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REVIEW

Advances in cGAS-STING Signaling in Fibrosis Diseases: Therapeutic Target in Pathological Scars

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Abstract: Fibrosis is characterised by an excessive response to tissue injury during wound healing, resulting in excessive scarring, which can affect any organ and lead to deformity or death. Fibrogenesis is a highly orchestrated process in which extracellular matrix deposition becomes unstructured, disrupting normal tissue architecture and subsequently impairing proper organ function through complex molecular signals and cellular responses. Inflammation is an important trigger for both regeneration and fibrosis after tissue damage—particularly due to inflammatory cytokines released by various recruited and activated immune cells—which can provoke an excessive inflammatory response in a short time. The cyclic GMP-AMP synthase (cGAS)–stimulator of interferon genes (STING) pathway has emerged as a key mediator of inflammation in the context of infection, cellular stress, tissue damage, and fibrosis. This reflects its capacity to sense and regulate cellular responses to ubiquitous danger-associated molecular patterns, mainly microbial or host-derived DNA. The cGAS–STING pathway plays a pivotal role in the development and progression of fibrotic diseases by linking cellular stress and DNA damage to chronic inflammation and fibroblast activation, thereby driving pathological tissue remodeling and extracellular matrix accumulation. However, a systematic summary of cGAS–STING in fibrotic diseases is lacking. Therefore, this review focuses on the effects and molecular mechanisms of cGAS–STING signalling in fibrotic diseases. We outline the principal elements of the cGAS–STING signalling cascade and discuss the mechanisms underlying the association of cGAS–STING activity with fibrosis in different organs. Finally, we elucidate the recently developed cGAS and STING antagonists and summarise their potential clinical applications in fibrotic diseases.

Keywords: fibrosis, inflammation, cGAS-STING, fibroblast, extracellular matrix

Introduction

Fibrosis, or tissue scarring, refers to the irreversible progression of fibrogenesis, which occurs in multiple organs—such as the liver, lungs, kidneys, heart, skin, or central nervous system—and leads to their dysfunction.[1,2] The dominant pathology of organ fibrosis is featured by increased fibrous connective tissue and decreased parenchymal cells in organs.[3] Organ fibrosis is a major contributor to global morbidity and mortality, accounting for approximately 45% or more of deaths in developed societies.[4] However, due to the unclear cellular and molecular mechanisms that regulate fibrosis, effective antifibrotic targets and therapeutic interventions remain scarce.

Insights into the fibrotic tissue environment have deepened our understanding of the progression and resolution of fibrogenesis, in which immune cells, inflammasomes, inflammatory cytokines, and intracellular signaling pathways play pivotal roles.[5–7] The innate immune system provides the first line of defense against tissue injury and plays a pivotal role in the initiation of fibrosis, while the adaptive immune system contributes to the chronicity and specificity of the fibrotic response—particularly in autoimmune-associated fibrosis. In essence, innate immunity initiates and orchestrates the fibrotic response, whereas adaptive immunity sustains and refines its progression.[8–10] The interplay between the innate and adaptive immune systems is crucial in

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determining whether tissue injury resolves or progresses to chronic fibrosis. Therefore, understanding this immunological balance opens new avenues for immunomodulatory therapies that target fibrosis at various stages.

The stimulator of interferon genes (STING), discovered by Glen N. Barber's team in 2008, is a crucial mediator that engages in innate immunity, inflammation and infectious diseases.[11,12] Cyclic GMP-AMP synthase (cGAS), positioned upstream of STING, detects pathogens and aberrant DNA, producing cyclic GMP-AMP (cGAMP) as a secondary messenger that activates STING. This activation leads to the phosphorylation of downstream molecules such as interferon regulatory factor 3 (IRF3), TANK-binding kinase 1 (TBK1), and nuclear factor kappa B (NF-κB).[13] Activation of the cGAS–STING pathway triggers the production of type I interferons (IFN-I) and proinflammatory cytokines, such as interleukin-1β (IL-1β), IL-6, and tumor necrosis factor-α (TNF-α), thereby enhancing the immune response.[13,14]

Beyond infectious diseases, an increasing number of studies have shown that cGAS–STING signaling is also involved in autoimmune, cancerous, fibrotic, and aging-related neurodegenerative diseases.[15] For example, the excessive inflammation response induced by aberrant activation of cGAS-STING resulted in fibrotic pulmonary diseases.[16] Moreover, a variety of natural extractives, such as licorice extract and naringenin, have demonstrated potential immunoregulatory effects by inhibiting the cGAS–STING pathway, thereby preventing liver inflammation and fibrogenesis.[17,18] In addition, a non-canonical cGAS-STING signaling, cGAS-STING-PERK-eukaryotic initiation factor 2α (eIF2α) pathway, was shown to participate in lung and kidney fibrosis.[19] Notably, cGAS–STING-mediated inflammation plays a critical role in organ fibrosis. Therefore, with the discovery of inhibitors targeting the cGAS–STING pathway, inflammation and fibrosis driven by this signaling cascade could be significantly ameliorated.

This review is devoted to detailing the molecular and cellular mechanisms of cGAS–STING signaling across various organ fibrotic diseases. Furthermore, a comprehensive compilation of cGAS–STING-related antagonists applied in fibrotic diseases is presented. We also discuss relevant challenges and offer our perspectives on directions for future research.

Overview of cGAS-STING Signaling

The cGAS–STING pathway is a crucial mediator that regulates inflammation in response to infections, cellular stress, and tissue injury. Insights into the structure, molecular components, activation mechanisms, and crosstalk of cGAS–STING signaling are highly significant for the development of targeted therapeutics for human inflammatory diseases.

Structural and Molecular Biology of the cGAS-STING Signaling

The cGAS–STING signaling pathway is primarily composed of cGAS, cGAMP, and STING. Discovered by Zhijian J. Chen's team in 2013, cGAS functions as both a sensor and receptor of DNA. It was initially thought to be a cytosolic protein that remains inactive under physiological conditions.[20] In 2019, Jonathan C. Kagan et al first demonstrated that inactive cGAS is localized at the plasma membrane through the function of an N-terminal phosphoinositide-binding domain, which prevents unwanted activation by avoiding recognition of small amounts of DNA scattered in the cytoplasm.[21]

Upon invasion by external pathogens or internal cellular damage, microbial and host-derived DNAs are often exposed. When extraneous or autologous DNAs appear outside the nucleus or specific organelles like mitochondria, cGAS catalytic activity is triggered through interaction with short double-stranded DNA (dsDNA).[15] Once activated, cGAS catalyzes the synthesis of 2′3′-cGAMP from GTP and ATP.[22] Subsequently, cGAMP, acting as a second messenger, activates STING by binding to its cyclic dinucleotide (CDN)-binding pocket, initiating a signaling cascade that leads to the production of type I interferons (IFN-I) and other immune mediators.[23,24]

STING is a transmembrane protein localized to the endoplasmic reticulum (ER) that functions as a pattern recognition receptor (PRR) capable of detecting CDN.[11,25,26] It consists of a cytosolic N-terminal domain, a four-segment transmembrane region, and a cytosolic C-terminal domain (CTD).[27] STING typically exists as a dimer, with its CTD forming a V-shaped structure that binds cGAMP at the dimer interface through both direct and solvent-bridged hydrogen bonds.[28,29] Upon cGAMP binding, STING undergoes a conformational change that triggers its translocation from the endoplasmic reticulum (ER) to the Golgi apparatus and leads to its accumulation in perinuclear vesicles.[30–32] When STING translocates to the ER–Golgi intermediate compartment (ERGIC), it recruits TBK1, which phosphorylates both IRF3 and itself.[33,34] Phosphorylated IRF3 then dimerizes and translocates to the nucleus, where it promotes the expression of IFN-I and interferon-stimulated genes (ISGs), orchestrating a robust antiviral response[34] (Figure 1).

