Journal of Inflammation Research

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REVIEW

Focus on the cGAS-STING Signaling Pathway in Sepsis and Its Inflammatory Regulatory Effects

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Abstract: Sepsis is a severe systemic inflammatory response commonly occurring in infectious diseases, caused by infection with virulent pathogens. In the pathogenesis of sepsis, the cyclic guanosine monophosphate (GMP)-adenosine monophosphate (AMP) synthase-stimulator of interferon genes (cGAS-STING) signaling pathway serves a crucial role as a fundamental immunoregulatory mechanism. This signaling pathway activates STING upon recognizing intracellular DNA damage and pathogen-derived DNA, subsequently inducing the production of numerous inflammatory mediators, including interferon and inflammatory cytokines, which in turn trigger an inflammatory response. The aim of this paper is to explore the activation mechanism of the cGAS-STING signaling pathway in sepsis and its impact on inflammatory regulation. By delving into the mechanism of action of the cGAS-STING signaling pathway in sepsis, we aim to identify new therapeutic strategies for the treatment and prevention of sepsis.

Keywords: sepsis, cGAS, STING, inflammation

Introduction

Sepsis is a critical condition characterized by multi-organ dysfunction and potentially leading to organ failure, resulting from an over-activated inflammatory response triggered by infection. Furthermore, host immune dysfunction, attributed to this excessive inflammatory response, is closely associated with increased mortality rates in sepsis patients.[1–3] The excessive inflammatory response and the ensuing cytokine storm have been long identified as primary contributors to the elevated mortality rates among sepsis patients.[4,5] However, recent years have seen that drugs targeting cytokine receptors, including Tumor necrosis factor-α (TNF-α), Interleukin-1β (IL-1β), and others, have failed to significantly improve clinical outcomes in sepsis patients.[6,7] Recent research has elucidated that both innate immune dysfunction and acquired immunosuppression are of equal importance in contributing to the multiorgan failure and mortality associated with sepsis.[8] Consequently, preserving the normal functionality of both innate and acquired immune mechanisms is pivotal for the effective treatment of sepsis.[3,9] In recent years, research into the cyclic guanosine monophosphate (GMP)-adenosine monophosphate (AMP) synthase-stimulator of interferon genes (cGAS-STING) signaling pathway has been extensive, highlighting its critical role in sensing aberrant intracellular DNA and triggering the host's immune response.[10,11] Current research indicates that aberrant activation of this pathway may induce significant production of type I interferon (IFN-I) and other inflammatory cytokines, potentially influencing the onset and progression of the body's inflammatory response. In the pathological context of sepsis, infection-induced cell death or tissue damage results in the release of large amounts of DNA into the cytoplasm, with the activation of the cGAS-STING signaling pathway potentially serving as a crucial regulatory point in the inflammatory response.[12] However, the role of the cGAS-STING signaling pathway in sepsis and its regulatory mechanisms in the pathophysiological process of sepsis development have not been fully elucidated.

Received: 26 February 2024
Accepted: 29 May 2024
Published: 5 June 2024

In this article, we review the current research status of the cGAS-STING signaling pathway in the occurrence and development of sepsis as reported in previous studies. We also explore its application in the treatment of sepsis, aiming to provide valuable insights for future therapeutic strategies and research directions.

Overview of the cGAS--STING Signaling Pathway

The cGAS-STING signaling pathway is an important signaling pathway involved in the immune response, initiating the immune response by recognizing aberrant intracellular DNA. Its aberrant activation or dysregulation has been demonstrated to closely associate with the development of various diseases, including infectious diseases, autoimmune disorders, and tumors.[13–15] This pathway primarily comprises two core proteins: the intracellular DNA sensor cGAS and the downstream effector protein STING.

