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REVIEW

The Activation of cGAS-STING in Acute Kidney Injury

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Abstract: The activation of the cGAS-STING pathway is associated with many sterile inflammatory and inflammatory conditions, including acute kidney injury. As a cytoplasmic DNA sensor, sensitization of the cGAS-STING pathway can ignite the innate immune response in vivo and trigger a series of biological effects. In recent years, there is increasing evidence showing that the cGAS-STING pathway plays a vital role in acute kidney injury, a non-inflammatory disease induced by activation of innate immune cells, and closely related to intracellular reactive oxygen species, mitochondrial DNA, and the cGAS-STING pathway. This review provides a prospect of the cGAS-STING pathway and its relationship to acute kidney injury.

Keywords: mitochondrial DNA, innate immunity, reactive oxygen species, mitochondrial dysfunction, acute kidney injury

Introduction

AKI, which is characterised by necroinflammation due to damage and necrosis of the kidney's intrinsic cells,[1] is a common clinical syndrome, occurring in 10–15% of hospitalized patients, whereas in the ICU this percentage is as high as 50%.[2] The development of AKI is involved in the production of reactive oxygen species (ROS), mitochondrial dysfunction and cytoplasmic leakage of mitochondrial DNA, which further activates the cGAS-STING pathway, an innate immune defence soldier, and prompts a series of inflammatory responses in the organism.[3–5] In recent years, researches on acute kidney injury has focused heavily on cGAS-STING, which complements our understanding of the pathophysiological mechanisms of acute kidney injury and provides new directions for its therapy. Expanding researches have shown that this route is tightly linked to mitochondrial malfunction, ROS, and mtDNA, which are common pathologic mechanism for AKI. In terms of the role of cGAS-STING pathway in AKI, we also summarize the mitochondrial dysfunction involving ROS and mtDNA release in this review.

Mitochondrial Dysfunction

Mitochondria are the energy-producing organelles in cells and are pivotal to AKI. Mitochondrial dysfunction occurs throughout AKI, here we firstly reviewed the mitochondrial ROS, mtDNA, and its mtDNA cytoplasmic leakage.

ROS

The kidneys are prominent in maintaining homeostasis of the human body, depending on their busy ion transport and consumption of large amounts of ATP. Ninety percent of the kidneys' ATP is supplied through aerobic oxidation, and any disruption of the balance of renal oxygen supply and demand will increase the risk of AKI.[6] Under physiological situation, small amounts of intracellular ROS, such as superoxide anion, mediate host defence responses and transduction function to maintain normal physiological states.[7,8] ROS, which are mainly produced by mitochondria and endoplasmic

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reticulum,[8,9] at high concentrations are toxic to mitochondria and cells.[8] The imbalance in oxygen supply and the increased production of ROS in the kidney due to endogenous and exogenous stress not only damage respiratory proteases and mtDNA.[3–5] Excessive ROS leads to breaks in mitochondrial DNA (mtDNA), which encodes subunits containing defective protein subunits and further impairs the production of ATP and ROS[10,11]. According to researches, ROS has been linked to AKI for a variety of reasons, including massive ROS causing mitochondrial stress and cytochrome C release, which will trigger cell apoptosis, promoting renal apoptosis and inflammation, stimulate cGAS-STING signaling pathway and ultimately resulting in the progression of AKI and renal inflammation.[8,10,12–17] More importantly, ROS production rises may both contribute to and result from AKI.[15,18,19]