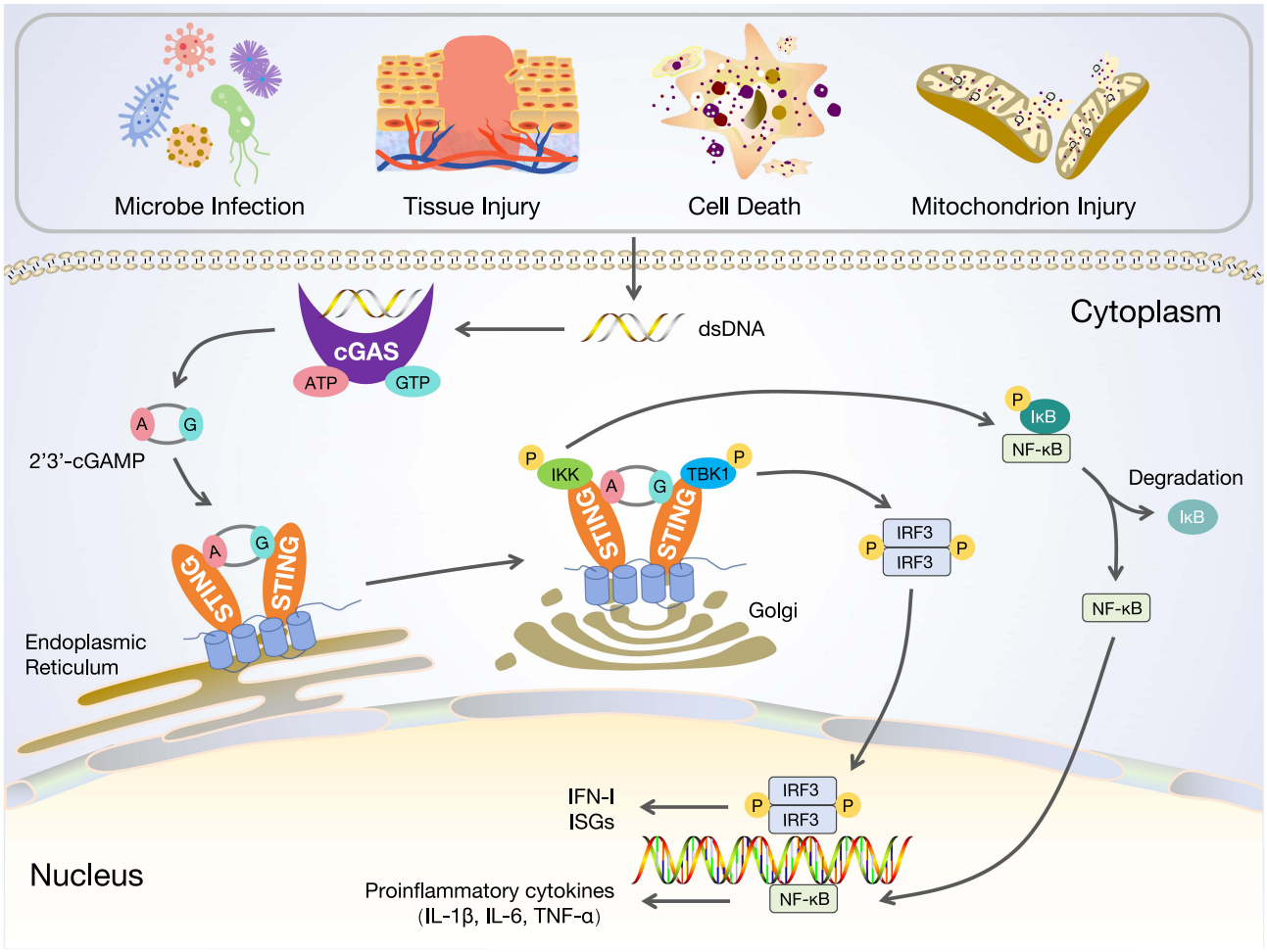

Figure 1 Molecular mechanism of the cGAS-STING signaling. Double-stranded DNA (dsDNA)—from microbes, damaged tissues or dead cells, and injured mitochondria—present in the cytoplasm will be sensed by cyclic GMP-AMP synthase (cGAS). Then cGAS will catalyze ATP and GTP into the second messenger 2′,3′-cyclic GMP-AMP (cGAMP), which will further activate the stimulator of interferon genes (STING) that located at the endoplasmic reticulum in a conformational change of oligomerization. The activated STING will move to Golgi. At Golgi, STING will recruit and phosphorylate the TANK-binding kinase 1 (TBK1) and/or inhibitor of kappa B kinase (IKK), thereafter phosphorylating interferon regulatory factor 3 (IRF3) into dimerization and inhibitor of nuclear factor-kappa B (IκB) into degradation, resulting in IRF3 and nuclear factor-kappa B (NF-κB) activation and translocation into the nucleus to induce transcription of type I interferon (IFN-I) and interferon-stimulated genes (ISGs) as well as proinflammatory cytokines, such as IL-1β, IL-6, TNF-α.

The above process is referred to as the canonical cGAS–STING signaling pathway. In other words, non-canonical cGAS–STING signaling pathways also exist. To date, several non-canonical pathways have been reported, including cGAS-STING/NF-κB, cGAS-STING/p38-MAPK, cGAS-STING-NLRP3, cGAS-STING-PERK-eIF2α, and cGAS-STING-induced LC3 lipidation-mediated autophagy.[35–38] The upstream activation of NF-κB in the cGAS–STING/NF-κB pathway is similar to that of IRF3, but the downstream effects primarily lead to enhanced inflammation through the production of proinflammatory mediators such as IL-1β, IL-6, and TNF-α[39] (Figure 1).

