cGAS–STING pathway in ischemia-reperfusion injury: a potential target to improve transplantation outcomes

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Transplantation is an important life-saving therapeutic choice for patients with organ or tissue failure once all other treatment options are exhausted. However, most allografts become damaged over an extended period, and post-transplantation survival is limited. Ischemia reperfusion injury (IRI) tends to be associated with a poor prognosis; resultant severe primary graft dysfunction is the main cause of transplant failure. Targeting the cGAS–STING pathway has recently been shown to be an effective approach for improving transplantation outcomes, when activated or inhibited cGAS–STING pathway, IRI can be alleviated by regulating inflammatory response and programmed cell death. Thus, continuing efforts to develop selective agonists and antagonists may bring great hopes to post-transplant patient. In this mini-review, we reviewed the role of the cGAS–STING pathway in transplantation, and summarized the crosstalk between this pathway and inflammatory response and programmed cell death during IRI, aiming to provide novel insights into the development of therapies to improve patient outcome after transplantation.

KEYWORDS

allografts, cGAS-STING, ischemia-reperfusion injury, programmed cell death, transplantation, inflammation

1 Introduction

The innate immune response mediated by the cyclic guanosine monophosphate-adenosine monophosphate (cGAMP) synthase-stimulator of interferon (IFN) genes (cGAS–STING) pathway has long been the front-line defense against pathogens, such as bacteria, parasites, DNA viruses, or retroviruses (1, 2). However, owing to the sequence-

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Abbreviations: IRI, Ischemia-reperfusion injury; cGAS-STING, cyclic guanosine monophosphate-adenosine monophosphate synthase-stimulator of interferon genes; cGAMP, cyclic guanosine monophosphate-adenosine monophosphate; cGAS, cyclic GMP-AMP synthase; IFN, interferon; dsDNA, double-stranded DNA; STING, synthase-stimulator of interferon genes; PCD, programmed cell death; ER, endoplasmic reticulum; IRF3, IFN regulatory factor 3; TBK1, TANK-binding kinase 1; SAVI, STING-associated vasculopathy with onset in infancy; EC, endothelial cell.

independent identification of double-stranded DNA (dsDNA), relevant research on the cGAS–STING pathway has indicated that cellular function extends beyond resisting the invasion of foreign pathogens, and unnecessary activation by accidental sensing of self-derived DNA or mutations can lead to autoinflammatory diseases (3). For example, STING-associated vasculopathy with onset in infancy (SAVI) commonly develops in patients with gain-of-function mutations in TMEM173 (4, 5). Aicardi-Goutières syndrome mainly presents with an aberrant generation of type I IFN, and accumulation of DNA damage may be an important driver of STING-related inflammatory responses (6, 7).

During organ acquisition, preservation, and transplantation, ischemia-reperfusion injury (IRI) exacerbates damage to donor graft tissues when blood flow is restored after a certain ischemic time. A deficient arterial blood supply invariably leads to a redox imbalance and creates a hypoxic environment in donor graft tissues. Surgical blood reperfusion can lead to severe oxidative damage and an inflammatory response following reoxygenation. This series of events aggravates allograft injury and may lead to primary graft dysfunction, which is associated with high mortality and morbidity (8, 9). The cellular and molecular events that occur during IRI are complex and involve innate immune system activation and programmed cell death (PCD) (10, 11). However, their interplay is still not clearly understood. In the context of limited treatment options, it is urgent to develop less toxic and higher specificity immunosuppressors to better control graft rejection and avoid mortality related to their toxicity (12).

In the present review, we offer an overview of the cGAS–STING pathway and highlight its role in patients who have undergone transplantation. We then summarize the pharmacological basis for targeting the cGAS–STING pathway for treating IRI to explore potential treatment approaches for IRI following transplantation.

2 Overview of the cGAS–STING pathway

Cyclic GMP-AMP synthase (cGAS) serves as a novel cytosolic DNA sensor that stimulates IFN production by binding to abnormal DNA within the cytoplasm and activates STING, this activation then triggers host innate immunity in response to "danger signals" (13, 14). The overview of the cGAS–STING signaling pathway is illustrated in Figure 1. The binding of abnormally accumulated dsDNA to cGAS in the cytoplasm greatly induces a phase transition, during which cGAS is activated. Recognition is independent of a specific sequence (15–18). Owing to the dsDNA-induced oligomerization of cGAS, a dimerized cGAS–dsDNA complex is catalytically formed (19–21). Activated cGAS promotes conformational changes in the catalytic pocket that allow the cyclization of GTP and ATP as substrates for conversion into cGAMP as a second messenger (22, 23).

