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Review Article

MicroRNAs and cGAS-STING Axis: Modulating Innate Immunity in Pathophysiological Contexts

Jamal Amri[1,2], Mohammad Reza Zarei[1,2], Elham Esmaeilzadeh[1,2], Reza Meshkani[1*]

[1] *Department of Clinical Biochemistry, Faculty of Medicine, Tehran University of Medical Sciences, Tehran, Iran*

[2] *Students Scientific Research Center, Tehran University of Medical Sciences, Tehran, Iran*

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* **Corresponding Author:**

Reza Meshkani, PhD, FCLS, Department of Clinical Biochemistry, Faculty of Medicine, Tehran University of Medical Sciences, Tehran, Iran.

Email: rmeshkani@tums.ac.ir

ABSTRACT

The cyclic GMP–AMP synthase–stimulator of interferon genes (cGAS–STING) signaling pathway is a central component of innate immunity that senses cytosolic double stranded DNA and initiates type I interferon and inflammatory responses. Controlled activation of this pathway is essential for antimicrobial defense and antitumor immune surveillance. In contrast, dysregulated or persistent signaling can promote chronic inflammation, tissue damage, autoimmune disorders, or immune evasion in cancer and infectious diseases. Therefore, tight regulation of cGAS–STING activity is critical for maintaining immune homeostasis. MicroRNAs (miRNAs) have emerged as key post transcriptional regulators that fine tune cGAS–STING signaling by directly targeting core pathway components or indirectly modulating related immune signaling molecules. This article provides a comprehensive review of current evidence describing miRNA mediated regulation of the cGAS–STING axis across diverse pathological contexts, including malignancies, viral and bacterial infections, and autoimmune or inflammatory diseases. In various cancers, miRNA mediated suppression of this pathway contributes to reduced interferon signaling, immune escape, therapy resistance, and tumor progression, although in certain cellular settings, controlled inhibition of cGAS–STING may exert protective or antitumor effects. During infectious diseases, some miRNAs are exploited by pathogens to attenuate innate immune sensing, whereas others enhance host defense by modulating negative regulators of immune signaling. In autoimmune and inflammatory disorders, dysregulated miRNA expression can either restrain excessive inflammation or exacerbate disease progression. Overall, this review underscores the miRNA–cGAS–STING regulatory axis as a dynamic and context specific network with broad relevance across human diseases.

Keywords: cGAS–STING; miRNAs; cancer and infections; autoimmune; inflammatory diseases

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Introduction

Cyclic GMP-AMP synthase–stimulator of interferon genes (cGAS–STING) pathway has emerged as the core components of the innate immunity. cGAS recognizes double-stranded DNA (dsDNA) derived from microbial sources such as viral and bacterial genomes, as well as self-DNA released into the cytoplasm. Upon dsDNA binding, cGAS undergoes conformational activation and catalyzes the synthesis of the second messenger cyclic GMP-AMP (cGAMP) (1). cGAMP subsequently binds to STING, an endoplasmic reticulum (ER)-resident adaptor protein, triggering STING oligomerization and its translocation to perinuclear compartments, where downstream signaling is initiated. Activated STING recruits TANK-binding kinase 1 (TBK1), leading to phosphorylation and activation of interferon regulatory factor 3 (IRF3), as well as activation of the nuclear factor κB (NF-κB) pathway (2). These signaling events culminate in the induction of type I interferons (IFN-I) and a broad array of pro-inflammatory cytokines. Through these responses, the cGAS–STING pathway plays a critical role in antiviral defense and antitumor immunity. However, inappropriate or sustained activation of this pathway can result in chronic inflammation, tissue damage, and the development of autoimmune diseases (3).