mtDNA

Mitochondrial DNA (mtDNA) is a double-stranded circular DNA independent of nuclear DNA, compared to nuclear DNA, MtDNA is more vulnerable to damages from oxidative stress, which may be explained by (1) the positioning of mtDNA close to the ROS-producing electron transport chain and the absence of protective histones.[20,21] (2) mtDNA lacks enzyme system for DNA repair.[17] MtDNA leakage and mitochondrial dysfunction were found in ischemia-reperfusion injury, sepsis-induced AKI and cisplatin-induced AKI.[16,19,22–25] The resulting released cellular debris and circulating mtDNA are potent inflammatory molecules that stimulate innate and adaptive immune responses. In addition, disruption of mitochondrial transcription factor A (TFAM) may lead to mitochondrial energy deficiency and mtDNA cytoplasmic release, cytokine and chemokine release and the activation of immune cells cGAS-STING pathway and NF-κB.[3,5,11,12,16,19,23,26–33] Blood and urine mtDNA levels were shown to be higher in patients with various kinds of AKI, suggesting that they could be utilized as a marker for clinical evaluation of AKI and its prognosis.[34,35] In AKI, mitochondria mediate STING activation,[9,16] which may be due to mtDNA release, implying that mitochondria are directly associated with the STING pathway and are involved in the development of AKI pathogenesis.

Mechanisms of mtDNA Release

Normally, mtDNA is stable in the mitochondrial matrix in the form of a nucleoid structure with TFAM.[36] Following are some potential mechanisms by which mtDNA may be released into the cytoplasm in AKI, shown in Figure 1.

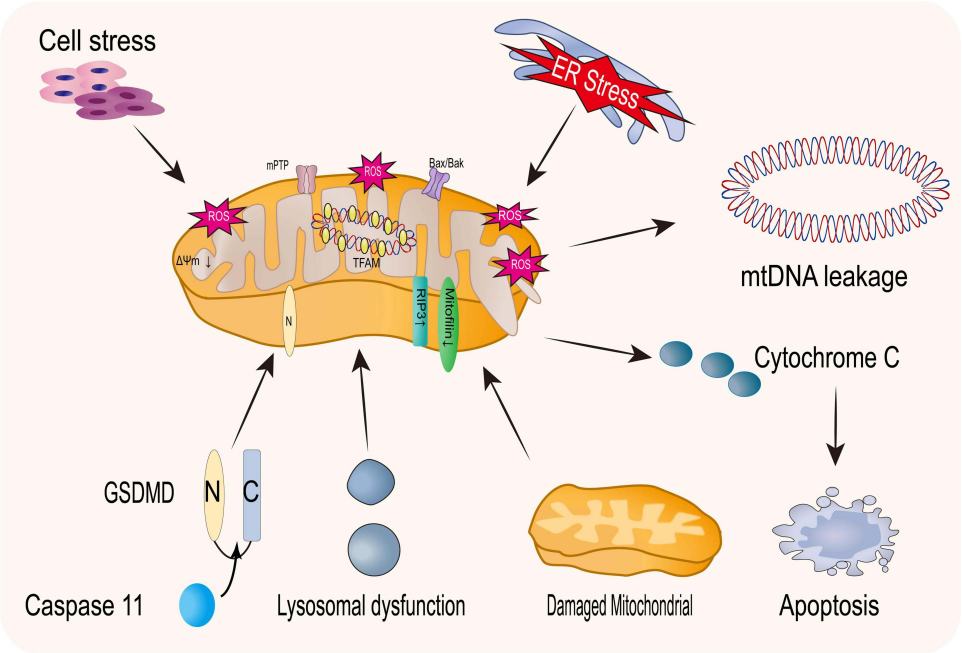

Figure 1 Mechanisms of mtDNA leakage. Conditions such as mitochondrial damage, endoplasmic reticulum stress, and lysosomal dysfunction, will increase the production of ROS, decrease mitochondrial membrane potential, and open Bax/Bak macropores and mitochondrial permeability transition pores, resulting in the release of mitochondrial DNA into the cytoplasm. Meanwhile, cytochrome C is transported from the mitochondria to the cytoplasm, which causes apoptosis.