Important sources of DNA within the cytoplasm include damage-associated DNA released from nuclear and mitochondrial leakage, as well as exogenous pathogen-associated DNA resulting from microbial infection (24, 25). Compared with bacterial cyclic dinucleotides, dsDNA-activated cGAS contains a linear 2'-5'-linked dinucleotide between GMP and AMP that effectively activates human STING (26, 27). Furthermore, higher DNA-binding valences and longer-packed DNA structures facilitate cGAMP production and innate immune signaling (15). Via gap junctions, receptor-based transport, and membrane fusion approaches, activated cGAS can trigger cGAMP transfer from original cells to bystander cells as additional routes to induce downstream signaling cascades (28, 29), which is illustrated in Figure 2. Regarding canonical cGAS–STING signaling, cGAMP is produced as an agonist for STING, and its binding to STING located in the endoplasmic reticulum (ER) induces a 180° rotation for ligand
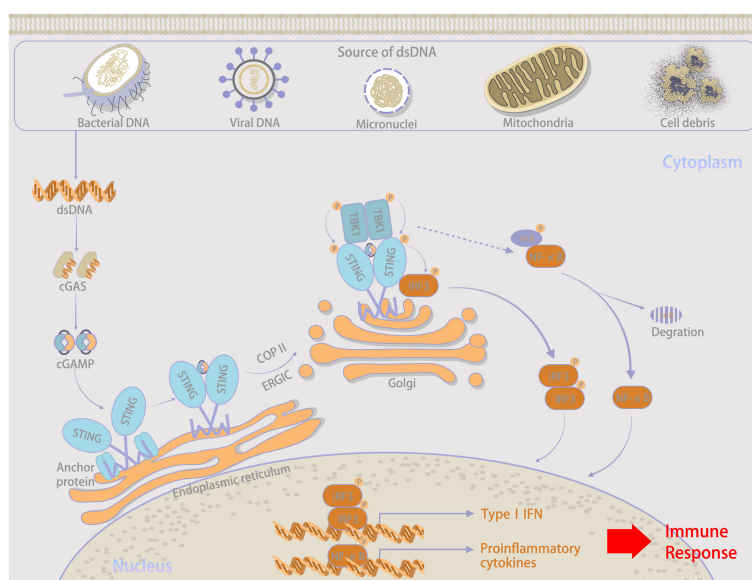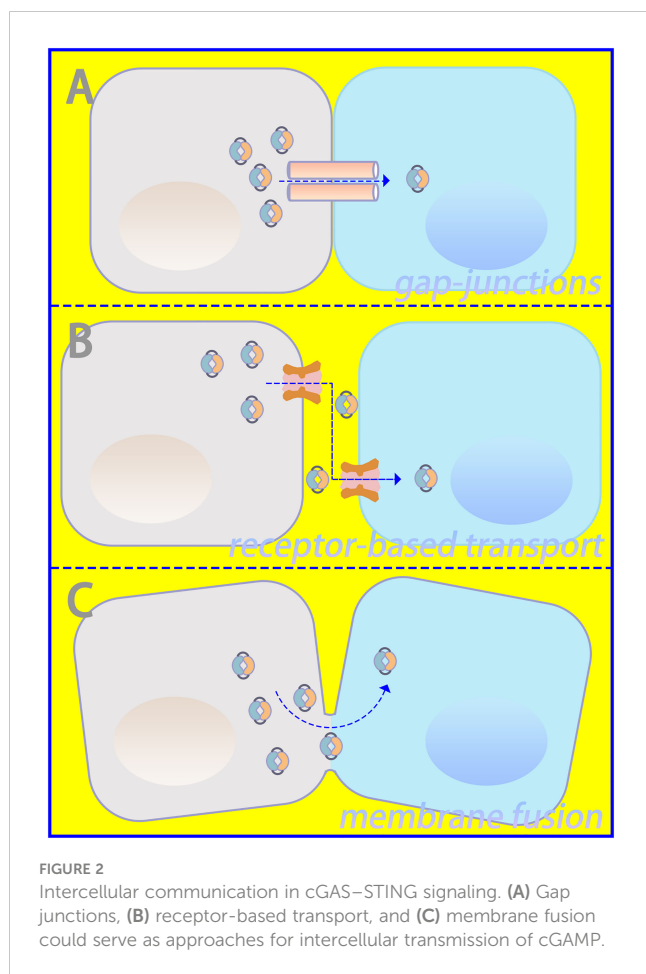

FIGURE 1
Overall explanations about the cGAS–STIBG signaling pathway.