Accumulating evidence identifies miroRNAs (miRNAs) as the important modulators of cGAS–STING signaling. Multiple studies have demonstrated that miRNAs can directly target key components of this pathway, including cGAS and STING, or indirectly regulate downstream signaling molecules and transcription factors, thereby fine-tuning the magnitude and duration of pathway activation(4). Depending on the cellular and pathological context, miRNA-mediated regulation may either enhance cGAS–STING signaling to promote antiviral and antitumor responses or suppress it to prevent excessive inflammatory damage. Conversely, pathogens and tumor cells frequently exploit host miRNA regulatory mechanisms to attenuate cGAS–STING signaling and evade immune surveillance, facilitating viral persistence, immune tolerance, and tumor progression (5). Increasing evidence also implicates miRNA-mediated dysregulation of the cGAS–STING pathway in inflammatory and autoimmune disorders, highlighting the context-dependent dual roles of miRNAs as either protective or pathogenic regulators of innate immune responses. Despite the growing number of studies linking miRNAs to regulation of the cGAS–STING pathway, current knowledge remains fragmented and largely disease-specific. Most investigations focus on individual miRNAs or limited experimental models, resulting in an incomplete and sometimes contradictory understanding of miRNA-mediated control of this pathway across different pathological conditions. Therefore, a comprehensive synthesis that organizes existing findings within a coherent, disease-oriented, and mechanism-based framework is needed. In this comprehensive review, we summarize current evidence on miRNA-mediated regulation of the cGAS–STING pathway across a broad spectrum of diseases, including cancer, viral and bacterial infections, and inflammatory and autoimmune disorders.

Methodology

This narrative review was conducted to summarize and critically analyze the existing evidence regarding the role of miRNAs in regulation of the cGAS–STING pathway. Relevant studies were identified through literature searches in PubMed, Web of Science, Scopus, and Google Scholar, focusing on research investigating the interaction between miRNAs and components of the cGAS–STING signaling axis. Search terms included combination of keywords such as cGAS–STING, STING signaling, cGAS, microRNA, miRNA, innate immunity, interferon, immune-associated diseases, infectious, non-infectious pathologies and inflammation. Studies were selected based on their relevance to miRNA-mediated regulation of core elements of the cGAS–STING pathway or molecules functionally associated with this signaling cascade. The included literature encompassed experimental cellular studies, animal models, and investigations involving human samples, with an emphasis on the functional impact of miRNAs on modulation of the cGAS–STING pathway under different pathological conditions. The identified studies were organized according to major disease categories, including cancer, viral and bacterial infections, and inflammatory or autoimmune diseases. Finally, key data were extracted from each eligible study. For each miRNA, information regarding the associated disease or condition, target gene or protein and its effect, type of regulation (direct or indirect), and the overall impact on cGAS–STING pathway activity was recorded. These data served as the basis for the preparation of the summary table (Table 1).

The cGAS–STING Pathway: A Central Component in Innate Immunity

The cGAS–STING pathway constitutes one of the most vital cytosolic DNA-sensing systems in innate immunity. Acting as an early warning mechanism, this pathway detects aberrant DNA in the cytoplasm and initiates robust antiviral, inflammatory, and antitumor immune responses. Precise regulation of cGAS–STING signaling is essential, as both insufficient and excessive activation can have profound pathological consequences, ranging from immune evasion and susceptibility to infection to chronic inflammation, autoimmunity, and cancer (6, 7).

Activation of the cGAS–STING pathway begins

Table 1. Comprehensive Overview of miRNAs Involved in Regulation of the cGAS–STING Pathway Across Various Diseases