cGAS is a DNA-sensing nucleotidyltransferase, constituted by a single protein molecule that encompasses a disordered N-terminal structural domain (NTD) and a C-terminal structural domain (CTD). cGAS harbors a DNA-binding domain and a catalytic structural domain within its CTD (amino acids 160–522).[16–18] cGAS can identify aberrant DNA within the cell, including exogenous viral DNA or mislocalized intracellular DNA. Upon detecting these abnormal DNAs, cGAS becomes activated and initiates the synthesis of a signaling molecule known as cGAMP.[19] Importantly, cGAS activation is initiated by abnormal DNA aggregation originating either from in vivo or in vitro sources, thereby indicating that the cGAS-STING system lacks pathogen specificity.[20] Furthermore, two primary factors are necessary for augmenting cGAS activity: the existence of a DNA-binding interface within its catalytic structural domain and the presence of a nucleic acid-binding domain (NTD, ie, amino acids 1–159).The function of the NTD is not limited solely to facilitating the formation of a liquid-phase condensate of cGAS with DNA but also encompasses the modulation of its cellular localization.[21,22] In the absence of DNA, the NTD directs the localization of cGAS to the cytoplasmic membrane through its interaction with phosphatidylinositol-4,5-bisphosphate (PI (4,5) P2), thereby impeding the activation of cGAS's own DNA.[23] Upon DNA binding, the NTD may dissociate from PI (4,5) P2, leading to the translocation of cGAS into the cytoplasm and nucleus.

In mammals, upon the binding of cGAS to double-stranded DNA (dsDNA), the active form of cGAS in the cytoplasm catalyzes the formation of 2'-3'-cGAMP from ATP and GTP. As a second messenger, 2'-3'-cGAMP binds to STING, thereby activating it.[24] cGAMP then interacts with an intracellular protein known as STING, a crucial component in the adaptive immune response. This interaction initiates a series of downstream signals, including the production of pro-inflammatory factors and the activation of immune cells.[25] Consequently, the synthesis of cGAMP is considered a pivotal initial step in initiating cGAS-mediated antiviral responses across various species.[26,27] STING is a 379-amino acid protein characterized by a structure predominantly comprised of a transmembrane domain (amino acids 1–137), a cyclic dinucleotide binding domain (amino acids 138–340), and a C-terminal tail (CTT, amino acids 341–379).[28] In its inactive state, STING is anchored to the endoplasmic reticulum (ER) membrane via its interaction with the strict interaction module 1 (STIM1).[29] Binding of cGAMP to STING induces the closure of its ligand-binding domain, leading to the dissociation of the STING CTT, aggregation of STING molecules, and their trafficking from the intermediate region of the ER to the Golgi complex (ERGIC) and then to the Golgi apparatus, this process relies on the Coat Protein Complex (COPII) and ADP ribosylation factor (ARF).[30–32] Within the Golgi, STING undergoes palmitoylation at the cysteine 88 and 91 residues, a modification that not only enhances its aggregation but also plays a pivotal role in recruiting TBK1 (TANK-binding kinase 1) and facilitating the interaction between TBK1 and IRF3.[33,34] The C-terminal region of STING harbors the PLPLRT/SD sequence, which is accountable for the recruitment and activation of TBK1. Subsequently, TBK1 phosphorylates STING, leading to the phosphorylation of the CTT of STING.[35,36] After STING activation, it needs to be retrogradely transported from the Golgi apparatus to the endoplasmic reticulum, a process that primarily depends on the Coat Protein Complex-I (COP-I).[37] This reverse transport is critical for regulating STING's signal transmission. Following this, the phosphorylated STING recruits IRF3, which has been phosphorylated by TBK1, leading to the dimerization of IRF3 and its subsequent nuclear transport.[38] Activated STING prompts the production of interferons and pro-inflammatory factors, including TNF-α, IL-6, among others, through the activation of transcription factors like IRF3 (interferon regulatory factor 3) and NF-κB. This production triggers an inflammatory response, mobilizing immune cells to eliminate infection and repair tissue damage.[39–41] Upon the termination of signaling, STING is translocated to lysosomes for degradation.[42] A diagram of the mechanism is shown in Figure 1.