FIGURE 2
Intercellular communication in cGAS−STING signaling. **(A)** Gap junctions, **(B)** receptor-based transport, and **(C)** membrane fusion could serve as approaches for intercellular transmission of cGAMP.

binding with the transmembrane domain as a reference, which unlocks the right-handed cross−over connections.

Therefore, during the rearrangement of the STING dimer, the ligand-binding pocket is closed. This important conformational transition enables the oligomerization and release of STING from anchoring proteins, which are further translocated by integrating with cytoplasmic coat protein II complex vesicles (30–32). Cytoplasmic coat protein I-mediated retrograde membrane trafficking is also significant for STING activation (33, 34). Under the assistance of ADP-ribosylation factor GTPases and cytoplasmic coat protein II, higher-order complex STING is transferred from the ER through the ER-Golgi intermediate compartment to the Golgi apparatus. There, STING and the transcription factor IFN regulatory factor 3 (IRF3) are phosphorylated by recruited TANK-binding kinase 1 (TBK1), and nuclear factor κB is activated simultaneously (35–38). Phosphorylated IRF3 further oligomerizes and migrates into the nucleus with nuclear factor κB, and both synergistically initiate the expression of type I IFN and inflammatory cytokines, contributing to the innate immune response (39, 40).

3 cGAS−STING pathway and transplantation outcomes

Few studies have tried to elucidate the role of the cGAS–STING pathway in transplantation models. Some preclinical and clinical

studies have demonstrated STING as an effectiveness therapeutic target for graft-versus-host disease following allogeneic hematopoietic stem cell transplantation (41). However, research on solid organ transplantation is still in its infancy, and thus more attention should be paid to this field.

The traditional Chinese herbal medicine ingredient ginsenoside Rb3 could alleviate oxidative stress caused by ischemia-reperfusion damage (42, 43). Li et al. used ginsenoside Rb3 to suppress adhesion molecule expression in endothelial cells (ECs) and improve microcirculation of murine transplanted skin flaps. They confirmed that the protective effect of IRI resulted from the inhibition of STING–IRF3 signaling (44). Besides, Yang et al. demonstrated that tumor necrosis factor-α-induced protein-8 like 2 (TIPE2), a negative immunoregulator for immune homeostasis, showed a positive correlation with apoptosis and TIPE2 expression in the graft, which might activate ferroptosis-mediated transplant rejection. TIPE2$^{-/-}$ mice that had undergone heart transplantation experienced insufficient IFN-γ production through the TBK1 signaling axis and increased expression of glutathione peroxidase 4 compared with wild-type mice. Mechanistically, TIPE2 deficiency may inhibit IFN-γ generation in T cells by suppressing the TBK1 signaling axis, prevent lipid peroxidation, and relieve ferroptotic cell death in an injured allograft (45, 46). Mesenchymal stromal cell therapy combined with low-dose tacrolimus is a feasible and safe therapeutic regimen (47, 48). Surprisingly, Chen et al. revealed that combination treatment using low-dose tacrolimus (FK506) and mesenchymal stem cells is beneficial to graft survival, possibly due to weakened graft inflammation by suppressing IFN-γ production and TBK1/IRF3 phosphorylation (49). The generation of STING-deficient mice through gene deletion is more conducive to improving our understanding of the cGAS–STING pathway and its importance in transplantation, and clinical trials are urgently needed.