miRNAs	Disease/Condition	Target Gene/Protein & Effect	Regulation Type (Direct/Indirect)	Overall Effect on cGAS-STING Pathway	Ref
		Cancer			
miR-27	tongue squamous cell carcinoma (TSCC) associated with HPV	STING (Downregulates)	Direct	Activation	(16)
miR-181a	Breast and ovarian cancer (PARPi Resistance)	STING (Downregulates)	Direct	Inhibition	(17)
miR-181a	Oncogenic transformation (serous ovarian cancer)	STING & RB1 (Downregulates)	Direct	Inhibition	(18)
miR-25	Glioblastoma (GBM)	cGAS (Downregulates)	Direct	Inhibition	(19)
miR-93	Breast cancer	STING (Downregulates)	Direct	Promotion of tumorigenesis	(20)
miR-25 & miR-93	Breast cancer (Hypoxia)	cGAS (Downregulates)	Indirect	Inhibition	(21)
miR-181a-2-3p	Colon Cancer	STING (Downregulates)	Direct	Promotion	(22)
		Viral and Bacterial Infections			
miR-23a/b	HSV-1 Infection & Autoimmunity (Trex1 KO model)	cGAS (Downregulates)	Direct	Inhibition	(23)
miR-24	HSV-1 Infection	STING (Downregulates)	Direct	Promotion of viral replication	(25)
miR-576-3p & miR-217	Oropouche Virus (OROV) Infection	STING & TRAF3, DCP2 & MAPK1 (Downregulates)	Direct/Indirect	Promotion of viral replication	(26)
miR-576-3p	Inflammatory Diseases	STING, MAVS, TRAF3 (Downregulates)	Direct	Inhibition	(27)
miR-210	Rhabdovirus Infection (in fish)	STING/MITA (Downregulates)	Direct	Inhibition	(28)
gga-miR-181a-5p	Fowl Adenovirus Serotype 4 (FAdV-4) Infection	STING (Downregulates)	Direct	Promotion of viral replication	(29)
miR-26a	Feline Herpesvirus 1 (FHV-1) Infection	SOCS5 (Downregulates)	Indirect	Activation	(30)
miR-24	Brucella Infection	STING (Downregulates)	Direct	Promotion of Bacterial Replication	(24)
		Autoimmune and Inflammatory Diseases			
miR-1976	Nonalcoholic Fatty Pancreas (NAFP)	DDX58, NFKB1, CHUK (Downregulates)	Indirect	Inhibition	(37)
miR-340-5p	Subarachnoid Hemorrhage (SAH)	STING (Downregulates)	Direct	Inhibition	(31)
let-7i	Traumatic Brain Injury (TBI)	STING (Downregulates)	Direct	Inhibition	(32)
miR-24	Intestinal epithelial cells	STING (Downregulates)	Direct	Inhibition	(33)
miR-24-3p	Hepatic Ischemia & Reperfusion Injury	STING (Downregulates)	Direct	Inhibition	(34)
miR-4691-3p	Dental Pulp Inflammation	STING (Downregulates)	Direct	Inhibition	(35)
miR-4767	Acute Lung Injury (ALI)	cGAS (Downregulates)	Direct	Inhibition	(36)
miR-29a & miR-378b	Dendritic Cells (DCs)	IRF7 & TBKBP1 (Downregulates)	Indirect	Activation	(4)

miRNA: microRNA, cGAS: cyclic GMP-AMP synthase, STING: Stimulator of Interferon Genes, IFN-I: Type I Interferon, TSCC: Tongue Squamous Cell Carcinoma, GBM: Glioblastoma, PARPi: Poly(ADP-ribose) polymerase inhibitors, EVs: Extracellular Vesicles, HSV-1: Herpes Simplex Virus 1, OROV: Oropouche Virus, NAFP: Nonalcoholic Fatty Pancreas, SAH: Subarachnoid Hemorrhage, TBI: Traumatic Brain Injury, ALI: Acute Lung Injury, HGSOC: High-Grade Serous Ovarian Cancer, TNBC: Triple-Negative Breast Cancer, FAdV-4: Fowl Adenovirus Serotype 4, RB1: Retinoblastoma 1, DDX58: DEAD-Box Helicase 58, NFKB1: Nuclear Factor Kappa B Subunit 1, CHUK: Conserved Helix-Loop-Helix Ubiquitous Kinase, MAVS: Mitochondrial Antiviral-Signaling Protein, TRAF3: TNF Receptor Associated Factor 3, DCP2: Decapping Protein 2, MAPK1: Mitogen-Activated Protein Kinase 1, IRF7: Interferon Regulatory Factor 7, TBKBP1: TANK-binding kinase binding protein 1, SOCS5: Suppressor of Cytokine Signaling 5, circELK4: circular RNA ELK4, circSamd4a: circular RNA Samd4a.

