, it is possible to develop inhibitors that affect the posttranslational modification of STING1. In addition, the atypical role of STING1 in autophagy and Ca^{2+} signaling has been confirmed. The combination of genetic technology and chemical screening in these areas may help identify new drugs for the treatment of sepsis and other STING1-related diseases.

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Ethical statement

Not applicable.

Declaration of competing interest

The authors declare no conflicts of interest or financial interests.

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Author contributions

Ruo-Xi Zhang wrote the manuscript. Rui Kang and Dao-Lin Tang edited the manuscript. All authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

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