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Opinion

Shedding Light on The cGAS-STING Pathway: A New Tale of An Old Story in The Cell

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Abstract

Perception of microbial DNA is an evolutionarily conserved defending mechanism that alerts the host immune system to respond to sporadic pathogenic infections, although distinguishing foreign DNA from abundant self-DNA remains a major challenge to host cells. Cyclic guanosine monophosphate (GMP)-adenosine monophosphate (AMP) synthase (cGAS) is a central DNA sensor that provokes the innate immunity via production of the second messenger cyclic GMP-AMP (cGAMP), which subsequently engages the stimulator of interferon gene (STING), an adaptor protein. Recent studies uncovered that cytoplasmic chromatin triggers inflammation through surveillance of micronuclei by the cGAS-STING pathway, a process linking genome instability to innate immune responses. Importantly, several lines of emerging evidence suggest that activation of cGAS-STING induces cellular senescence, which is accompanied by the development of a senescent-associated secretory phenotype (SASP), a hallmark feature of senescent cells. Indeed, there are mechanisms intimately associated with genomic DNA damage, cytosol inflammation and cellular senescence, critical events that can determine cell fate but are bridged by enhanced cGAS-STING activities in genotoxic conditions or upon carcinogenic events. Despite the presence of a few unsolved issues, translation of the rapidly accumulated data and development of avenues to target the cGAS-STING pathway

may present new options for clinical intervention of auto-inflammation, cellular senescence and age-related pathologies.

Key words: cGAS-STING, Cytosol Sensor, Genomic DNA, Innate Immunity, Cellular Senescence, Senescence-Associated Secretory Phenotype, Targeted Therapy.

Introduction

Although DNA damage response (DDR) can maintain genome integrity and influence cell destiny, accumulating evidence suggests that genomic instability frequently triggers inflammatory responses (Figure 1). In cell culture, genotoxic agents such as topoisomerase inhibitors and ionizing irradiation induce the expression of type I interferons (IFNs) and a few other cytokines (1, 2). DNA damage also enhances the expression of molecules associated with natural killer (NK) cells such as NKG2D ligands (3). These cell surface proteins attract NKG2D+ NK cells and activated CD8+ T cells to target damaged cells as part of immune surveillance (4). Interestingly, expression of such NKG2D ligands seems to result from the induction of type I IFNs as a response to DNA damage events, including but not limited to cellular senescence (3, 5-7).

A novel and distinct cytosolic DNA sensing pathway is recently disclosed to be the major link between DNA damage and innate immunity. DNA usually resides in the nucleus and mitochondria, while its appearance in the cytoplasm acts as a danger-associated molecular pattern (DAMP) to induce immune responses. Cyclic guanosine monophosphate (GMP)-adenosine monophosphate (AMP) synthase (cGAS) is the sensor that functionally perceives DNA fragments as a DAMP and stimulates production of type I IFNs and other cytokines (8, 9). DNA physically binds cGAS in a sequence-independent manner before inducing a conformational change of the catalytic center of cGAS, which converts guanosine triphosphate (GTP) and ATP into cyclic GMP-AMP (cGAMP), the second messenger (10). Composed of two phosphodiester bonds including one between the 2'-hydroxyl group of GMP and 5′-phosphate of AMP and the other between the 3′-hydroxyl of AMP and 5′-phosphate of GMP (11-13), this molecule, termed 2'3′-cGAMP, is an endogenous high-affinity ligand for the adaptor protein-stimulator of IFN gene (STING) (14, 15).

STING exists as a transmembrane homodimer, localized to the endoplasmic reticulum (ER) and binding cyclic dinucleotides such as cGAMP and the bacterial second messengers including cyclic di-GMP and cyclic di-AMP (10, 16). Binding to cGAMP causes a conformational change of STING, which subsequently translocates from the ER to the Golgi apparatus (17, 18). Intracellular translocation of STING releases its carboxyl terminus to subsequently recruit and activate TANK-binding kinase 1 (TBK1) and IFN regulatory factor 3 (IRF3) through a phosphorylation-dependent mechanism (19, 20). In addition, STING activates NF-κB, the latter together with IRF3 turns on the transcription of type I IFNs and multiple cytokines (Figure 1).