with the recognition of dsDNA in the cytoplasm, a compartment where DNA is normally absent. cGAS recognizes dsDNA in a sequence-independent but length- and structure-dependent manner, enabling the detection of a broad spectrum of DNA species. These include pathogen-derived DNA from viruses and bacteria, as well as self-DNA released into the cytosol under pathological conditions such as genomic instability, DNA damage, cellular senescence, mitochondrial dysfunction, or mitotic errors that lead to micronuclei formation and nuclear envelope rupture. This wide sensing capacity makes cGAS a central guardian of cellular integrity (8). Upon dsDNA binding, cGAS undergoes conformational rearrangements that activate its enzymatic function. Activated cGAS catalyzes the conversion of ATP and GTP into the cyclic dinucleotide second messenger cGAMP. This small but potent molecule serves as a critical molecular bridge between DNA sensing and downstream immune signaling. In addition to acting within the producing cell, cGAMP can be transferred to neighboring cells, thereby amplifying and spreading innate immune responses within tissues (2, 9).

cGAMP binds to STING, an adaptor protein primarily localized to the membrane of the ER. Ligand binding induces STING dimerization and oligomerization, followed by its translocation from the ER to ER–Golgi intermediate compartments and perinuclear regions. This intracellular trafficking is not merely a passive event but a prerequisite for full signal propagation, allowing STING to assemble functional signaling platforms required for downstream activation (10). At these signaling sites, activated STING recruits TBK1, leading to TBK1 phosphorylation and activation. TBK1 subsequently phosphorylates the transcription factor IRF3. Phosphorylated IRF3 dimerizes and translocates into the nucleus, where it drives the expression of type I interferons (IFN-I) and a wide array of interferon-stimulated genes (ISGs). These gene products establish an antiviral state, restrict pathogen replication, and promote communication between innate and adaptive immune compartments (11, 12). Concurrently, STING activation can engage the NF-κB signaling pathway, resulting in the production of diverse pro-inflammatory cytokines. This inflammatory arm of cGAS–STING signaling acts in concert with interferon responses to strengthen host defense, recruit immune cells, and orchestrate coordinated immune reactions at the tissue level (13).

Beyond its canonical role in host defense against infections, the cGAS–STING pathway plays a context-dependent role in cancer immunity. Activation of this pathway within tumor cells or antigen-presenting cells can induce cell cycle arrest, senescence, or cell death, while also enhancing antitumor immune surveillance through dendritic cell activation and promotion of cytotoxic T-cell responses (14). Conversely, suppression or dysfunction of cGAS–STING signaling represents a common mechanism of immune evasion within the tumor microenvironment. Importantly, excessive or unresolved activation of this pathway has been implicated in the pathogenesis of inflammatory and autoimmune diseases, underscoring the delicate balance required for its proper function(15).

Collectively, the cGAS–STING pathway occupies a central position at the intersection of innate immunity, inflammation, infection, and cancer. Its activity is controlled through multiple regulatory layers to ensure appropriate magnitude, duration, and contextual specificity of immune responses. Disruption at any level of this regulatory network can shift the balance from protective immunity toward pathological inflammation or immune suppression. These characteristics make the cGAS–STING pathway a focal point of intense investigation in molecular immunology and translational medicine and provide a strong conceptual foundation for exploring fine-tuning regulatory mechanisms that modulate this pathway under diverse physiological and pathological conditions.

Regulatory Roles of miRNAs in the cGAS–STING Pathway Across Various Diseases

In this section, we summarize how miRNAs regulate cGAS–STING signaling through direct or indirect targeting of pathway components, thereby influencing immune evasion in infections, tumor progression, and inflammatory outcomes in autoimmune and inflammatory disorders, highlighting their potential as therapeutic targets.