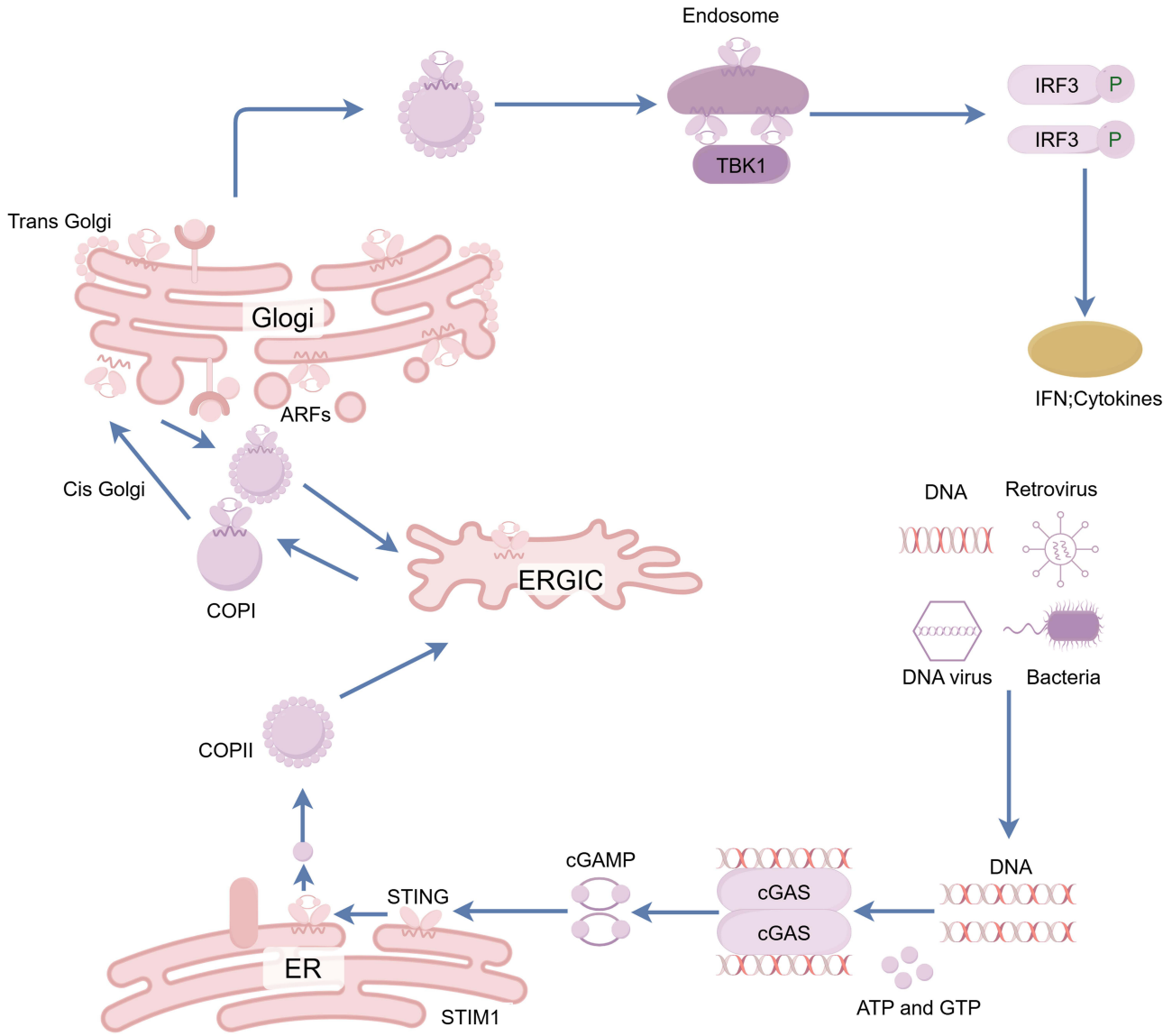

Figure 1 Schematic diagram of cGAS STING signaling pathway mechanism.
Notes: The cGAS-STING pathway is an intracellular signaling mechanism activated when cells recognize DNA (eg, from viruses, bacteria, or damaged cells). This DNA is recognized by the cytoplasmic enzyme cGAS and catalyzes the formation of the secondary messenger cGAMP. This messenger then activates the membrane protein STING, which initiates immune and inflammatory responses by inducing the expression of interferons and other inflammatory factors.
Abbreviations: COPI, Coat Protein Complex I; COPII, Coatomer Protein Complex II; STIM1, strict interaction module 1; MVB, Multivesicular Bodies; ARFs, ADP-ribosylation factors; TBK1, TANK-binding kinase 1.

Inflammatory and Immune Effects Triggered by Activation of the cGAS-STING Signaling Pathway in Sepsis

When cells are infected with bacteria, viruses, or encounter abnormal DNA, the cGAS-STING pathway becomes activated, initiating a sequence of responses to organize defense against pathogen invasion. These responses encompass immune reactions initiated by immune cells against pathogen invasion and aberrant intracellular DNA, alongside associated inflammatory and organism-wide immunoprotective mechanisms.[40] The cGAS-STING signaling pathway plays multiple roles in sepsis-induced inflammatory immunity, encompassing interferon activity, production of inflammatory mediators, disruption of inflammatory regulation, and activation of immune cells, among other functions.[43] A deeper understanding of the cGAS-STING signaling pathway's mechanism in sepsis can facilitate the development of

new therapeutic strategies to enhance the prognosis and therapeutic outcomes of sepsis. Below are the primary effects of cGAS-STING pathway activation.