SAVI is an autoinflammatory disease arising from gain-of-function mutations in the *STING 1* gene from abnormal encoding, leading to the overproduction of type I IFN (5). Three patients diagnosed with SAVI who underwent solid organ transplantation have been reported. The first patient was a 1-year-old infant with SAVI who underwent liver transplantation and immunosuppressive therapy but developed severe multiple biliary cysts and cholangitis in the transplanted liver at the age of 3. Intensive tacrolimus, hydroxychloroquine, prednisolone, and mycophenolate mofetil were administered; however, the patient experienced fatal gastrointestinal bleeding 1 year later (50). The second patient was a 34-year-old woman with SAVI who underwent double-lung transplantation but experienced acute primary graft dysfunction, with acute liver and systemic vasculature complications; she finally died from multiple organ failure (51). The last patient was a 17-year-old girl with SAVI who underwent lung transplantation and developed systemic inflammatory symptoms within 4 months; she was treated with three immunosuppressors, including mycophenolate mofetil, tacrolimus, and prednisolone; however, her symptoms relapsed during prednisolone dose reduction (52). Despite reporting on individual cases, these studies indicated that the abnormal activation of STING in patients receiving transplantation

probably led to extremely poor outcomes, even when immunosuppressive therapy was administered. Although the relationship between SAVI and the cGAS–STING pathway is not yet clear, inhibiting STING may be beneficial for improving the outcome of transplant recipients. However, research into this area is still lacking and is considered an important area for future studies.

4 Crosstalk between cGAS–STING pathway and IRI

4.1 IRI: an important player in allograft injury

IRI is a major transplant issue, mostly because there is still no effective treatment plan. Recently, it has been demonstrated that targeting the cGAS–STING pathway may be a feasible approach to improve transplantation outcomes by alleviating IRI. In general, the inflammatory response and PCD following ischemia and reperfusion play vital roles in triggering transplant rejection (53, 54). Both transplantation and non-transplantation models of IRI share these key pathogenic mechanisms to increase the incidence rate and mortality, and the cGAS–STING pathway participates in their regulation (2, 55). This suggests a possible relation between post-transplant IRI and the cGAS–STING pathway. Therefore, we have summarized the regulatory mechanisms of the cGAS–STING pathway in IRI in Figure 3; Table 1, providing new insights for the development of new treatment strategies. Besides, we extracted potential therapeutic agents for treating IRI that may help improve transplant prognosis.

4.2 Inflammatory response in IRI

Although it is yet to be fully explored, it would not be surprising to find that the inflammatory response of post-transplant IRI can be triggered by cGAS–STING pathway. Damage-associated molecular patterns (DAMPs) induced by injury are recognized by cGAS, which trigger immune-mediated inflammation. In general, targeting cGAS–STING pathway may help reduce the inflammatory response in transplantation models.

Increased cytosolic DNA can be recognized by the pathogen recognition receptor cGAS and trigger STING activation-induced inflammation, especially for mitochondrial DNA (mtDNA). Elevated mtDNA accumulation caused by IRI is related to delayed graft function (24, 79, 80). Phosphoglycerate mutase 5-mediated Bax dephosphorylation triggers mtDNA release, activating the cGAS–STING pathway and causing acute kidney injury following IRI (56). Furthermore, kidney IRI increases receptor-interacting protein 3 levels to facilitate mtDNA damage and leakage and then activates the cGAS–STING–p65 pathway by promoting cytosolic mtDNA expression and increases the transcription of pro-inflammatory factors (57). In contrast, mixed lineage kinase domain like (MLKL) pseudokinase knockout significantly enhances PTEN-induced kinase 1-mediated mitophagy activation to alleviate oxidative stress in hepatocytes,

thereby inhibiting macrophage cGAS–STING activation and liver IRI (58). These make mtDNA an important target for inhibiting cGAS–STING pathway activation. In addition, a flap endonuclease I inhibitor has been shown to inhibit mtDNA fragment release and cGAS–STING pathway activation (81), which should be further verified in transplantation models. Notably, IRI, especially for apoptosis, is often associated with mitochondrial damage and mtDNA release, shaping a positive feedback circuit (82, 83). Thus, combination therapy for inhibiting cGAS–STING signaling and concurrent mtDNA fragment release may have a synergistic effect. Nowadays, some preclinical studies have made progress. STING inhibitor H-515 can prevent extracellular cold-inducible RNA-binding protein, a potent DAMP, from activating STING and causing intestinal and distant organ injuries (59). Moreover, by transcriptionally upregulating cGAS expression, histone deacetylase 3 (HDAC3) activates the cGAS–STING pathway in a p65-dependent manner; tissue inflammation and injury are triggered; accordingly, HDAC3 inhibitors, such as trichostatin A and MS275, can reverse this detrimental effect (60). Post-translational modifications of cGAS play critical roles in regulating its activity and stability (84, 85), and thus regulation of cGAS expression and function may be another intervention approach.