Cancer

The cGAS–STING pathway has a context-dependent role in cancer, mediating antitumor immunity while also being exploited by tumors to evade immune surveillance. miRNAs are key regulators of this balance, modulating cGAS–STING signaling to influence tumor progression, metastasis, and therapy resistance, and representing promising biomarkers and therapeutic targets in oncology.

miR-27 in tongue squamous cell carcinoma (TSCC): In human papillomavirus (HPV)–positive tongue squamous cell carcinoma, miR-27 directly targets and suppresses STING expression. Reduced level of miR-27 is observed in clinical TSCC samples, resulting in enhanced STING activation and increased production of immunosuppressive cytokines such as C-C motif chemokine ligand 22 (CCL22), which promotes the recruitment of regulatory T cells (Tregs). This cascade contributes to the establishment of an immunosuppressive tumor microenvironment and facilitates tumor progression, underscoring a context-dependent protumorigenic role of STING in this cancer subtype (16).

miR-181a in breast and ovarian cancers: miR-181a directly suppresses STING expression in breast and ovarian cancer cells. In poly (ADP-ribose) polymerase (PARP) inhibitor–resistant triple-negative breast cancer (TNBC) and ovarian cancers, elevated miR-181a level contributes to resistance against PARP inhibitors and platinum-based therapies through attenuation of STING signaling. This suppression is accompanied by reduced production of pro-inflammatory cytokines, including interleukin-6 (IL-6) and interleukin-12B (IL-12B), as well as diminished interferon-γ (IFNG) responses, features that correlate with poor prognosis in TNBC patients. Notably, miR-181a can be transferred from resistant to sensitive cancer cells, enabling dissemination of therapeutic resistance within the tumor population (17).

miR-181a in oncogenic transformation and early tumorigenesis: In models of oncogenic transformation involving fallopian tube secretory epithelial cells (FTSECs), precursor cells of high-grade serous ovarian cancer (HGSOC), miR-181a suppresses both STING and the tumor suppressor retinoblastoma-associated protein 1 (RB1). By concurrently inhibiting these pathways, miR-181a enables cells harboring severe genomic instability to evade interferon-mediated cell death, thereby promoting the survival and expansion of genomically damaged cells. This mechanism represents an early immune-evasion strategy that facilitates tumor initiation and progression (18).

miR-25 in glioblastoma: In glioblastoma, miR-25 is transferred from hypoxic tumor cells to macrophages within the tumor microenvironment, where it directly suppresses cGAS expression. This downregulation disrupts cGAS–STING pathway activation and reduces IFN I production, thereby weakening antitumor immune responses. Consequently, immune cell recruitment and activation are impaired, contributing to an immunosuppressive microenvironment and poorer disease outcomes (19).

miR-93 in breast cancer: In breast cancer, miR-93 functions as an oncogenic miRNA by directly targeting and suppressing STING expression, thereby facilitating tumorigenesis. Increased expression of eyes absent homolog 2 (EYA2) is positively correlated with elevated miR-93 levels, establishing an oncogenic EYA2/miR-93/STING regulatory axis. Activation of this axis enhances breast cancer cell proliferation, migration, and invasion, while simultaneously inhibiting apoptosis. Collectively, the EYA2/miR-93/STING pathway represents a critical molecular mechanism contributing to breast cancer progression and pathogenesis (20).

miR-25 and miR-93 in hypoxic breast cancer: Under hypoxic conditions in breast cancer, miR-25 and miR-93 indirectly suppress cGAS expression via regulation of nuclear receptor coactivator 3 (NCOA3), an epigenetic factor required for maintaining the basal cGAS expression. This regulatory mechanism allows hypoxic tumor cells to evade immune responses triggered by danger-associated molecular patterns (DAMPs), particularly mitochondrial DNA. Clinically, reduced cGAS expression is associated with impaired antitumor immunity and poorer prognosis (21).

miR-181a-2-3p in colorectal cancer: In contrast to the predominantly protumorigenic roles of the miR-181 family, miR-181a-2-3p is downregulated in colorectal cancer and exerts a tumor-suppressive function. Restoration of miR-181a-2-3p expression inhibits STING, leading to reduced cancer cell proliferation and migration alongside increased apoptotic activity. These findings highlight the context-dependent nature of miRNA–STING interactions and position miR-181a-2-3p as a promising therapeutic and biomarker candidate in colorectal cancer (22).