Production of Interferons (IFNs)

The activation of the cGAS-STING pathway triggers the production of IFN-I, including interferon beta (IFN-β). Interferons represent a crucial class of cytokines that regulate the activation state of immune cells, inhibit viral replication and transmission, and boost the resistance of other immune cells against pathogens. In both human and mouse cells, the synthesis of antiviral IFN-I and related gene products represents the most prominent downstream effector function of cGAMP signaling, widely regarded as the pathway's primary component exerting antiviral functions.[44] The activation of IRF3(interferon regulatory factor 3) and its subsequent induction of IFN-I and other Interferon-stimulated genes (ISGs) constitute the most comprehensively understood process governed by the cGAS-STING pathway's activation.[45] Furthermore, IRF3 activity is also crucial for the induction of numerous other target genes, including those encoding inflammatory cytokines[46]. In the septic state, cGAS becomes activated when the host cell recognizes the pathogen's DNA, thereby activating STING, which then promotes IFN-I expression through the IRF3 pathway. Whereas the inhibition of the cGAS-STING pathway and the subsequent attenuation of IFN-I signaling can mitigate LPS-induced multiorgan functional impairment in a mouse model.[47,48]

Production of Inflammatory Factors

Besides interferon production, the activation of the cGAS-STING pathway also contributes to generating inflammatory mediators, including tumor necrosis TNF-αand IL-6[25]. Activation of the cGAS-STING pathway can initiate the activation of the NF-κB signaling pathway. Activated STING proteins can facilitate TBK1 activation and further phosphorylation of the IκB kinase complex (IKK) through interaction with TBK1. The phosphorylated IKK complex then releases NF-κB, previously inhibited by it, thereby permitting NF-κB to enter the nucleus and initiate transcription of inflammatory factor genes.[49,50] Beyond the NF-κB signaling pathway, activation of the cGAS-STING pathway additionally activates the IRF signaling pathway. This is achieved as activated STING proteins interact with TBK1, prompting TBK1 to phosphorylate IRF family members, including IRF3.[51] Furthermore, interferons generated via the activation of the cGAS-STING pathway activate downstream JAK kinases upon binding to their corresponding receptors. Activated JAK kinases phosphorylate STAT proteins (signal transducers and activators of transcription), enabling their dimerization and subsequent nuclear entry, thereby promoting the transcription of inflammatory factors.[52] These inflammatory mediators play critical roles in activating immune cells, eliciting inflammatory responses, and facilitating tissue repair processes, thereby regulating immune responses and anti-pathogen mechanisms. In sepsis, the cGAS-STING pathway can be activated by either cellular debris or pathogen DNA. This activation can induce a robust inflammatory response that aids in clearing the infection; however, an excessive inflammatory response may simultaneously result in tissue damage, thereby heightening the risk of lethality in sepsis.[53]

Activation and Enhancement of Immune Cells

The activation of the cGAS-STING pathway triggers both the activation and enhancement of immune cells, thereby strengthening the body's resistance against pathogens. Interferon production through this pathway activates the interferon receptor, subsequently activating the downstream JAK-STAT signaling pathway. These signals ultimately lead to the activation and functional enhancement of immune cells.[54] Activated immune cells, including macrophages, dendritic cells, and natural killer cells, participate in the pathogen clearance process by exerting cytotoxic effects and secreting immunomodulatory molecules.[25,55] Prior research has demonstrated that mitochondrial DNA(mt DNA) mediates immune paralysis of dendritic cells in sepsis through STING signaling, whereas the deletion of STING can reverse mtDNA-mediated DC immune paralysis and enhance the prognosis of endotoxemia and sepsis.[56] Macrophages play a pivotal role in the immune response to sepsis, and recent research has shown that deletion of Cgas attenuates sepsis-induced acute lung injury by facilitating the shift of macrophages from the M1 phenotype to the M2 phenotype.[57] Furthermore, evidence also indicates that STING may promote sepsis-induced multiorgan injury by triggering macrophage iron death in a cGAS- and interferon-independent manner.[58]