Effects of cGAS-STING Signaling Activation

The initiation of cGAS–STING signaling in mammalian cells is closely associated with antiviral activity, primarily through the downstream induction of IFN-I and ISGs.[40] As our understanding of the molecular mechanisms and cellular roles of cGAS–STING signaling deepens, it has become clear that activation of this pathway leads to multiple effects. Beyond antiviral defense, the cGAS–STING pathway is also closely linked to cancer immunology and tumorigenesis.[41] Pharmacological targeting of STING has shown promise in promoting antitumor immunity.[42] Moreover, prior research has indicated that overactivation of the cGAS–STING pathway is associated with several autoimmune diseases, including rheumatoid arthritis, Aicardi-Goutières syndrome, and systemic lupus erythematosus.[43] Although the cGAS–STING signaling pathway typically

regulates immune surveillance by detecting viral, bacterial, and damaged self-DNAs, its overactivation can be detrimental.[44] In the context of neuroinflammation, sustained activation of the cGAS–STING pathway contributes to neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, and multiple sclerosis.[45–48]

In terms of cellular functions, the cGAS–STING signaling pathway is involved in processes such as DNA repair, metabolism, cellular aging, cell death, and autophagy.[15] The translocation of cGAS into the nucleus, which depends on importin-α and phosphorylation of cGAS at tyrosine 215, occurs in response to DNA damage.[49] Thereafter, cGAS associates with double-stranded DNA breaks and interacts with poly (ADP-ribose) polymerase 1 (PARP1), impeding the formation of the PARP1–Timeless complex and thereby suppressing DNA repair.[49] Additionally, cGAMP can inhibit homologous recombination (HR) by reducing cellular NAD^+ levels and suppressing poly ADP ribosylation, a crucial post-translational modification required for assembling DNA repair proteins.[50] The cGAS–STING signaling pathway also plays a role in lipid and glucose metabolism, potentially contributing to obesity, diabetes, nonalcoholic fatty liver disease (NAFLD), and cardiovascular diseases (CVDs).[51–53] Cellular senescence is a biological process that facilitates generational change but has also emerged as a significant contributor to aging, age-related pathologies, and tumorigenesis.[54,55] Recent studies have found that cGAS–STING signaling contributes to pro-tumorigenic effects and aging-related diseases by triggering the senescence-associated secretory phenotype (SASP) in senescent cells.[56,57] Cell death encompasses a variety of types, including apoptosis, necroptosis, pyroptosis, ferroptosis, and autophagic/lysosomal cell death.[58,59] More importantly, cGAS-STING signaling is involved in all of them.[60] Particularly, cGAS-STING signaling-mediated autophagy is highly exploited.[38] However, there remains a significant gap between our understanding of cGAS–STING signaling and the pathological mechanisms and cellular functions it mediates.

Crosstalk of cGAS-STING Signaling with Other Signaling Transductions and Cellular Processes

Upstream Regulators

Caspase family members are protease enzymes essential for initiating cell death through their unique cysteine-dependent protease activity. In this process, a cysteine residue in the active site performs a nucleophilic attack, cleaving target proteins immediately after aspartic acid residues.[61] The majority of caspases act as negative regulators of the cGAS–STING pathway. For example, Caspase-1 reduces IFN-β production by binding to and cleaving cGAS at residues $D^{140/157}$, subsequently dampening TBK1 phosphorylation and IRF3 nuclear translocation in *Mycobacterium bovis*–infected cells.[62,63] Conversely, the absence of Caspase-1 leads to increased IFN-I production during DNA virus infections. Similarly, Caspase-3 cleaves cGAS at D^{319}, MAVS at $D^{429/490}$, and IRF3 at $D^{121/125}$ in cells infected with DNA or RNA viruses, resulting in decreased IFN-I production.[64] Additionally, in humans, caspase-4 and caspase-5, along with caspase-11 in mice, act as upstream activators of caspase-1, facilitating the cleavage of IL-1β and IL-18.[65,66] However, the specific cleavage sites on cGAS require further investigation. Moreover, Caspases-3, −7, and −9 promote IFN-β secretion from apoptotic cells while inhibiting STING recruitment, as well as the phosphorylation and dimerization of TBK1 and IRF3.[67] This suggests that they function as inhibitors of signaling pathways activated by mitochondrial DNA (mtDNA)-mediated damage-associated molecular patterns (DAMPs), thereby reducing IFN-α/β production via the cGAS–STING–TBK1–IRF3 axis.[67] Subsequently, the cGAS–STING signaling pathway initiates caspase-3, −7, and −9 dependent apoptosis by promoting the degradation of X-linked inhibitor of apoptosis (XIAP), following TBK1/IKK-mediated phosphorylation of XIAP at serine 430.[68]

Downstream Signaling

Pyroptosis is a highly inflammatory form of programmed cell death characterized by cell rupture, typically occurring during infections with intracellular pathogens and playing a crucial role in the antimicrobial response.[69] When pathogens infiltrate cells or cellular stress disrupts mitochondrial homeostasis, double-stranded DNA can accumulate in the cytoplasm, triggering inflammatory responses via activation of the cGAS–STING pathway. This, in turn, initiates pyroptosis through the formation of a large supramolecular complex—known as the inflammasome (or pyroptosome)—in response to intracellular danger signals.[70] Additionally, inflammasome-associated proteins—such as caspase-1, gasdermin D, the CARD domain of ASC, and potassium channels—play regulatory roles in the cGAS–STING

pathway.[70] This intricate crosstalk leads to a cascade amplification effect, intensifying the immune response and potentially exacerbating the pathological processes underlying inflammatory and autoimmune diseases.

Autophagy is an essential and evolutionarily conserved cellular process that degrades unnecessary or dysfunctional components through a lysosome-dependent mechanism. In 2019, research teams led by Zhijian J. Chen and Quan Chen identified a novel link between autophagy and the cGAS–STING signaling pathway. They discovered that STING can activate autophagy as a primary function of the pathway—independently of TBK1 activation and interferon induction. Instead, this process relies on WD repeat domain phosphoinositide-interacting protein 2 (WIPI2) and autophagy-related protein 5 (ATG5) to facilitate LC3 lipidation, thereby promoting the formation of autophagosomes.[38,71] Autophagy plays a dual role in cGAS–STING signaling by both promoting inflammatory responses and facilitating the degradation of STING.[72,73] Since then, an increasing number of studies have confirmed that several substances—such as Meteorin-like hormone (Metrnl), the deubiquitinating enzyme TRABID, Activin A, Unc-93 homolog B1 (UNC93B1), and metformin—can inactivate cGAS–STING signaling through autophagy-dependent mechanisms, thereby alleviating disease or suppressing pathological cellular processes.[74–78]

Functional Interaction

NF-κB is a critical inflammatory pathway that regulates the immune response to infection and can be activated downstream of cGAS–STING signaling as a transcriptional regulator. Moreover, NF-κB activation—mediated by signaling pathways such as Toll-like receptors (TLRs), interleukin-1 receptor (IL-1R), tumor necrosis factor receptors (TNFRs), growth factor receptors (GFRs), and protein kinase C (PKC)—can induce microtubule depolymerization, which inhibits STING's trafficking and degradation in lysosomes via the microtubule network.[79] Taken together, these findings indicate that cGAS–STING signaling can initiate NF-κB activation, while NF-κB activation, in turn, enhances cGAS–STING signaling by regulating microtubule-mediated STING trafficking.