Viral and bacterial infections

Viruses have evolved sophisticated strategies to evade host immune surveillance, among which miRNA-mediated manipulation of the cGAS–STING pathway represents a highly effective mechanism. This interference may occur through direct suppression of key pathway components or through modulation of interconnected signaling cascades, ultimately leading to attenuation of antiviral interferon responses and enhanced viral replication (23). Similar to viruses, bacteria have evolved mechanisms to manipulate host miRNA regulatory networks in order to evade innate immune detection and promote intracellular survival. In particular, suppression of cGAS–STING signaling via host miRNAs represents an effective strategy used by certain intracellular bacterial pathogens to dampen interferon mediated immune responses and establish persistent infection (24).

miR-23a/b in herpes simplex virus type 1 (HSV1) infection and autoimmunity: miR-23a and miR-23b directly suppress cGAS expression by targeting its mRNA, thereby negatively regulating cytosolic DNA sensing. During HSV1 infection, the endogenous levels of miR-23a/b are reduced, resulting in increased cGAS expression and enhanced activation of innate antiviral responses, including elevated production of IFN I and interferon-stimulated genes. Conversely, enforced elevation of miR-23a/b attenuates DNA-triggered immune responses and increases cellular susceptibility to HSV1 infection. Beyond viral infection, miR-23a/b also plays a protective role in autoimmune contexts. In conditions characterized by aberrant accumulation of self-DNA, such as three prime repair exonuclease 1 (TREX1) deficiency, reduced miR-23a/b expression

is associated with excessive cGAS activation and chronic interferon responses. Restoration of miR-23a/b levels suppresses cGAS activity and alleviates autoinflammatory signaling, highlighting their dual relevance in antiviral defense and immune homeostasis (23).

miR-24 in HSV-1 infection: HSV-1 induces the expression of miR-24 as an immune evasion mechanism. miR-24 directly targets STING, leading to suppression of its synthesis and consequent attenuation of downstream antiviral signaling. Inhibition of STING results in reduced IFN I production and compromised activation of antiviral transcriptional programs, thereby creating a cellular environment that favors viral replication. This miRNA-mediated disruption of the cGAS–STING pathway represents an efficient strategy employed by HSV-1 to weaken host innate immune defenses (25).

miR-576-3p and miR-217 in oropouche virus (OROV) infection: During infection with OROV, an RNA virus, host cells exhibit increased expression of miR-576-3p and miR-217, both of which contribute to viral immune evasion. miR-576-3p directly suppresses STING expression, leading to attenuation of interferon-mediated antiviral responses and enhanced viral replication. In parallel, miR-217 acts as a proviral factor by targeting host genes involved in regulating antiviral signaling and cellular stress responses, further facilitating viral persistence(26).

miR-576-3p as a negative feedback regulator of antiviral immunity: Independent of specific viral strains, miR-576-3p functions as a primate-specific negative feedback regulator of antiviral immunity. This miRNA directly targets STING, mitochondrial antiviral signaling protein (MAVS), and TNF receptor–associated factor 3 (TRAF3), collectively restraining excessive interferon production following viral challenge. By limiting prolonged or exaggerated immune activation, miR-576-3p helps maintain immune equilibrium; however, elevated miR-576-3p levels also increase host susceptibility to a broad range of viral infections. Reduced expression of this miRNA has been observed in inflammatory disorders, underscoring its role in immune homeostasis (27).

miR-210 in rhabdovirus infection: In aquatic species, miR-210 acts as a negative regulator of antiviral innate immunity by directly targeting and suppressing STING/MITA expression during rhabdovirus infection. Downregulation of STING/MITA attenuates innate immune signaling, resulting in diminished IFN I production. This impairment of downstream inflammatory and antiviral pathways creates a permissive cellular environment for viral survival and replication. Consequently, miR-210–mediated inhibition of STING/MITA represents a key mechanism that facilitates efficient rhabdovirus propagation in aquatic hosts (28).