Frequently involved in rapid innate immune responses, the cGAS-STING pathway represents an evolutionarily conserved defense mechanism against viral or other pathogenic infections (21, 22). Given its role in activating immune surveillance, it has been assumed that this pathway primarily functions as a tumor suppressor. However, mounting evidence has suggested that depending on the context, signaling mediated by the cGAS-STING axis can also have pro-tumorigenic and metastasis-promoting functions, and its chronic activation can paradoxically induce

the formation of an immune-suppressive tumor microenvironment (23). The process can result from continuous chromosome segregation errors in cancer cells and promote their malignant properties including enhanced invasion and metastasis to distant organs (24, 25). Since the molecular attributes of the cGAS-STING pathway and its central roles in eliciting cellular immunity against infection of various microbial pathogens and tumor progression have been well established, we will in this article primarily focus on the recently emerging biological functions of this axis in mediating DNA damage-induced immune responses and one of the critical pathological outcomes, cellular senescence.

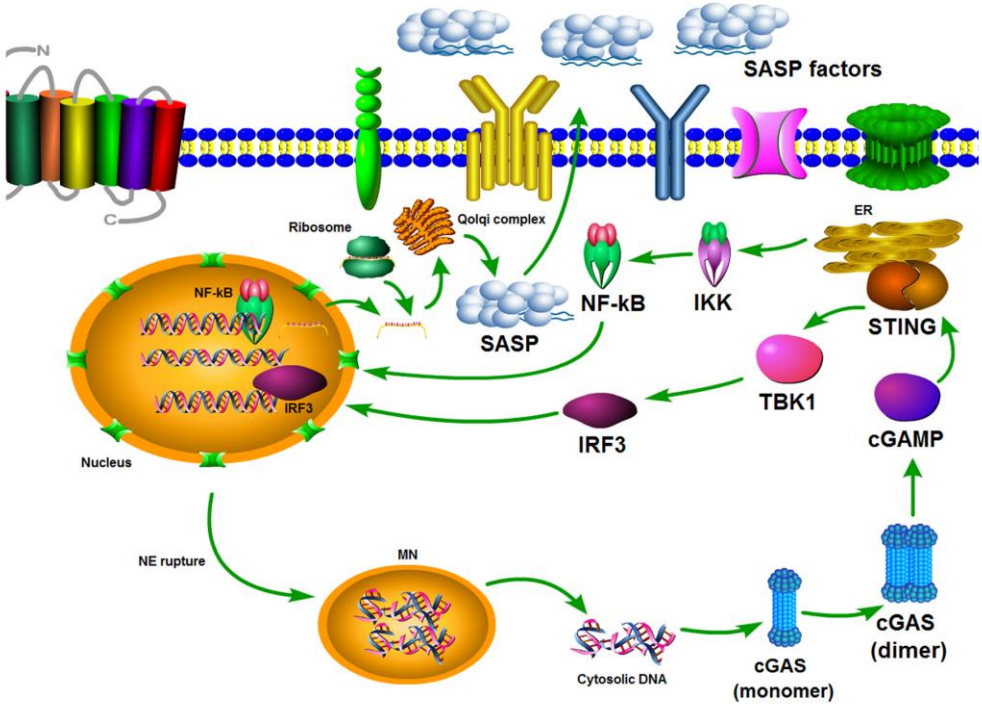

Figure 1. The cGAS-STING pathway detects cytoplasmic chromatin after genomic DNA damage and activate type I IFNs and other cytokines. Like DDR, the immune response is induced by various forms of genotoxic stress, including but not limited to ionizing radiation, oncogenic signaling, oxidative stress and telomere shortening. Nuclear DNA damage can generate cytoplasmic chromatin pieces in several possible ways, among which one is predominant. That is, genomic damage causes chromosome to missegregate in subsequent cell divisions, while the chromosome failing to partition into the new nuclei will form MN. When the NE ruptures, the DNA content is released and exposed to cGAS surveillance. Active cGAS dimerizes to synthesize cGAMP from GTP and ATP, while cGAMP acts as a second messenger to activate STING which localizes on the ER surface. Subsequently, STING activates transcription factors IRF3 and NF-κB via kinases TBK1 and IKK, respectively. IRF3 and NF-κB translocate into the nucleus to initiate expression of IFNs and other cytokines. Similarly, damage to mitochondrial can also lead to accumulation of cytosol DNA fragments, resulting in cGAS activation and cell auto-inflammation.