Yes-associated protein (YAP) functions as a transcriptional coregulator, promoting the expression of genes that drive cell proliferation while simultaneously suppressing those that induce apoptosis.[80] Studies have shown that cGAMP directly promotes YAP phosphorylation at serine residues S127 and S397, thereby regulating cell proliferation through the YAP signaling pathway.[81,82] Additionally, activation of the cGAS–STING pathway can trigger the Hippo signaling pathway, resulting in the inactivation of YAP1 and its paralog TAZ (also known as WWTR1), which contributes to the suppression of tumorigenesis.[83,84] Interestingly, previous research has found that activation of YAP/TAZ can inhibit cGAS–STING signaling, thereby impairing immune surveillance in non-small cell lung cancer (NSCLC).[84]

cGAS-STING Signaling in Fibrosis Diseases

cGAS-STING Signaling in Pulmonary Fibrosis

Pulmonary fibrosis (PF) refers to a group of lung diseases characterized by progressive scarring and stiffening of lung tissue, leading to an irreversible decline in the lungs' oxygen diffusion capacity.[85] PF is classified as one of the interstitial lung diseases (ILDs), which can result from identifiable causes such as environmental pollutants, certain medications, and infections. Similar to other ILDs, idiopathic pulmonary fibrosis (IPF)—a form with no known cause—is defined as a chronic, progressive fibrotic lung disease.[86,87] The current understanding of PF pathogenesis is that it results from an abnormal wound-healing response in lung tissue, triggered by various disease-specific factors. These factors activate key effector cells—primarily pulmonary fibroblasts—leading to excessive inflammation and fibrosis.[88,89] Acute lung inflammation is considered a precursor to PF, while chronic inflammation is thought to promote its progression.[90,91] Recent studies have highlighted that the aberrant activation of the cGAS-STING pathway contributes to pulmonary inflammation and fibrosis.

A previous study showed that polystyrene microplastics—emerging environmental pollutants—induced ferroptosis, leading to varying degrees of lung damage and fibrosis in a mouse model by activating the cGAS–STING signaling pathway, and inhibition of both ferroptosis and cGAS–STING signaling reduced lung injury and pulmonary fibrosis following exposure to polystyrene microplastics.[92] Similarly, Ficolin B—a recognition molecule secreted via alveolar macrophage-derived exosomes—was found to exacerbate bleomycin-induced lung injury through cGAS–STING-mediated ferroptosis.[93] Additionally, PF was induced in mice by pharyngeal aspiration of a novel nanomaterial, graphitized multi-walled carbon nanotubes (GMWCNTs), which triggered high expression of the cGAS–STING signaling pathway at the gene level, but co-administration of a STING inhibitor effectively reduced GMWCNT-induced pulmonary inflammation and fibrosis.[94] Furthermore, honokiol—a natural

extract from Magnolia bark with known antioxidant and anti-inflammatory properties—was shown to attenuate silica-induced pyroptosis and protect against PF by modulating the cGAS–STING signaling pathway, offering potential therapeutic applications for silicosis and related inflammatory responses.[95] Moreover, fluvoxamine, a selective serotonin reuptake inhibitor, has demonstrated therapeutic effects in IPF by reducing fibroblast activation and migration in response to transforming growth factor-beta 1 (TGF-β1) stimulation, through inhibition of the cGAS–STING signaling pathway and its downstream targets[96] (Figure 2).

Paradoxically, some research illustrated that STING plays a protective role in PF that is independent of IFN-I signaling but associated with prolonged neutrophilic inflammation, showing that STING deficiency leads to aggravated PF, characterized by increased collagen deposition in the lungs and excessive expression of remodeling factors[97] (Figure 2).