MtDNA leakage through BAX-mediated macropore. BAX overexpression is found in cisplatin-induced acute kidney injury.[25] BAI1, an inhibitor of BAX, can decrease the amount of mtDNA in the cytoplasm.[16,27] When cells receive the apoptosis signal, the opening of the Bax/Bak pore facilitates the mitochondrial outer membrane permeability and releasing of cytochrome C into the cytoplasm, initiating caspase cascade and promoting apoptosis.[37] Moreover, this also establishes the extrusion of the mitochondrial inner membrane into the cytoplasm and further elicits mitochondrial inner membrane permeabilization and delivery of mtDNA into the cytoplasm.[28]

Mitochondrial permeability transition pore (mPTP) induces the transmission of mtDNA into cytosol in a VDAC1-dependent manner.[11,29] Nevertheless, it has also been illustrated that mtDNA exocytosis does not require the opening of mPTP.[27] These inconsistent results suggest that more research is needed to elucidate the role of mPTP in mtDNA leakage.

Gasdermin D (Gsdmd) provokes mitochondrial membrane pore formation to prompt the mitigation of mtDNA.[5] Under cellular stress, Gasdermin D is activated and cleaved by Caspase-11 to form GSDMD-NT, which translocates to the mitochondrial membrane, generating pores in the mitochondrial membrane and fostering the effluence of mtDNA and evoking cGAS-STING. It also causes the exacerbation of the production of mitochondrial ROS and loss of mitochondrial membrane potential, further promoting mtDNA leakage.[5]

In ischemia-reperfusion kidney injury, receptor-interacting protein kinase 3 (RIP3)—which was found to co-localize with Mitofilin in mitochondria. Overexpression of RIP3 in vitro engendered the leakage of mtDNA into the cytoplasm and a reduction in mitochondrial membrane potential and an accumulation in ROS, which was alleviated by RIP3 knockdown.[30] It is hypothesized that stimulation of RIP3, a protein capable of activating necroptosis pathway-related proteins, may be involved in the cytoplasmic leakage mtDNA, boosting an inflammatory cascade response.

Others: Mitochondrial defects or improper clearance of impaired mitochondria, defective lysosomal function, and endoplasmic reticulum stress can all instigate mtDNA leakage.[31,38,39] This may be due to organelle interactions, mitochondrial dysfunction and the opening of the mitochondrial permeability transition pore (mPTP) leading to mtDNA cytoplasmic release under stressful conditions.[11]

MtDNA leaks into the cytoplasm and is recognized by the body as an endogenous pathogen, which stimulates the cGAS and elicits an immune response in the body to yield aseptic inflammation.[40,41] The cGAS-STING pathway is basically designed to detect and limit the propagation of exogenous DNA.[42] Endogenous DNA produced by the host itself as well as bacterial and viral infections can activate cGAS to trigger an intrinsic immune response.[28,43,44] Mitochondrial dysfunction and mtDNA leakage caused by AKI can activate the intracellular cGAS-STING pathway.[28] The cGAS-STING pathway transmits signals in three main phases after activation: sensing of double-stranded DNA (dsDNA) of cGAS, intracellular signalling and activation of the immune response, which will be discussed below.

Activation of cGAS-STING Pathway

cGAS Sensing of dsDNA

Human cGAS (cyclic GMP-AMP synthase, hcGAS) is encoded by the CGAS gene located at 6q13 and contains 522 amino acids. The protein is expressed in the nucleus, cytoplasm and cell membrane,[28] which contains an N-terminal structural domain, a nucleotidyl transferase (NTase) and a Mab21 structural domain (C-terminus),[45] with two positively charged DNA binding sites (A-site and B-site) in juxtaposition to the phosphoribose backbone of DNA. Binding of negatively charged DNA to the A site induces conformational changes in the protein, forming enzymatically catalyzed pockets with the substrates ATP and GTP, and these conformational changes enhance the efficiency of its binding to dsDNA.[46] In contrast, binding to the B site outlines the cGAS-DNA complex.[47] The cGAS recognises endogenous and exogenous double-stranded DNA, neutrophil traps,[31,48] as well as DNA:RNA hybrids and further synthesizes cGAMP.[49] However, neither single-stranded RNA nor DNA can effectively activate cGAS. When the length of free dsDNA in the cytoplasm is greater than 16 bp, cGAS dimerizes and forms a cGAS-dsDNA complex containing two cGAS molecules and two dsDNA molecules,[50] using ATP and GTP to generate the second messenger cyclic guanosine monophosphate–adenosine monophosphate (cyclic GMP-AMP, cGAMP). DNA length is too short to activate cGAS in human cells even

at high concentrations.[51,52] It can be seen that cGAS recognizes dsDNA in a length-dependent manner,[53] regardless of sequence or concentration.