Gga-miR-181a-5p in Fowl Adenovirus (FAdV-4) infection: In avian viral infections, gga-miR-181a-5p directly targets STING, resulting in suppression of host antiviral defenses. Reduced STING activity weakens interferon-dependent immune responses, thereby promoting replication of FAdV-4. This miRNA-mediated inhibition of cGAS–STING signaling represents a conserved viral evasion strategy across species(29).

miR-26a in Feline Herpesvirus 1 (FHV-1) infection: In contrast to virus-exploited miRNAs, miR-26a enhances antiviral immunity by indirectly amplifying IFN I signaling. By suppressing suppressor of cytokine signaling 5 (SOCS5), a negative regulator of interferon signaling, miR-26a strengthens downstream interferon-dependent responses and inhibits viral replication. Induction of miR-26a during infection thus represents a host-protective mechanism linked to effective cGAS-dependent antiviral defense (30).

*miR-24 in Brucella infection***:** Brucella species, which are facultative intracellular bacteria, exploit host miRNA regulation to suppress innate immune signaling. During infection, Brucella induces the expression of miR-24, which directly downregulates STING, leading to attenuation of cGAS–STING–dependent immune responses. Reduced STING expression weakens interferon signaling and facilitates bacterial survival and replication within host macrophages. This miRNA-mediated immune suppression is dependent on bacterial secretion machinery, enabling Brucella to actively manipulate host gene regulation and evade immune surveillance. Importantly, inhibition of miR-24 restores STING expression and significantly limits bacterial replication, highlighting miR-24 as a key molecular mediator of chronic *Brucella* infection and a potential therapeutic target for controlling intracellular bacterial persistence (24).

Autoimmune and Inflammatory Diseases

Dysregulated activation of the cGAS–STING pathway in response to self-derived DNA is a key driver of chronic inflammation and autoimmune pathology. While this pathway is essential for host defense, it's inappropriate or sustained activation leads to excessive interferon production, inflammatory tissue damage, and disease progression. miRNAs act as critical modulators of cGAS–STING signaling by fine-tuning pathway components, thereby exerting either protective anti-inflammatory effects or promoting pathogenic inflammation depending on cellular and disease context (31).

miR-340-5p in subarachnoid hemorrhage (SAH): In SAH, miR-340-5p directly suppresses STING expression in microglial cells. Elevated miR-340-5p levels are associated with reduced neuroinflammation, characterized by decreased production of pro-inflammatory cytokines, attenuation of microglial activation, improvement of neuronal injury, and reduced neuronal apoptosis. Through downregulation of STING-dependent inflammatory signaling, miR-340-5p exerts a strong neuroprotective effect in acute brain injury (31).

Let-7i in traumatic brain injury (TBI): Let-7i functions as a direct negative regulator of STING within the central nervous system. Following traumatic brain injury, decreased let-7i expression correlates with enhanced STING activation and increased neuroinflammatory responses. Restoration of let-7i suppresses STING expression, leading to reduced inflammation, diminished neuronal damage, inhibition of excessive gliosis, and significant improvement in cognitive and motor functions, highlighting let-7i as an important regulator of post-traumatic neuroinflammation (32).

miR-24 in STING regulation and intestinal immune homeostasis: miR-24 directly inhibits STING expression and serves as a key negative regulator of innate immune signaling in epithelial tissues. By restraining STING activity, miR-24 prevents aberrant activation of DNA-sensing pathways and contributes to intestinal immune homeostasis. This regulatory role underscores the importance of miR-24 in maintaining balanced innate immune responses under physiological conditions (33).

miR-24-3p in liver ischemia–reperfusion injury: In liver ischemia–reperfusion injury, miR-24-3p, the mature functional form of miR-24, directly targets and suppresses STING expression, resulting in dampened inflammatory signaling and reduced hepatocellular apoptosis. Elevated levels of miR-24-3p are associated with attenuated hepatic injury and decreased production of pro-inflammatory mediators, highlighting its protective role in sterile inflammation and ischemic stress (34).

miR-4691-3p in dental pulp inflammation: In inflammatory conditions of the dental pulp, miR-4691-3p negatively regulates STING expression. Elevated levels of miR-4691-3p suppress downstream cGAS–STING signaling, leading to reduced production of inflammatory cytokines. This regulatory mechanism functions as a negative feedback loop that restrains excessive inflammatory responses and protects dental pulp tissue from immune-mediated injury (35).