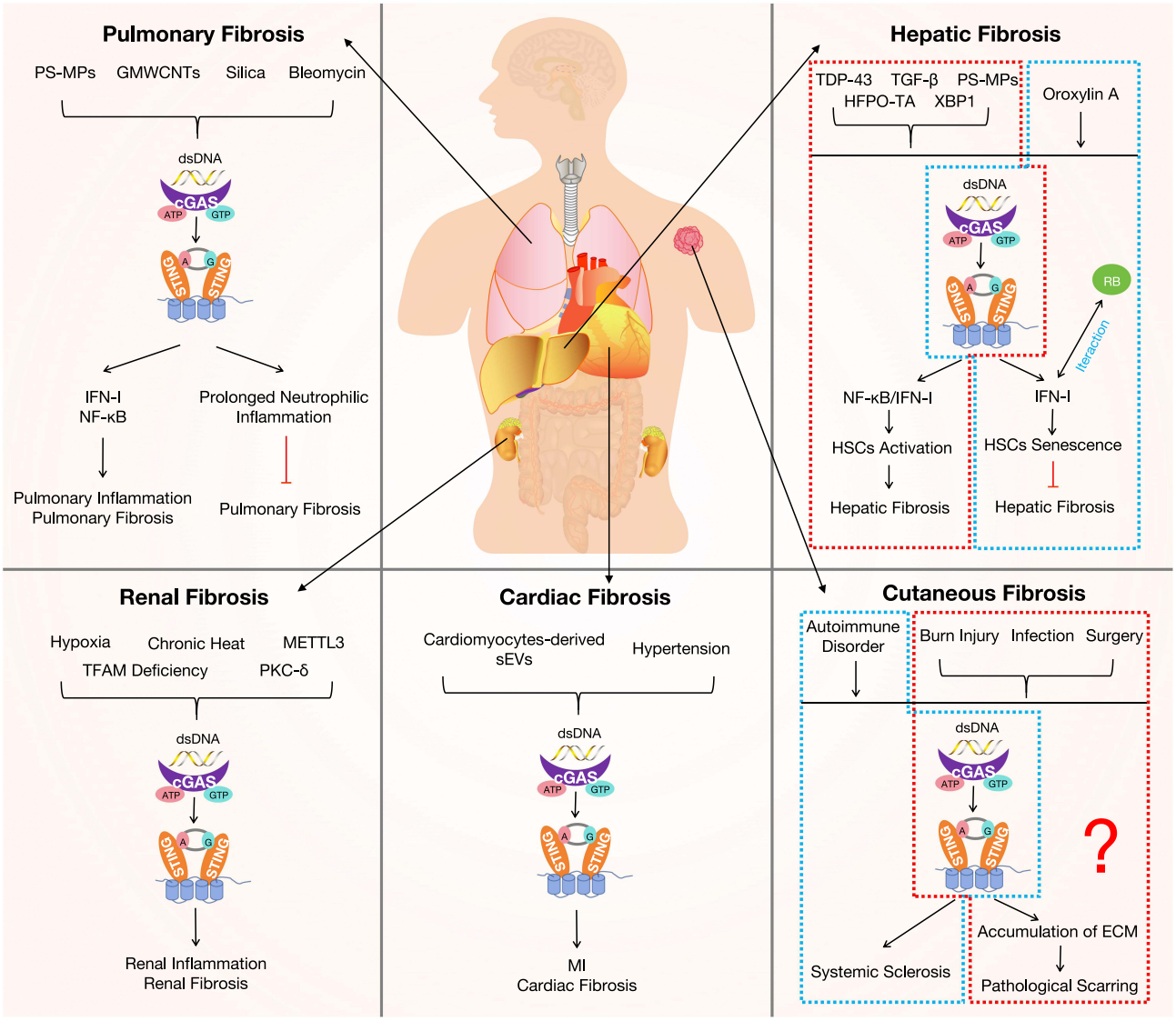

Figure 2 cGAS-STING signaling in pulmonary, hepatic, renal, cardiac, and cutaneous inflammation and fibrosis. In pulmonary fibrosis, polystyrene microplastics (PS-MPs), graphitized multi-walled carbon nanotubes (GMWCNTs), silica and bleomycin could activate cGAS-STING signaling and result in pulmonary inflammation and fibrosis. Previous research also illustrated that STING plays a protective role in pulmonary fibrosis associated with prolonged neutrophilic inflammation. In hepatic fibrosis, TAR DNA-binding protein 43 (TDP-43), transforming growth factor-beta (TGF-β), polystyrene microplastics (PS-MPs), hexafluoropropylene oxide trimer acid (HFPO-TA) and X-box binding protein 1 (XBP1) could upregulate cGAS-STING activation and lead to hepatic stellate cells (HSCs) activation, resulting in hepatic fibrosis. Whereas Oroxylin A could antagonize hepatic fibrosis by cGAS-STING/IRF3-induced HSCs senescence via IRF3 and retinoblastoma (RB) interaction. In renal fibrosis, hypoxia, chronic heat, N6-adenosine-methyltransferase 70 kDa subunit (METTL3), mitochondrial transcription factor A (TFAM) deficiency and protein kinase C-delta (PKC-δ) could activate cGAS-STING signaling and result in renal inflammation and fibrosis. In cardiac fibrosis, cardiomyocytes-derived small extracellular vesicles (sEVs) and hypertension could induce myocardial infarction (MI) and cardiac fibrosis by activating cGAS-STING signaling. In cutaneous fibrosis, the autoimmune disorder is the cause of Systemic Sclerosis and leads to cGAS-STING activation, resulting in fibrosis in the skin. However, burn injury, wound infection or surgery-induced pathological scarring, characterized by excessive accumulation of extracellular matrix (ECM), could be driven through cGAS-STING activation or not is unknown.

Anyhow, the paradoxical effects of cGAS-STING signaling in pulmonary fibrosis may stem from differences in the microenvironments studied or from crosstalk with other signaling pathways. Therefore, further investigation into the precise role of cGAS-STING signaling in PF is essential to develop effective therapies.

cGAS-STING Signaling in Renal Fibrosis

Renal fibrosis (RF) represents the final common pathway of progressive kidney diseases, culminating in irreversible renal failure. It is characterized by excessive extracellular matrix (ECM) deposition that leads to parenchymal scarring, making it the most prevalent pathological feature of chronic kidney diseases (CKDs).[98] Due to the severity and irreversibility of kidney failure, treatment options such as hemodialysis, peritoneal dialysis, or kidney transplantation often impose significant inconvenience and financial burdens on patients.[99,100] Currently, it is widely accepted that RF represents a failed wound-healing process in kidney tissue. This leads to tubular atrophy, persistent interstitial inflammation, tissue fibrosis, glomerular scarring, and reduced vascular density following sustained injury. The process involves activation of mesangial cells and fibroblasts, as well as tubular epithelial-mesenchymal transition, which serve as the primary sources of matrix-producing cells in kidney disease.[101,102] Inflammation triggered by kidney injury initially acts as a protective response; however, when prolonged and excessive, it contributes to the progression of renal diseases, ultimately leading to end-stage RF.[103] Therefore, as one of the key inflammatory pathways, cGAS-STING signaling presents significant regulations in renal inflammation and fibrosis.

Studies have demonstrated that the cGAS-STING signaling pathway promotes RF under hypoxic conditions, a process linked to glycolysis mediated by 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3 (PFKFB3). Inhibition of STING or IRF3 effectively reduced the elevated expression of PFKFB3 and alleviated hypoxia-induced RF. These findings suggest that the cGAS-STING/IRF3/PFKFB3 signaling axis may serve as a promising therapeutic target for renal inflammation and early-stage RF.[104] In addition, previous research demonstrated that m6A RNA modification, facilitated by the 70 kDa subunit of N6-adenosine-methyltransferase (METTL3), may promote renal fibrosis by specifically enriching and stabilizing the cGAS-STING signaling pathway.[105] Interestingly, Ki Wung Chung et al observed significant mitochondrial defects in both human and animal models of renal fibrosis, characterized by a deficiency of mitochondrial transcription factor A (TFAM) in renal tubular cells.[106] Furthermore, they discovered that improper packaging of mtDNA led to its leakage into the cytosol, triggering cGAS-STING activation in renal cells of TFAM knockout mice. Additionally, deletion of STING ameliorated renal fibrosis in these mouse models, highlighting a critical regulatory role of cGAS-STING signaling in renal inflammation and fibrosis.[106] Moreover, chronic heat exposure was found to induce renal fibrosis and mitochondrial damage in laying hens by activating the mtDNA-cGAS-STING signaling pathway, which subsequently triggered inflammation.[107] Thereafter, protein kinase C-delta (PKC-δ) was found to be significantly upregulated in renal fibrosis biopsy samples from both humans and mice. Furthermore, the PKC-δ inhibitor rottlerin attenuated renal fibrosis induced by unilateral ureteral ligation and suppressed activation of the cGAS-STING signaling pathway, highlighting PKC-δ as a key regulator of renal fibrosis via this pathway[108] (Figure 2).

Based on the above research findings, the cGAS-STING signaling pathway plays a critical role in the pathogenesis and progression of renal inflammation and renal fibrosis. Therefore, targeting molecules or employing techniques that modulate the cGAS-STING pathway may offer promising new therapeutic strategies for kidney inflammation and RF.

cGAS-STING Signaling in Hepatic Fibrosis

Hepatic fibrosis (HF) is characterized by excessive accumulation of connective tissue in the liver due to an overly exuberant wound-healing response triggered by chronic or repeated injury. This condition occurs in most types of chronic liver diseases (CLDs), especially those with inflammatory components, and can ultimately lead to portal hypertension—where scarring impedes blood flow through the liver—or cirrhosis, which distorts normal liver structure and function.[109,110] However, unlike pulmonary or renal fibrosis, some forms of HF are potentially reversible. Based on current understanding, HF develops when hepatic stellate cells (HSCs) become activated and transdifferentiate into hepatic myofibroblasts in response to injury or inflammation.[109,111] Hepatitis refers to liver inflammation caused by viral infections or liver injury and can present as either an acute condition (lasting less than six months) or a chronic condition (persisting for six months or more).[112,113] The key difference is that acute (short-term) hepatitis often resolves on its own, whereas chronic hepatitis can lead to severe and potentially fatal complications, including cirrhosis, liver cancer, and

liver failure.[114] With increasing research into the pathogenesis of liver diseases, the cGAS–STING signaling pathway has been shown to promote liver inflammation and fibrosis.[115]