Regulation of Autophagy

Autophagy serves as an intracellular mechanism dedicated to the degradation and removal of abnormal proteins, harmful organelles, and pathogens. Activation of the cGAS-STING pathway has been implicated in the process of autophagy[59]. The activation of the cGAS-STING pathway can regulate and partake in the autophagy process via modulation of the mTOR signaling pathway, interaction with LC3-II, and promotion of autophagy-associated molecule expression.[43,60–62] This association underscores the cGAS-STING pathway's pivotal role in maintaining intracellular homeostasis, scavenging waste products, and regulating the immune response. Current research indicates that impaired cellular autophagy due to sepsis can lead to aberrant activation of STING signaling, resulting in an uncontrolled inflammatory storm and cell death.[63] Notably, autophagy is regulated not only by the STING signaling pathway but also influences the activity of this pathway. By limiting STING aggregation and activation, autophagy plays a crucial role in preventing excessive immune responses and inflammation.[64]

Organ Tissue Damage Caused by Activation of cGAS-STING Signaling Pathway in Sepsis

Research has demonstrated that the cGAS-STING signaling pathway plays a pivotal role in the onset and progression of sepsis. Upon pathogenic microbial infection causing intracellular DNA damage or RNA metabolism disruption, cGAS enzymes detect the abnormal DNA or RNA within the cell and activate the STING signaling pathway. Activation of this signaling pathway elicits an inflammatory response and stimulates immune cell activation to combat infection.[16,25] However, overactivation of the cGAS-STING signaling pathway can result in the excessive release of inflammatory mediators and subsequent tissue damage via the production of IFN-I and pro-inflammatory cytokines, significantly contributing to the exacerbation of sepsis.[39] In patients with sepsis, the pathophysiological processes triggered by this excessive inflammatory response and immune cell activation constitute major risk factors for multi-organ failure and death[3,18]. Additionally, some researchers have discovered that STING induces cell death by directly interacting with cytoplasmic nuclear receptor coactivator 4(NCOA4), thereby releasing free ferrous iron and leading to lipid peroxidation.[58]

Sepsis Thrombosis

Previous research has indicated that sepsis patients exhibit enhanced immune system activity, and activation of the STING signaling pathway initiates an inflammatory response along with coagulation abnormalities.[65,66] Zhang et al discovered that a TMEM173 (encoding STING)-dependent increase in cytoplasmic calcium ions prompted the division and activation of GSDMD (Gasdermin D, a effector protein that mediates cell pyroptosis by forming pores on the cell membrane), which in turn triggered the release of F3, a crucial promoter of blood coagulation. Inhibiting this pathway halted systemic coagulation and enhanced animal survival across three sepsis models (cecum ligation and puncture, or bacteremia with Escherichia coli or Streptococcus pneumoniae infections), suggesting the STING gene's pivotal role in regulating blood coagulation during lethal bacterial infections.[67] Additionally, researchers have observed that platelet STING associates with the secretion-associated protein STXBP2, maintaining the SNARE (Soluble NSF Attachment Protein Receptor, a type of protein primarily responsible for regulating the fusion of intracellular vesicles) complex's efficient assembly. cGAMP-induced palmitoylation of platelet STING further facilitates this assembly, resulting in an overproduction of platelet granules during infection. Subsequently, they developed a blocking peptide, C-ST5, targeting STING's potential binding site to STXBP2, demonstrating a significant reduction in thrombus formation in septic mice.[68] Furthermore, the platelet activation and related coagulation disorders resulting from STING activation may be mediated through the promotion of platelet-immune cell interactions.[69] It is noteworthy that sufficient clinical evidence supporting a direct association between STING and coagulation in sepsis is currently lacking. Further in-depth research in this domain is necessary to elucidate the specific mechanisms of STING in sepsis-related coagulation and to evaluate its potential clinical implications.

Acute Lung Injury in Sepsis

In cases of lung injury induced by pathogen stimulation, DNA fragments released from damaged lung tissue can activate the STING signaling pathway, thereby promoting the production and release of inflammatory cytokines and leading to

acute lung injury development.[70,71] Liu et al discovered that elevated levels of circulating mtDNA and STING activation are correlated with the severity of the disease in patients with SALI (Sepsis-Associated Lung Injury). These effects were markedly improved by STING knockdown in sepsis and mtDNA administration models.[72] Furthermore, researchers have identified that the cytoplasmic DNA-STING-NLRP3 axis plays a role in and contributes to the development of lipopolysaccharide-induced acute lung injury in septic mice.[73] Additionally, NETs in sepsis can induce endothelial cell injury by producing substantial amounts of tissue factor (TF) through STING activation, amplifying the dysregulation between inflammatory and coagulation responses, leading to a poor prognosis in SI-ALI (Sepsis-Induced Acute Lung Injury) mice.[69] Inhibiting the overactivation of the STING pathway effectively attenuated lung edema and inflammatory cell infiltration.[74]