Intracellular Signal Transduction

STING (stimulator of interferon genes, STING) is a transmembrane protein localized to the endoplasmic reticulum, consisting of a short cytoplasmic segment N-terminal, a four-transmembrane structural domain, a linker region and a C-terminal tail (CTT) attached to the ligand-binding domain (LBD).[47] The human STING, encoded by the STING1 gene (also known as TMEM173; NET23; STING), located at 5q31, comprises 379 amino acids. STING is normally present in the cytoplasm in an inactive, dimer state. When cGAMP is bound in the ligand-binding pocket of STING, the ligand-binding structural domain is rotated 180° relative to the transmembrane structural domain, then STING is activated[54] and TANK-binding kinase 1 (TBK1) is recruited to phosphorylate its C-terminal tail to form the STING-TBK1 complex. Depending on cytoplasmic coat protein complex II (COP-II) and ADP-ribosylation factor (ARF), GTPases are shifted from the endoplasmic reticulum to the ER-Golgi intermediate compartment (ERGIC). In spite of that, TBK1 phosphorylates interferon regulatory factor 3 (IRF3), facilitating its translocation to the nucleus. Besides, it also recruits IκB kinase (IKK), which phosphorylates IκB, an inhibitor of the transcription factor nuclear factor kappa-B (NF-κB), leading to translocation of NF-κB to the nucleus.[55,56] Figure 2 shows how cGAS-STING pathway is activated in cells.

Activation of the Immune Response

Activated IRF3 and NF-κB translocate from the cytoplasm to the nucleus and regulate the transcription of type I interferon-β (IFNβ), the expression of interferon-stimulated gene (ISG), tumour necrosis factor and chemokines.[55] The cGAS and STING that complete the transport task are ubiquitinated and packaged into autophagosomes mediated by E3-ubiquitin ligases, which are digested in autophagic lysosomes and degraded to prevent overactivation of the pathway and cause autoimmune diseases.[17]