miR-4767 in acute lung injury (ALI): In ALI, miR-4767 directly targets cGAS, thereby restraining activation of the cGAS–STING pathway in pulmonary immune cells. Reduced miR-4767 expression results in excessive pathway activation, promoting inflammatory cell death and subsequent lung tissue damage. Accordingly, preservation of miR-4767 expression is critical for limiting uncontrolled inflammation during acute lung injury (36).

miR-1976 in non-alcoholic fatty pancreas (NAFP): In NAFP, miR-1976 indirectly regulates inflammatory signaling associated with the cGAS–STING pathway by suppressing multiple innate immune and inflammatory regulators. Reduced miR-1976 expression leads to enhanced activation of pathway-associated components, resulting in increased inflammation and pancreatic fibrosis. Loss of miR-1976 thus contributes to disease progression through amplification of inflammatory responses (37).

miR-29a and miR-378b in dendritic cells: In activated dendritic cells, miR-29a and miR-378b indirectly enhance cGAS–STING pathway signaling by targeting regulatory components downstream of STING. Dysregulated expression of these miRNAs augments type I interferon production, alters cytokine profiles, and promotes heightened immune activation, thereby contributing to inflammatory pathology (4).

Collectively, these findings demonstrate that miRNAs exert highly context-dependent effects on autoimmune and inflammatory diseases through precise modulation of the cGAS–STING signaling axis. By either suppressing excessive pathway activation or amplifying inflammatory outputs, miRNAs critically influence tissue damage, disease severity, and immune homeostasis. Elucidating these regulatory networks provides a strong rationale for exploiting miRNAs as diagnostic biomarkers and therapeutic targets for controlling aberrant innate immune responses.

Conclusion and Future Perspectives

The cGAS–STING signaling pathway functions as a fundamental sentinel of innate immunity, bridging cellular DNA sensing to the activation of interferon and inflammatory cascades. Nevertheless, its delicate balance determines outcomes that range from protective immune defense to chronic inflammation, tissue injury, and tumorigenesis. Over the past decade, growing evidence has revealed that miRNAs are integral fine-tuners of this pathway, influencing immune responses across infection, cancer, and autoimmunity. Collectively, studies reviewed here demonstrate that specific miRNAs including miR-181a, miR-24, let-7i, miR-23a/b, miR-340-5p, miR-1976, and others, govern the activation or suppression of key cGAS–STING components. Through this regulation, miRNAs critically determine whether immune activation promotes pathogen clearance and tumor inhibition or, conversely,

leads to chronic inflammation and autoimmunity. This dualistic role underscores the intricate interplay between miRNA expression patterns, cell type, and disease context. Importantly, the contextual nature of these effects emphasizes that miRNAs act not simply as "on/off" regulators but as dynamic modulators within a broader immunogenetic network.

From a translational perspective, miRNAs hold major promise as non-invasive biomarkers due to their stability in biological fluids and their strong association with disease progression and therapy response. Parallel to this, therapeutic manipulation of miRNAs, using mimics or inhibitors, has begun to show preclinical efficacy in modulating cGAS–STING activation. Such approaches could open new avenues in immuno-oncology, antiviral therapy, and the management of inflammatory disorders. However, to fully exploit these opportunities, several challenges must be addressed. (i) The context dependency of miRNA–cGAS–STING interactions demands comprehensive mapping across tissue types and disease stages. (ii) Advanced technologies such as multi-omics profiling, high-throughput screening, and single-cell transcriptomics are needed to uncover novel regulatory miRNAs and define their precise molecular targets. (iii) Targeted nanocarrier systems and RNA-based delivery platforms must be optimized to achieve tissue specificity while minimizing immune toxicity or off-target effects. (iv) Large-scale clinical validation is essential to bridge experimental findings with real-world applications.

In summary, elucidating and harnessing the miRNA–cGAS–STING regulatory axis marks a frontier in molecular immunology. Continued interdisciplinary efforts, from computational modeling to clinical translation, will move this field closer to RNA-based precision medicine, where immune modulation can be both selective and restorative, ultimately transforming diagnostics and therapeutic strategies across diverse disease landscapes.

Conflict of Interest

The authors declare that there are no conflicts of interest.

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