Evidence has shown that activation of the cGAS–STING signaling pathway, triggered by TAR DNA-binding protein 43 (TDP-43)-induced mtDNA release, is involved in HF. Moreover, the activation of cGAS–STING signaling and the colocalization of mitochondria with TDP-43 were found to correlate with the severity of HF.[116] Subsequently, another study reported similar findings: activation of the cGAS–STING signaling pathway, along with mtDNA release induced by TGF-β, is essential for the transcriptional regulation and transdifferentiation of HSCs, a key event in the initiation of HF. They also found that inhibition of STING effectively blocked TGF-β-induced HSCs transdifferentiation and reduced HF both prophylactically and therapeutically.[117] In addition, recent studies have demonstrated that polystyrene microplastics not only contribute to lung injury and PF, but their prolonged accumulation also induces HF. Rong Shen et al revealed that polystyrene microplastics smaller than 1μm can enter cells and accumulate in the liver via the bloodstream, and even at low concentrations, these particles may cause hepatic injury and dysfunction by activating the cGAS–STING–NF-κB signaling pathway.[118] Similarly, hexafluoropropylene oxide trimer acid (HFPO-TA), a contemporary substitute for perfluorooctanoic acid with emerging environmental toxicity, has been shown to induce a cascade of pathological events in mice.[119] Specifically, HFPO-TA exposure increased mitochondrial reactive oxygen species (mtROS) levels, activated the cGAS–STING signaling pathway, and triggered NLRP3-mediated pyroptosis, ultimately leading to HF.[119] These findings suggest that HFPO-TA–induced HF involves a mtROS-driven cGAS–STING–NLRP3 pyroptotic signaling axis.[119] Furthermore, X-box binding protein 1 (XBP1), a transcription factor essential for regulating immune-related gene expression, has been shown to activate STING signaling in macrophages by promoting the cytosolic leakage of self-derived mtDNA, thereby contributing to the progression of HF.[120] Accordingly, Li Chen et al demonstrated that naringenin, a natural flavonoid with anti-inflammatory properties, functions as a specific antagonist of cGAS, which effectively prevents HSCs activation and disrupts the secretion of proinflammatory factors mediated by the cGAS-STING signaling pathway, thereby impeding the progression of HF in murine models[18] (Figure 2).

Interestingly, a recent study demonstrated that treatment with Oroxylin A—a naturally occurring O-methylated flavone derived from Scutellaria baicalensis Georgi—can activate ferritinophagy in HSCs via the cGAS-STING signaling pathway, thereby inducing HSCs senescence and subsequently attenuating HF.[121] Additionally, Qirou Wu et al unexpectedly discovered that IRF3, activated through the cGAS-STING signaling pathway, forms significant endogenous nuclear complexes with retinoblastoma protein (RB), a key regulator of the cell cycle. This interaction attenuates RB hyperphosphorylation, thereby promoting HSCs senescence. These findings reveal an unforeseen yet pivotal role of STING–IRF3–RB signaling in inducing HSCs senescence and limiting the progression of HF[122] (Figure 2).

Similar to its role in PF, the cGAS–STING signaling pathway exhibits both protective and pathogenic effects in HF. Therefore, further investigation is essential to elucidate the precise pathophysiological mechanisms by which cGAS–STING signaling contributes to liver inflammation and fibrosis.

cGAS-STING Signaling in Cardiac Fibrosis

Cardiac fibrosis (CF) is a pathological condition marked by excessive ECM deposition in the myocardium, or abnormal thickening of the pericardium and endocardium—particularly around heart valves such as the tricuspid and pulmonary valves—resulting from aberrant proliferation and activation of cardiac fibroblasts (CFs). This process increases the risk of arrhythmias, impairs cardiac function, and ultimately contributes to the development of heart failure.[123,124] Similar to HF, changes associated with CF may be reversible in certain contexts, as the condition can be self-limiting and may resolve completely with appropriate intervention or removal of the underlying cause.

The most extensive fibrotic remodeling of the heart typically occurs following acute cardiomyocyte death, which results in the abrupt loss of a substantial number of cardiomyocytes. This event triggers a robust inflammatory response and subsequently leads to the replacement of necrotic myocardium with collagen-rich scar tissue.[124] Additionally, pressure overload conditions—such as hypertension and aortic stenosis—as well as volume overloads caused by valvular regurgitant lesions, along with cardiomyopathies like hypertrophic or post-viral dilated cardiomyopathy, can also lead to extensive CF. This fibrotic remodeling increases myocardial stiffness and impairs diastolic function, ultimately contributing to ventricular dilation and the progression to heart failure.[123,124]

Heart inflammation is the body's innate immune response to cardiac infection or injury and is generally classified into three main types based on the affected tissue: endocarditis (inflammation of the inner lining of the heart chambers and valves), myocarditis (inflammation of the heart muscle), and pericarditis (inflammation of the protective sac surrounding the heart).[125] To date, activation of the cGAS–STING signaling pathway has been identified as a key promoter of the early inflammatory response, as well as of pathological cardiac remodeling and dysfunction.[126] Recent research has shown that small extracellular vesicles (sEVs) derived from cardiomyocytes, containing mitochondrial components, can enter CFs and initiate CF by promoting CFs activation and proliferation through the cGAS–STING signaling pathway.[127] Thus, inhibitors of the cGAS-STING signaling pathway have demonstrated protective effects against CF. Lavinia Rech et al confirmed that pharmacological inhibition of STING using C178 or H-151 reduced infarct expansion, myocardial scarring, and hypertrophy three weeks after reperfused myocardial infarction in a preclinical murine model.[128] At the same time, another study confirmed that treatment with H-151 significantly preserved myocardial function and attenuated cardiac fibrosis[129] (Figure 2).

Consequently, inhibitors targeting the cGAS-STING signaling pathway may represent promising therapeutics to improve wound healing and pathological remodeling, thereby alleviating CF.

cGAS-STING Signaling in Cutaneous Fibrosis

The hallmarks of skin injury—pathogen invasion and localized tissue damage—result in the release of DNA. When this free DNA accumulates in the cytoplasm, it activates the cGAS-STING signaling pathway, triggering the production of IFN-I, inflammatory cytokines, and chemokines, thereby connecting wound healing and scar formation with immune system activation.[130] In the environment of tissue injury, resident cells and immune cells release an excess of growth factors—such as fibroblast growth factor (FGF), TGF-β1, IL-1, and IL-6—which activate fibroblasts and promote their differentiation into secretory myofibroblasts through the fibroblast-to-myofibroblast transition process.[131] The high quantity of myofibroblasts leads to the excessive production of ECM proteins.[132]

Systemic sclerosis (SSc), also known as scleroderma, is a complex autoimmune disease targeting connective tissues and often resulting in progressive skin fibrosis.[133] The activation of fibroblasts plays a pivotal role in the progression of fibrosis in SSc, characterized by connective tissue thickening and excessive accumulation of ECM, especially collagen types I and III.[131] Previous studies demonstrated that centromere dysfunction leads to chromosomal instability—manifested as aneuploidy and micronuclei formation—in SSc, and they found that the formation of micronuclei in SSc is closely linked to cGAS-STING pathway activation and correlates with the clinical severity of skin fibrosis[134] (Figure 2).