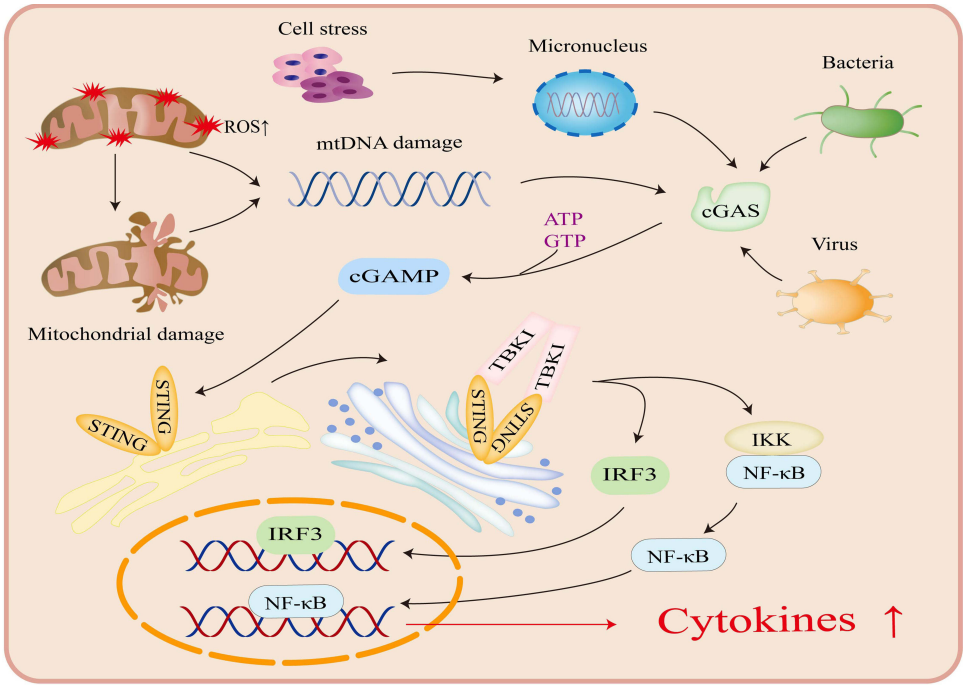

Figure 2 Activation of cGAS-STING pathway. CGAS detects exogenous and endogenous DNA, with ATP and GTP to form the second messenger cyclic GMP-AMP (cyclic GMP-AMP, cGAMP). STING recognizes cGAMP and undergoes a conformational change before translocating to the Golgi via the ER-Golgi intermediate compartment. In spite of that, it will recruit TANK-binding kinase 1, which will further phosphorylates interferon regulatory factor 3 (IRF3), facilitating its translocation to the nucleus. Besides, it also recruits IκB kinase (IKK), which phosphorylates IκB, resulting in translocation of NF-κB to the nucleus and promotes the release of cytokines.

cGAS-STING Pathway and AKI

The interconnection between cGAS-STING pathway and AKI is generally studied in relation to cisplatin nephrotoxicity, ischemia-reperfusion kidney injury, and sepsis-induced AKI. Cisplatin causes renal damage through mechanisms such as ROS accumulation, mitochondrial dysfunction, and apoptosis.[57] Researchers had found that mitochondrial DNA leakage and cGAS-STING pathway activation in cisplatin-induced kidney injury models so are sepsis-associated AKI.[16,19,24,33,58,59] Fucoidan-ferulic acid nanoparticles, baicalein, and the antioxidant myricetin can inhibit mitochondrial damage and activation of cGAS-STING pathway and improve cisplatin-induced renal injury and protect against acute kidney injury.[19,60,61] In one study, application of transgenic techniques to knock out mitochondrial transcription factor A (TFAM) in renal tubular cells was found to activate the cGAS-STING pathway, and mice with STING knockout or application of STING inhibitor C176 showed a significant reduction in cytokine levels and inflammatory cell markers, further improving renal fibrosis and chronic kidney disease.[12] Table 1

Table 1 Summary of Studies on AKI Associated with cGAS-STING Pathway

Author	Year of Publication	Animal Model/Disease	Cell lines	Potential Therapy
Wang et al[4]	2012	Cecal ligation and puncture (CLP) model of sepsis in mice	/	MnTMPyP
Tsuji et al[63]	2016	Cecal ligation and puncture (CLP) mice model of sepsis in mice	/	/
Visitchanakun et al[33]	2021	Cecal ligation and puncture (CLP) mice model and LPS injection mice	BMDM	cGAS deficiency (cGAS-/-)
Li et al[58]	2023	Ischemia/reperfusion (I/R)–induced AKI mouse model; Cisplatin-induced AKI mouse model	MTECs	PGAM5-deficiency (PGAM5-/-) and cGAS-deficiency (cGAS-/-)
Maekawa et al[16]	2019	Cisplatin-induced AKI model in mice	HK-2	STING KOs, C-176, siRNA knockdown cGAS or STING, EtBr
Gong et al[14]	2021	Cisplatin-induced AKI model in mice; Patients undergoing cisplatin chemotherapy	/	H151
Feng et al[30]	2022	Kidney injury after renal ischemia–reperfusion	HK-2	siRNA knockdown RIP3
Zhao et al[3]	2021	Kidney injury after renal ischemia–reperfusion	HK2, Raw 264.7	Mito-Tempo, siRNA knockdown TFAM
Liu et al[61]	2022	Cisplatin-induced AKI model in mice	HK-2	Baicalein-loaded silk fibroin peptide nanofibers
Qi et al[19]	2023	Cisplatin-Induced AKI model in mice	HK-2	Myricetin-loaded nanomicelles
Gao et al[60]	2022	Cisplatin-induced AKI mice model	HK-2	Fucoidan-proanthocyanidins nanoparticles
Gao et al[64]	2023	Cisplatin-induced AKI mice model	HK2	Fucoidan-proanthocyanidins nanoparticles
Liu et al[65]	2023	Cisplatin-induced AKI mice model	HK2	Silk fibroin peptide self-assembled nanofibers
Lu et al[66]	2023	Cisplatin-induced AKI mice model	/	Flavonoid derivative DMXAA
Qi et al[67]	2023	Cisplatin-induced AKI mice model	HKC-8	Yi-Shen-Xie-Zhuo formula
Luo et al[68]	2022	Cisplatin-induced AKI mice model	HK-2	β-Hydroxybutyrate