Recently increasing attention on macrophage-mediated innate immunity as a crucial player in allograft injury (86). Editing macrophage effector function may be an adjuvant therapy to alleviate inflammation. At present, most studies on the regulation of macrophages mediated by the cGAS-STING pathway have set liver IRI as the main research object. Aged mice are more susceptible to aggravated hepatic injury following ischemia-reperfusion, and stronger NLRP3 activation and pro-inflammatory activity of macrophages. Probably because aged parenchyma cells have more extracellular DNA than younger ones, which triggers a stronger STING/TBK1 signaling in macrophages. Consistent with previous studies, older donors are associated with reduced recipient and graft survival rates (61, 87, 88). Knockout of STING in Myelocyte can reduce liver IRI and inflammatory response, indicating that STING activation may promote the proinflammatory response of Monocyte derived macrophages in liver transplantation (62). In addition, Kupffer cells act as tissue-resident macrophages in the liver, playing an important role in in liver IRI as well, but the effect of cGAS-STING pathway toward it is still not clear. However, the promotion of microglial cell M1 polarization can be attenuated by the STING inhibitor C-176 during IRI-induced mtDNA release (63).

It is well known that T cell-mediated immune response is closely related to post-transplant IRI, which is an important factor affecting transplantation prognosis. The cGAS-STING pathway activates adaptive T cell responses by regulating dendritic cells and macrophages (64). By using cGAS-deficient donor tissue, the activation of CD8$^+$ T cells in the graft and the proportion of effector memory lymphocytes in the spleen were reduced, and the graft survival was significantly prolonged, this provided a basis for immunosuppressive therapy targeting T cells (65). In addition, the induction of transplantation tolerance depends on the presence of Treg. Surprisingly, activation of the cGAS-STING pathway can induce an increase in the production of
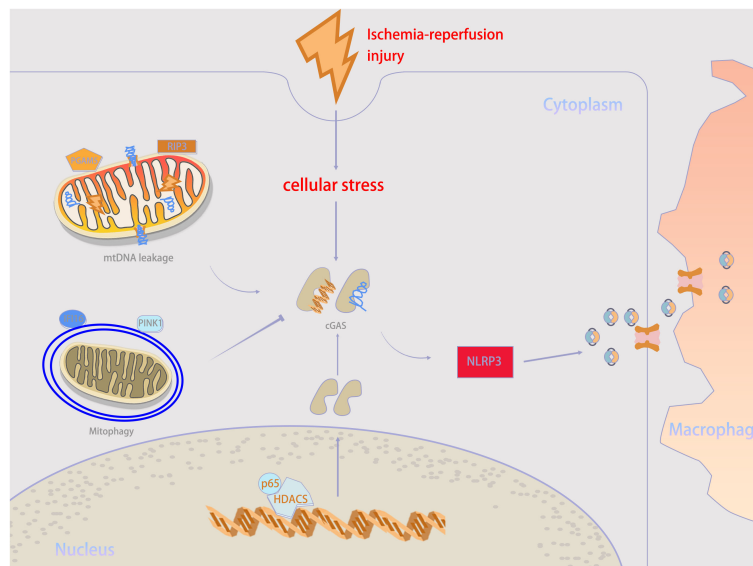
FIGURE 3

Mechanisms underlying cGAS−STING activity in ischemia−reperfusion injury (IRI) condition. When IRI happens, self-DNA recognition is the primary determinant for cGAS−STING activity. mtDNA leakage, which is executed by RIP3 and PGAM5, is an important source of cGAS stimulation during IRI. But mitophagy mediated by PINK1 and IFI16 help to counteract mtDNA stress. Besides, HDAC3 can upregulate cGAS expression. cGAMP can be transmitted from parenchymal cells to neighboring macrophages through intercellular transmission to activate immune response. PGAM5, phosphoglycerate mutase family member 5; RIP3, receptor-interacting protein 3; IFI16, interferon gamma-inducible protein 16; PINK1, PTEN-induced kinase 1; NLRP3, NOD-like receptor protein 3.

TABLE 1 cGAS-STING pathway-based regulation involved in IRI-related mechanism.