Pathological scarring, including hypertrophic scars and keloids, is a common form of cutaneous fibrosis characterized by thick, raised, red scars that extend above the normal skin surface due to excessive collagen deposition during wound healing.[135] Pathological scarring is considered a result of dysregulated inflammation during wound healing, along with persistent chronic inflammation in the reticular dermis.[136,137] Additionally, our previous study summarized the immunoregulatory roles of immune cells in wound healing and skin scarring, highlighting the potential involvement of cGAS-STING signaling modulation in scar formation.[138] Therefore, regulating the cGAS-STING–mediated inflammatory response during wound healing may offer a promising strategy to prevent or mitigate pathological scar formation (Figure 2).

Therapeutic Potential Targeting cGAS-STING Signaling in Fibrosis Diseases

Considering that immunomodulation of the cGAS-STING signaling pathway represents a promising target for first-in-class immunotherapies, inhibitors—particularly those targeting the key protein STING—have shown encouraging therapeutic potential in preclinical models of fibrotic diseases.[16] Each of these inhibitors is specifically discussed in the following paragraphs (Table 1).

RU.521

RU.521 is a potent and selective inhibitor of cGAS that effectively blocks cGAS-mediated upregulation of IFN-I. Studies have shown that intracisternal administration of RU.521 reduces microglial activation and neuroinflammation, as well as restores the balance between sympathetic and parasympathetic nervous system activities, which collectively contribute to lowering blood pressure.[139] This reduction in hypertension subsequently alleviates myocardial interstitial fibrosis, cardiomyocyte hypertrophy, and impaired cardiac function in Angiotensin II (Ang II)-induced hypertensive mice[139] (Figure 3).

Table 1 Application of cGAS–STING Pathway-Related Inhibitors in Fibrosis Diseases

Target	Inhibitor	Effect	Application	
			Subject	Disease
cGAS	RU.521[139]	Alleviating myocardial interstitial fibrosis, cardiomyocyte hypertrophy, and contractile dysfunction in Ang II–induced hypertensive mice	cGAS-/-mice	Heart Disease
STING	H-151[129]	Preserving myocardial function and alleviating cardiac fibrosis after myocardial infarction	Male C57BL/6J mice	Myocardial Infarction
	C-176 and C-178[94]	Decreasing pulmonary inflammation and fibrosis in mice induced by graphitized multi-walled carbon nanotubes	Male C57BL/6 mice	Pulmonary Fibrosis
	IFM-0044907[117]	Blocking hepatic stellate cells transactivation and reversing carbon tetrachloride-induced hepatic fibrosis	Male C57BL/6N mice	Hepatic Fibrosis
	20(S)-Protopanaxadiol & Heterophyllin B[140,141]	Reducing expression of fibrotic hallmarks and improving survival rate by phosphorylating adenosine 5′-monophosphate-activated protein kinase (AMPK)	Male C57BL/6 mice	Pulmonary Fibrosis
	Tanreqing injection and Juglanin[142,143]	Alleviating bleomycin -induced lung fibrosis by inhibiting inflammatory responses	Male C57BL/6J mice	Pulmonary Fibrosis
	Qingfei Xieding[144]	Alleviating fibrosis in MLE-12 cells and bleomycin-induced lung fibrosis through reactivating autophagy and inhibiting mitochondrial injury	MLE-12 (mouse lung epithelial cell line), Male C57BL/6 mice	Pulmonary Fibrosis

H-151

H-151 is a potent and selective covalent antagonist of STING that effectively suppresses STING palmitoylation and reduces TBK1 phosphorylation, demonstrating strong inhibitory effects both in vitro and in vivo. Shiyu Hu et al showed that H-151 treatment markedly decreases the IFN-I response in bone marrow-derived macrophages (BMDMs) stimulated by cardiac dsDNA, which the suppression leads to reduced apoptosis of adult cardiomyocytes and decreased scar formation in cardiac fibroblasts cultured with conditioned medium from BMDMs.[129] These findings indicate that H-151-mediated inhibition of STING can preserve myocardial function and attenuate cardiac fibrosis following myocardial infarction (Figure 3).

C-176 and C-178

C-176 and C-178 are nitrofuran derivatives that selectively bind covalently to the transmembrane cysteine residue 91 of STING, effectively blocking activation-induced STING palmitoylation. These compounds also possess the ability to cross the blood-brain barrier. A recent study demonstrated that treatment with C-176 significantly reduced histopathological features in a mouse model of PF induced by GMWCNTs.[94] Specifically, it decreased alveolar wall thickening, alveolar collapse, and inflammatory cell infiltration. Also, mRNA and protein expression levels of cGAS, STING, NF-κB, IL-1β, and TGF-β1 were markedly reduced after C-176 administration, suggesting that STING inhibition by C-176 may effectively mitigate pulmonary inflammation and fibrosis.[94] However, it was identified that the species-specific activity of C-178 and C-176 compounds directly targets mouse STING but not human STING[145] (Figure 3).

IFM-0044907

IFM-0044907 is a small-molecule inhibitor of STING. Suyavaran Arumugam et al demonstrated that IFM-0044907 effectively blocked the transactivation of HSCs and reversed carbon tetrachloride (CCl_4)-induced HF in mice.[117] These findings underscore the pivotal role of STING in HF and highlight IFM-0044907 as a promising therapeutic candidate for treating liver fibrosis (Figure 3).

Other Natural Products

Several natural products targeting the cGAS-STING signaling pathway have been identified to attenuate PF. For instance, 20(S)-Protopanaxadiol, derived from ginseng, and Heterophyllin B, extracted from Radix Pseudostellariae, demonstrated