summarises studies on AKI associated with cGAS-STING pathway. The above researches demonstrate that the cGAS-STING pathway plays an important role in AKI, and inhibition of the stir of this pathway may be a target for future AKI therapy. Otherwise, STING activation has been shown to be associated with the progression of glomerular disease and proteinuria, and the application of STING agonists can exacerbate podocyte and glomerular injury; conversely, the application of STING inhibitors can dramatically mitigate this injury.[62]

In conclusion, increased ROS production, mtDNA release, mitochondrial dysfunction, and activation of the cGAS-STING pathway are common pathophysiological mechanisms in diverse types of AKI. The exact mechanism is still unknown, but it may be related to the fact that STING controls the cell cycle and stabilizes chromosome structure.[69] However, treatment with these above-mentioned drugs did not completely reverse cisplatin-induced kidney injury, and more studies are needed in the future to develop new medications for acute kidney injury.

Future Perspectives and Potential Therapy

AKI is an aseptic inflammatory response induced by the body against its own cellular components. During this process, mtDNA is released and the resulting immune and inflammatory responses can interact to trigger the release of pro-inflammatory factors, which can further exacerbate the inflammatory response, creating a vicious cycle that aggravates the progression of AKI. MtDNA depletion by using EtBr can alleviate the activation of STING and reduce the inflammatory response.[25] STING is responsible for mtDNA-induced renal inflammation and fibrosis, which can be reduced by the STING inhibitor H151 and C-176[12,14,32] or STING KO.[25] Inhibition of cGAS and STING alleviates sepsis-associated AKI,[24] and cGAS defects either.[33] Additionally, the pathways through which mtDNA can be identified in the cytoplasm are cGAS-STING, inflammasome (AIM2 or NLRP3) and TLR9,[20,30,31,70] and the interaction of these pathways may also contribute to the development of AKI.

In the course of AKI treatment, it is imperative to clarify cause, but its potential similar pathogenesis may indicate that antioxidant treatment, mitochondrial DNA consumption and inhibition of the activated STING pathway are the prospective directions of AKI therapy. In addition, mitochondrial DNA activates the cGAS-STING pathway and can act as a marker for AKI.[34] Mitochondrial DNA consumption can hinder cGAS-STING pathway.[11] Targeted Gasdermin