Mechanism	Signaling axis/ Trigger	Involved cell/ organelle	Regulation description	Impact on IRI	Ref.
Innate immunity-mediated inflammatory response	PGAM5-Mitofilin-cGAS-STING	Mitochondria	Promote DAMP sensing	Proinflammatory	(56)
	RIP3–Mitofilin-cGAS-STING-p65	Mitochondria	Promote DAMP sensing	Proinflammatory	(57)
	PINK1-cGAS-STING	Macrophage	Promote PINK1-induced mitophagy to suppress STING-mediated inflammatory	Anti-inflammatory	(58)
	eCIRP-STING	Macrophage	Promote DAMP sensing	Proinflammatory	(59)
	HDAC3-p65-cGAS-STING	Microglial cell	Promote DAMP sensing	Proinflammatory	(60)
	STING-NLRP3	Macrophage	Upregulate NLRP3	Proinflammatory	(61)
	STING-TBK1/AMPK	Macrophage	Upregulate AMPK Downregulate HIF-1α	Anti-inflammatory	(62)
	mtDNA-STING	Microglial cell	Promote DAMP sensing	Proinflammatory	(63)
	dsDNA-cGAS-STING	T cells	Promote DAMP sensing	Proinflammatory	(64)
	IFI16-STING-NF-κB	Mitochondria	Promote mitophagy, EC activation	Anti-inflammatory	(65)
	cGAS-STING-ERS	Lung epithelial type II cell	Promote ERS	Proinflammatory	(66)
	TXNIP-NRF2-OASL1-STING/TBK1	Macrophage	Upregulate OASL1 to promote STING-mediated TBK1 activation	Proinflammatory	(67)
	STING-AMPK	Unavailable	Upregulate AMPK	Anti-inflammatory	(68)
		BMDM	Promote lipid peroxidation	Proinflammatory	(69)

(Continued)

TABLE 1   Continued

Mechanism	Signaling axis/Trigger	Involved cell/organelle	Regulation description	Impact on IRI	Ref.
	STING-mediated lipid peroxidation				
Programmed cell death	cGAS-STING-Bcl−2/Bax/Caspase−3	Cardiomyocyte	Activate Bcl−2/Bax/Caspase−3	Anti-apoptosis	(70)
	miR-24-3p-STING-IRF3	Hepatocyte	Upregulate miR-24-3p to downregulate STING	Anti-apoptosis	(71)
	cGAS-STING-NCOA4	Neuron	Upregulate NCOA4	Pro-ferritinophagy	(72)
	PI3K-PKB-cGAS-STING	Neuron	Activate PI3K-PKB pathway to suppress cGAS-STING-mediated over autophagy	Pro-autophagic cell death	(73)
	25-HC-mTOR/STING	Neuron	Downregulate mTOR/STING to suppress STING-mediated over autophagy	Anti-autophagic cell death	(74)
	cGAS-mediated regulation of autophagy	Hepatocyte	Regulate autophagy	Anti-autophagic cell death	(75)
	TBK1-FMR1	Renal tubular epithelial cells	Upregulate FMR1	Anti-ferroptosis	(76)
	mtDNA-STING-IFN/TNF-α	Intestinal endothelial cell	Upregulate IFN, TNF-α	Pro-necroptosis	(77)
	STING-calcium-dependent caspase 1-GSDMD	Macrophage	Upregulate calcium-dependent caspase 1-GSDMD	Pro-pyroptosis	(78)

BMDM, bone marrow derived macrophage; STING, stimulator of interferon genes; TBK1, TANK-binding kinase 1; TXNIP, thioredoxin-interacting protein; HIF-1α, hypoxia-inducible factor-1 alpha; AMPK, AMP-activated protein kinase; NLRP3, nucleotide-binding domain and leucine-rich repeat containing protein 3; eCIRP, extracellular cold-inducible RNA-binding protein; DAMP, damage-associated molecular pattern; IFI16, interferon gamma- inducible factor 16; EC, endothelial cell; cGAS, cyclic GMP–AMP synthase; ERS, endoplasmic reticulum stress; 25-HC, 25-Hydroxycholesterol; IRI, ischemia-reperfusion injury.

regulatory cytokine IL-10 and promote the inhibitory activity of Treg. Therefore, damage to grafts caused by T-cell-mediated adaptive immunity triggered by the cGAS-STING pathway may be the result of immune imbalance (89). Interestingly, although it has been speculated that STING gain-of-function mutations cause disease through abnormal type I interferon signaling, another study suggests that T cell-mediated adaptive immunity may be the main pathogenic factor, but more researches are needed to confirm it (90).