Sepsis-Associated Encephalopathy (SAE)

Previous research has indicated that STING is closely linked to secondary neuroinflammation and blood-brain barrier disruption post-stroke, with inflammatory mediators such as TNF-α, IL-1β, and IL-6 being released in significant quantities during sepsis. This release can lead to neurotoxic responses that further disrupt the blood-brain barrier. Hyperactivation of the STING pathway may exacerbate this disruption and increase the infiltration of inflammatory factors into the brain tissue.[75,76] Excessive inflammatory responses and blood-brain barrier disruptions also serve as significant risk factors for the onset and progression of septic encephalopathy.[77,78] A recent study demonstrated that levels of the programmed death hub molecule STING were significantly increased in the hippocampal tissues of mice with septic encephalopathy. Knockdown of STING was shown to improve cognitive functions in these mice. Investigation into the trends of PERK, STING, and RIPK3 (serine/threonine protein kinase 3) in the hippocampal tissues of SAE mice revealed that STING may inhibit neuronal necrosis through the RIPK3 pathway, thereby potentially preventing neuronal necrotic apoptosis and enhancing cognitive function.[79] Currently, research on the cGAS-STING signaling pathway in septic encephalopathy development remains in its early stages, having only initially revealed the correlation between STING and septic encephalopathy. Further experimental and clinical studies are required to validate these relationships more comprehensively.

Sepsis Intestinal Mechanical Barrier Damage

Sepsis intestinal mechanical barrier damage is characterized by the disruption of the intestinal tract's mechanical barrier during sepsis, leading to increased intestinal mucosa permeability and an imbalance in the intestinal flora.[80,81] Previous research has indicated that the activation of the STING pathway plays a role in septic intestinal mechanical barrier damage, with the release of inflammatory mediators and cells leading to enhanced intestinal mucosal permeability and cellular gaps, potentially disrupting intestinal mechanical barrier functionality.[53,82] Furthermore, the STING pathway activation is implicated in regulating the intestinal immune response to bacterial infections and inflammation in the context of sepsis-related intestinal mechanical barrier damage.[46] Additionally, some studies suggest that STING pathway activation might influence septic enteric mechanical barrier injury by modulating the stability of the intestinal flora.[83] Erttmann SF et al discovered that the intestinal flora activates the cGAS-STING signaling pathway in the organism's cytoplasm, maintaining basal systemic IFN-I production levels, as shown through a series of innate immune pathway-deficient mouse models and in vitro cell culture experiments, combined with 16S rDNA and high-throughput transcriptome sequencing. This bacterial flora-induced cGAS-STING-IFN-I activation is mediated not by cell surface-localized Toll-like receptor (TLR) signaling or direct host-bacteria interactions, but through bacterial-derived membrane vesicles. These vesicles deliver bacterial DNA to distal host cells and facilitate DNA and RNA virus clearance in a cGAS-dependent manner, enhancing host resistance to systemic viral infections.[84] These studies elucidate the relationship between STING pathway activation and mechanical barrier damage in the septic gut, detailing its effects on inflammatory responses and bacterial population stability. This knowledge may aid in developing new therapeutic strategies to enhance the prognosis of patients with septic gut injuries.

Sepsis-Induced Acute Liver Injury

Sepsis-induced acute liver injury represents a pathological condition characterized by abnormal or impaired liver function due to sepsis, typically resulting from severe bacterial infections.[85] During sepsis, the body releases numerous inflammatory mediators, including cytokines, which can directly or indirectly damage liver cells, leading to impaired liver function.[86] Recent studies suggest that in sepsis-related acute liver injury, STING signaling pathway activation is linked to an intensified inflammatory response and liver injury development. STING activation enhances IFN-I and inflammatory cytokine production, activating the liver's innate immune cells. This cascade of cytokine and immune cell activation may result in hepatic inflammation and cellular damage.[47] Furthermore, aberrant activation of the STING signaling pathway can contribute to hepatocellular necrosis, hepatic fibrosis, and impaired liver function. Interfering with STING pathway activation may attenuate the inflammatory response, mitigate hepatic injury, and facilitate recovery.[87] However, further research, particularly prospective clinical studies, is required to fully understand the STING signaling pathway's role in sepsis-induced acute liver injury and to develop effective therapeutic strategies or identify potential drug targets.