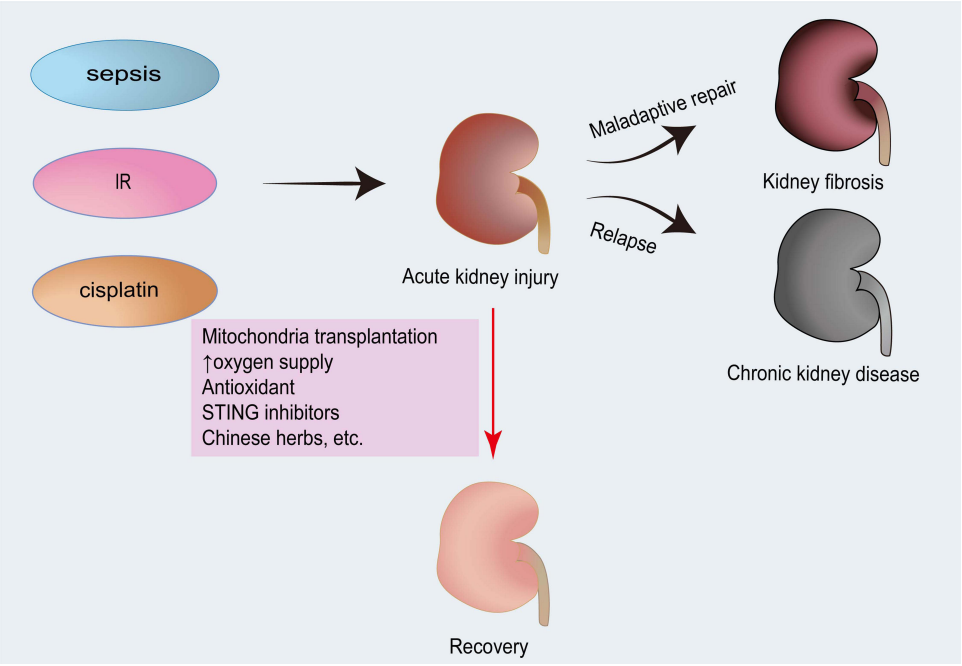

Figure 3 Potential treatment for AKI. Maladaptive repair can lead to kidney fibrosis, while relapse can cause CKD in the course of AKI. Several possible means such as antioxidants, STING inhibitors may be used as a promising therapeutic measure in the future.
Abbreviation: IR, Ischemia-reperfusion.

D and mtDNA-related pathways are also potentially applied to the regimen of AKI.[5,70] Antioxidants may lower DNA damage by decreasing ROS levels. Mounting the oxygen supply of the kidneys and improving the oxygen distribution of the nephron may be an effective remedy for AKI.[6] Figure 3 lists possible treatments for acute kidney injury.

The mtDNA-cGAS-STING pathway is strongly associated with some renal diseases and some therapeutic agents, such as levocarnitine and sacubitril/valsartan, attenuate the inflammatory response activated by mtDNA leakage by inhibiting inflammation-related pathways such as TLR9 and cGAS-STING signaling pathways.[71,72] Extracellular vesicles (EVs) derived from mesenchymal stem cells (MSCs) contain functional mitochondrial components such as mtDNA, mitochondrial proteins, and energy-related proteins from the tricarboxylic acid cycle.[73,74] MSC-EV-mediated TFAM mRNA transfer restores TFAM expression, mtDNA deletion, and OXPHOS defects in AKI renal tubular cells.[74] Hence, possible future development of extracellular vesicles containing functional mitochondria for patients with AKI may be a better choice. Recent studies propose that mitochondrial transplantation may be a novel therapeutic approach for mitochondrial diseases. Direct exogenous supplementation of mitochondria can replace damaged mtDNA, restore mitochondrial function, and inhibit oxidative stress, thereby reducing apoptosis.[75,76] Also, mitochondrial replacement therapy can be used for maternally inherited diseases caused by mtDNA mutations.[77] How to restrict mtDNA release and block this pathway may be an essential management for future medical research. Furthermore, some nanomaterial-coated herbal extracts and natural products can contribute to the treatment of renal injury, which also offers a new approach to treating AKI.[19,61]

Conclusions

The innate defense pathway cGAS-STING is indispensable in the ongoing process and remedy of AKI but has not been reported in obstructive nephropathy yet, which hints that future studies are needed to examine the function of the cGAS-STING pathway in AKI in greater detail. Additionally, similar results had been reported in diabetic nephropathy, chronic kidney disease, renal fibrosis, autoimmune nephropathy, and other renal diseases,[42] suggesting that the spur of the cGAS-STING pathway is a common pathophysiological process in both acute and chronic inflammatory diseases. The development of related drugs to block the activation of the cGAS-STING pathway may be a significant future.

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.

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Disclosure

All authors declare no conflicts of interest in this work.

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