ECs form the primary barrier between the host and solid organ allografts and are essential for inducing cell-mediated acute rejection following transplantation (91). Mitochondrial exposure may upregulate EC adhesion molecules and enhance inflammatory responses by activating ECs (92). Mitochondrial transplant was able to reduce the risk of primary graft dysfunction in lung transplant recipients during ex-vivo lung perfusion (93). Mitochondrial transplantation therapy has shown promise as a therapy in clinical practice, but there is still a lack of research on the underlying molecular mechanisms. A recent study suggested that exposing murine heart ECs to exogenous mitochondria triggers internalized mitochondria-activated IFI16–STING–NF-κB signaling. Subsequently, STING-dependent mitophagy stabilized the endothelium and weakened apoptotic activity, and activated ECs promoted T-cell-mediated co-stimulation blockade-resistant rejection (94); the cGAS–STING pathway possibly plays a significant role in this.

Communication between the ER and mitochondria bridges ER stress and activates the innate immune system (66). Inhibition of the cGAS–STING pathway suppresses ER stress, thereby attenuating lung IRI (95). Surprisingly, ER stress-induced NLRP3 inflammasome activation is possibly a pivotal driver during post-transplant IRI (67). Moreover, the macrophage TXNIP-mediated CYLD-NRF2-OASL1 axis possesses a regulatory effect, and TXNIP disruption suppresses STING-mediated TBK1 activation and subsequent inflammation (96). However, these regulatory effects on macrophages should be further verified in transplantation models.

The cGAS–STING pathway is also involved in controlling energy metabolism. Activated cGAS–STING signaling is accompanied by systemic and cellular metabolism abnormality, involving increased nutrient metabolism and decreased mitochondrial respiration (68). In adipocytes, TBK1 attenuates AMP-activated protein kinase (AMPK) activation to increase energy reserves but inhibits respiration, and promotion of tissue inflammation can be observed in adipocyte-specific TBK1 knockout models (97). Surprisingly, by activating AMPK signaling, the STING inhibitor C-176 improves intestinal IRI-induced acute lung injury (98). Notably, metabolic disorders are often accompanied with intensive mitochondrial damage (69). This indicates the need to determine whether modulation of cGAS–STING pathway-induced metabolism is beneficial to inflammation regulation.

4.3 Programmed cell death in IRI

The cGAS–STING pathway participates in a variety of cell death pathways, including pyroptosis, ferroptosis, necroptosis, apoptosis, and autophagy, but without obvious specificity. During IRI following transplantation, multiple types of PCD may coexist. The cGAS–STING pathway serves as a target to provide further insight into their relation.

A strong STING signaling is associated with apoptosis induction (99, 100). Scutellarin plays a protective role in IRI through downregulation of the NLRP3 inflammasome, and it inhibits Bcl−2/Bax/Caspase−3 and the cGAS–STING pathway to ameliorate graft dysfunction and apoptosis (101, 102). STING antagonists can probably be used in combination with it in transplant models. Additionally, the *in vitro* upregulation of miR-24-3p relieves cardiomyocyte apoptosis following IRI (71). This protective effect may be due to the targeting of STING by miR-24-3p to salvage the STING–IRF3 activation-mediated inflammatory response and cellular apoptosis (103). Currently, there is a lack of non-invasive biomarkers in clinical practice that can be used to predict transplant prognosis (72). Although significant miRNAs in tissues are hardly as useful as non-invasive biomarkers, they can be used to inspire later research on biological fluids. More studies are necessary to discover the correlation between miRNAs and transplantation prognosis.

Recent studies have indicated that autophagy is involved in IRI regulation. Direct regulation of autophagy alleviates IRI following transplantation (104). Ferritinophagy is a type of autophagy that targets ferritin to maintain balanced intracellular iron levels. NCOA4-mediated ferritinophagy plays a vital role in IRI, and suppression of the cGAS–STING pathway can diminish ferritinophagy, thus ameliorating IRI (105). Activin A, a well-known neuroprotective factor, is also involved in IRI alleviation through inhibition of cGAS/STING-mediated autophagic cell death (73). 25-hydroxycholesterol is an oxidized cholesterol associated with the pathophysiological pathways of cholesterol homeostasis, immune response, or cell survival, it alleviates IRI by inhibiting STING and excessive autophagy-induced cell death (74, 106). Combinations of these agents with STING antagonists may probably help to lower doses of immunosuppressive drugs and reduce toxicity. Interestingly, cGAS-mediated autophagy has been shown to relieve liver IRI, with this novel protective effect being independent of STING (75). The cGAS–STING pathway participates in the regulation of autophagic cell death in a bidirectional manner. These conflicting results may be related to the existence of multiple noncanonical cascades (76). Thus, future studies should aim to validate the precise mechanism involved in selective activation and understand whether it is equally applicable to other pathogenic process.