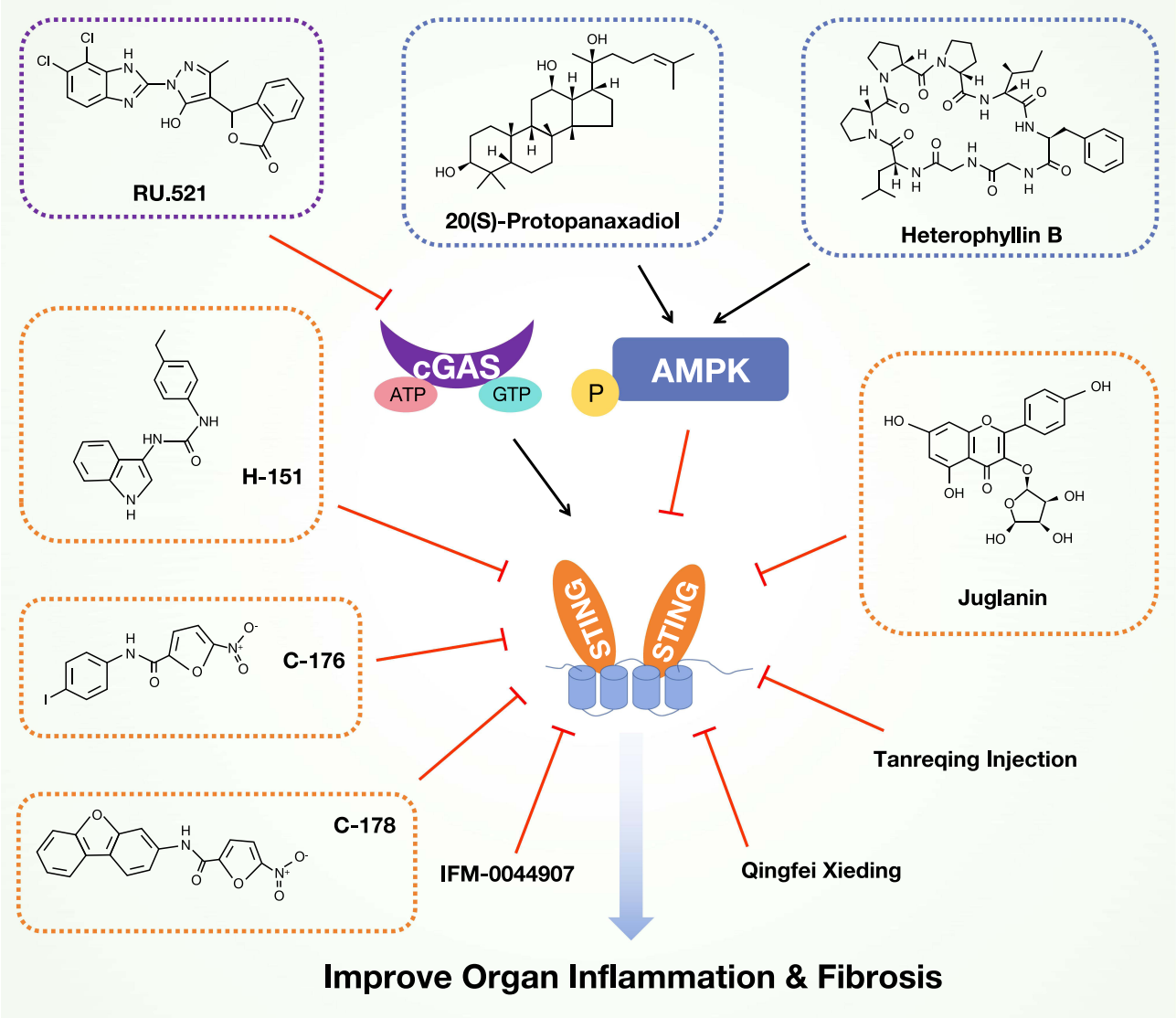

Figure 3 Application of inhibitors and natural products targeting cGAS and STING in fibrosis diseases.

promising pharmacological effects on bleomycin-induced PF by reducing STING expression through the phosphorylation and activation of AMPK.[140,141] Tanreqing injection (TRQ), a well-established traditional Chinese medicine, effectively alleviates bleomycin-induced pulmonary fibrosis by inhibiting STING signaling through modulation of endoplasmic reticulum stress pathways.[142] Juglanin, a compound derived from the green husks of walnuts (Juglans mandshurica) or the Chinese herb He Shou Wu, can reduce inflammation and attenuate pulmonary fibrosis by inhibiting STING in human lung fibroblasts and mouse epithelial cells, as well as downregulating fibrotic markers such as TGF-β1, α-SMA, fibronectin, matrix metalloproteinase-9 (MMP-9), and collagen I.[143] Qingfei Xieding prescription, a traditional Chinese medicine effective as an adjuvant treatment for pulmonary diseases, alleviated bleomycin-induced PF by activating autophagy and inhibiting inflammation mediated through the mtDNA-cGAS-STING pathway[144] (Figure 3).

However, despite the therapeutic potential of existing cGAS-STING signaling inhibitors, challenges persist in developing novel agonists and optimizing agonist delivery systems to enhance biotherapeutic outcomes.

Future Perspective

Organ fibrosis accounts for up to 45% of all deaths in the developed world due to its relentlessly progressive and irreversible nature.[4] Despite significant progress in understanding the pathobiology of fibrosis, effective therapies for

clinical patients remain limited. Given that inflammatory regulation plays a key role in the initiation and progression of fibrosis, targeting inflammatory pathways and molecules offers promising therapeutic potential.[146]

The cGAS-STING signaling pathway has emerged as a critical mediator of inflammation in response to infection, cellular stress, and tissue damage.[147] It has also shown significant roles in various pathological conditions, including inflammatory diseases, cancer, autoimmune disorders, fibrotic diseases, and neurodegeneration.[41,148–150] With growing research into the cellular and molecular mechanisms of cGAS-STING signaling in fibrotic diseases—including pulmonary, renal, hepatic, cardiac, and cutaneous fibrosis—most studies indicate that its aberrant activation acts as a promoter of organ fibrosis onset and progression.[16,106,115,126,134] Thus, strategies targeting the cGAS-STING signaling pathway have demonstrated therapeutic potential for fibrotic diseases. For instance, Quzhou Fructus Arantii-nB, fluvoxamine, and honokiol have been shown to alleviate PF by inhibiting cGAS-STING signaling; naringenin disrupts this pathway to prevent HF; and H-151 treatment significantly preserves myocardial function and attenuates CF by specifically targeting STING.[18,95,96,129,151] Consequently, these findings indicate that the cGAS-STING signaling pathway contributes to fibrotic processes, and its inhibition shows promising therapeutic potential for organ fibrosis. However, there is also evidence suggesting that cGAS-STING signaling may exert protective roles in certain contexts, such as PF and HF, highlighting the complexity and context-dependent nature of this pathway.[97,121,122] Therefore, further in-depth research is required to elucidate the crosstalk between cGAS-STING signaling and other signaling pathways involved in fibrotic processes, as well as to advance its pharmaceutical translation into clinical applications.

Pathological scars, such as hypertrophic scars and keloids, have long posed significant challenges for both patients and clinicians due to the lack of effective therapies—particularly in the case of keloids, which are characterized by a high recurrence rate.[152] This is largely due to the unclear pathogenesis of hypertrophic scars and keloids. Nevertheless, inflammation within the microenvironment of skin wounds and scars plays a critical role in the processes of wound healing and scar formation.[137] To date, no studies have specifically investigated the role of cGAS-STING signaling in the pathogenesis of hypertrophic scars or keloids. Given its established involvement in inflammation and fibrosis, this pathway may represent a promising therapeutic target, warranting further investigation.

To sum up, the role of cGAS-STING signaling in fibrotic diseases is complex and multifaceted, influenced by various factors such as individual variability, tissue microenvironment, the extent and duration of pathway activation, the functional state of resident cells, and potential contributions from comorbid conditions. Despite growing interest, current evidence remains insufficient to clearly define how cGAS-STING signaling modulates fibrotic processes or whether targeting this pathway can effectively reverse or halt organ fibrosis. Therefore, future research should aim to elucidate the precise cellular and molecular mechanisms involved, develop selective and safe therapeutic agents, and evaluate their efficacy in clinical settings. Continued exploration of the cGAS-STING pathway holds promise for advancing treatment strategies and improving outcomes in fibrotic diseases.

Conclusions

This review provides a comprehensive overview of the effects and molecular mechanisms of the cGAS-STING signaling pathway in fibrotic diseases. It outlines the core components of the cGAS-STING cascade, summarizes the mechanisms by which its activation contributes to fibrosis across multiple organs, and catalogs recently developed cGAS and STING antagonists explored in fibrotic disease models. Furthermore, it discusses the therapeutic potential and translational prospects of targeting this pathway in clinical settings.

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.

Disclosure

The authors report no conflicts of interest in this work.

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