Current Status of Research on Inhibitors Associated with the cGAS-STING Signaling Pathway in Sepsis

Hyperactivation of the cGAS-STING signaling pathway is crucial in the pathogenesis and progression of sepsis; therefore, inhibiting this pathway's activity could attenuate the inflammatory response, halt disease progression, and enhance patient prognosis.[43] A variety of drugs and molecular tools designed to inhibit the cGAS-STING signaling pathway have been developed and explored for sepsis treatment. These inhibitors work by either directly targeting two key molecules, cGAS and STING, or disrupting signaling by inhibiting downstream molecules,[3,50,88–90] demonstrating significant outcomes like attenuating the inflammatory response and reducing organ damage in animal models. For detailed information, refer to Table 1.

Furthermore, inhibitors targeting the cGAS-STING signaling pathway hold potential for improving sepsis prognosis, given the pathway's multifaceted roles within the organism. Inhibiting this pathway can affect immune function and disease resistance, necessitating careful determination of the inhibitor's optimal dosage and treatment duration to balance immune modulation with pathogen clearance. However, it is important to note that most therapeutic strategies targeting the cGAS-STING pathway remain in the research phase and have not yet seen widespread clinical application. More clinical observations and prospective studies are required to validate these approaches and assess their safety and efficacy. Thus, the primary approach to sepsis treatment remains early anti-infective therapy, supportive care, and organ support, with treatment plans tailored to each patient's unique circumstances and guided by medical expertise.

Table 1 Potential Therapeutic Drugs Targeting the cGAS STING Signaling Pathway in Sepsis

Literature	Year	Inhibitor	Drug Target	Model	Drug Effects
Li et al[46]	2022	RU.521/H-151	CGAS/STING	Mice	Reduce acute liver injury in sepsis
Yang et al[67]	2023	C-ST5	STING	Mice	Reduce thrombosis in sepsis
Zhu et al[68]	2023	H-151	STING	Mice	Reduce acute lung injury and thrombosis in sepsis
Wu et al[69]	2022	C-167/H-151	STING	Mice	Reduce acute lung injury
He et al[73]	2023	Ursodeoxycholic acid	STING	Mice	Reduce acute lung injury
Molly Kobritz et al[81]	2023	H-151	STING	Mice	Reduce acute intestinal injury in sepsis
Yu et al[86]	2023	Hederagenin	STING	Mice	Reduce acute liver injury in sepsis
Chen et al[88]	2023	Gelsevirine	STING	Mice	Reduce multi organ damage and inflammatory response
Liu et al[89]	2023	Alda-1	Mtdna	Mice / H9C2 cells	Reduce acute cardiac injury in sepsis

Notes: RU.521, a small molecule compound specialized to inhibit cGAMP synthase; H-151, a potent STING inhibitor; C-ST5, a synthetic peptide; C-167, a furan derivative that is also a potent STING inhibitor; UDCA, rsodeoxycholic acid; Hederagenin, a natural compound extracted from ivy; Gelsevirine, an alkaloid extracted from natural plants.

Conclusion

In summary, the cGAS-STING signaling pathway demonstrates significant potential application value in treating sepsis. Firstly, as an innovative immunotherapy pathway, it can bolster the body's infection resistance by regulating its activation, heralding new breakthroughs in sepsis treatment. Secondly, as a focal point for inflammation regulation, a deeper understanding of the cGAS-STING pathway's inflammation regulation mechanisms could unveil new targets for developing more precise anti-inflammatory therapies. Moreover, the pathway's involvement in immune memory regulation offers potential value for the long-term recovery of sepsis patients. This enables the development of individualized therapeutic strategies, facilitating more precise and effective treatments through targeted modulation of the cGAS-STING pathway. Finally, in-depth studies on the pathway's activation and inflammatory regulation could lead to the discovery of new clinical markers, enhancing early sepsis diagnosis and monitoring. Research in these domains will offer theoretical support for sepsis treatment and precision medicine, promising substantial improvements in future clinical practices.

Acknowledgment

Figure support was provided by Figdraw.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This review was supported by grant 82271238 from the National Natural Science Foundation of China.

Disclosure

The authors report no conflicts of interest in this work.

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