Ferroptosis is triggered under conditions of excessive oxidative stress, such as IRI (107, 108). Ferroptotic cell death contributes to inflammatory responses following transplantation (109). Mechanistically, this PCD is induced by activation of the cGAS–STING pathway via lipid peroxidation, this damage can be reversed by the anti-lipid peroxidation drug liproxstatin-1 (110). Surprisingly, lipid peroxidation induced by cellular stress also specifically weakens the STING pathway (70). Thus, more accurate experiments are required to explain their relationship. Additionally, Ubiquitin-specific protease 7 inhibition could reverse ferroptosis-induced IRI, probably because of the suppression of TBK1 degradation and DNA methyltransferase 1 (DNMT1)-mediated methylation of FMRP translational regulator 1 (77, 111).

Both pyroptosis and necroptosis are inflammatory forms of cell death (112, 113). The cGAS–STING–IFN pathway is responsible for maintaining mixed lineage kinase domain-like pseudokinase (MLKL) expression, which is a key component for initiating necroptosis (114). Interestingly, mtDNA released from ECs during intestinal IRI activates the STING pathway and triggers necroptosis through collaborative IFN and tumor necrosis factor-α signaling (115). The cGAS–STING–NLRP3 axis has been demonstrated to be the default mode of inflammatory body activation and pyroptosis. STING activation induces lysosomal cell death and triggers the classic mode of NLRP3 activation (78). STING deficiency in macrophages can inhibit pyroptosis and the subsequent intense inflammatory response during liver IRI; this protective effect is probably due to reduced calcium-dependent caspase 1-GSDMD processing in macrophages (116). However, these results need to be confirmed and complemented in transplantation models.

5 Outlook and future perspective

At present, immunosuppressors effectively control transplant rejection; however, considerable issues, such as opportunistic infections, higher occurrence of malignancy, and drug toxicity, have been linked to their use. Compared to immunosuppressor, the breadth of the cGAS-STING pathway in inflammation and PCD is its most powerful advantage, so it has the potential to serve as a multifunctional therapeutic target. Because the mechanism of IRI after transplantation is very complex, single immunosuppressor is limited and combinations are required to achieve the desired therapeutic effect. Superimposed drug toxicity inevitably deteriorates the prognosis. Among them, the most serious side effect of Immunosuppressive drug in transplantation is the severe infection caused by the excessively low immunity of the body (117). The activation of the cGAS-STING pathway has a highly collaborative characteristic, and partial rather than complete blockade seems sufficient to produce anti-inflammatory effects, and proper activity of the cGAS-STING pathway is allowed under obvious infection conditions. Therefore, it is feasible to retain necessary ability of anti-infection while achieve anti-inflammatory, and achieving this balance can help improve prognosis. In order to achieve this balance, a key aspect in the future is to better understand the minimum level of inhibition required for therapeutic benefits. In addition, personalized treatment is the biggest problem faced by the clinical application of immunosuppressors. A lot of efforts are being made to develop small molecule inhibitors targeting the cGAS-STING pathway, and precise treatment based on this pathway may become an important component of future clinical organ transplantation (118).

6 Conclusion

IRI is currently a serious complication after transplantation, mainly because there is still no effective therapy to manage it. Attempting to utilize the cGAS–STING pathway as a potential target can provide new insights and help develop treatment approaches for post-transplant IRI. So far, many drugs targeting the cGAS–STING pathway have played therapeutic roles in IRI based on the mechanisms of inflammation and PCD. The next step may include further analysis of the results of these agents in transplantation models and exploring more convincing evidence to elucidate their clinical translation value. In addition, the detailed molecular mechanism of the cGAS–STING pathway is not yet clear, and preventing unexpected and adverse cascade reactions are also issues that need to be addressed.

Author contributions

Conception and design: ZC and WH. Administrative support: WH. Collection and assembly of data: ZC, YL, and ZL. Data analysis and interpretation: ZC and YL. Drafting the article or revising it critically for important intellectual content: All authors. Final approval of manuscript: All authors. Accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: All authors.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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