Abbreviations: cGAS-STING, cyclic guanosine monophosphate (GMP)-adenosine monophosphate (AMP) synthase-stimulator of interferon gene; ER, endoplasmic reticulum; IFN, interferon; DDR, DNA damage response; MN, micronuclei; NE, nuclear envelope.

cGAS-STING links genomic instability to innate immunity

Genomic DNA is strictly compartmentalized within the nucleus to prevent auto-immunity (26). However, cGAS as a cytoplasmic sensor of double-stranded DNA, is potently activated in auto-inflammatory diseases and in response to DNA-damaging insults (27, 28). Accumulating evidence suggests that innate immune cells, such as macrophages and dendritic cells, play an important role as central instigators to provoke immune surveillance against pathogenic invasion, whereas adaptive immune cells, mainly T lymphocytes, are crucial as active executors of the host immunity in various conditions (29). Despite the lack of knowledge supporting how genomic DNA gains access to the cytosol, a recent study disclosed that cGAS localizes to micronuclei (MN) arising from genome instability caused by DNA damage in a monogenic auto-inflammation mouse model (Rnaseh2bA174T/A174T), a process that also occurs spontaneously in human cancer cells such as U2OS, an osteosarcoma epithelial line (30). Specifically, RNase H2 deficiency results in the formation of MN after missegregation of genomic DNA during cell division, while breakdown of the micronuclear envelope, a process associated with chromothripsis, induces rapid accumulation of cGAS, providing a mechanism by which self-DNA is exposed to the cytosol (30, 31). Integrating live-cell laser microdissection with single cell transcriptomics, the study established that interferon-stimulated gene expression is induced in cells harboring MNs, which represent an important source of immune-stimulatory DNA. Thus, recognition of MNs by cGAS may act as a cell-intrinsic immune surveillance mechanism that detects a wide range of carcinogenesis-inducing activities.

The generation of cytotoxic T lymphocytes that recognize specific antigens manifested on the surface of cancer cells constitutes an important host defensive response, which has evolved to prevent cancer development (32). In contrast, the ability of dying cancer cells to activate antigen-presenting cells (APCs) is strictly regulated to avoid unwarranted or overt inflammatory responses (33). A new study reported that engulfed cells containing cytosolic double-stranded DNA species (viral or synthetic), or cyclic di-nucleotides (CDNs) can stimulate APCs via extrinsic STING signaling, a process that eventually promotes antigen cross-presentation (34). Cytosolic STING activators such as CDNs represent cellular danger-associated molecular patterns (DAMPs) only generated by viral infection or after genotoxic stress that renders cancer cells highly immunogenic, thus presenting a mechanism that drives appropriate anti-cancer adaptive immunity and providing a therapeutic strategy for future clinics.

In most cases, cGAS-cGAMP-STING is a major pathway that mediates immune surveillance against infections by diverse classes of pathogens containing DNA or generating DNA in their life cycles. However, the role of the cGAS pathway is not restricted to antimicrobial defenses, as cGAS can be activated by any forms of double-stranded DNAs, including genomic and mitochondrial DNA (14, 35). In response to cellular stresses or environmental insults such as chemotherapy and radiation, genomic and/or mitochondrial DNA might enter the cytoplasm where it activates cGAS to trigger inflammatory responses. Of note, chronic activation of cGAS contributes to autoimmune disorders such as systemic lupus erythematosus or rheumatoid arthritis (27, 36-38). Gain-of-function mutations of STING can cause severe auto-inflammatory diseases collectively termed STING-associated vasculopathy with onset in infancy (SAVI) (39, 40). Activation of cGAS pathway is also linked to Parkinson's disease, whereby mutations of the Parkinson's disease-associated genes PARKIN and PINK1 lead to defective autophagy of damaged mitochondria (mitophagy) and release of mitochondrial DNA

fragments into the cytoplasm (41).

cGAS-STING mediates DNA damage-induced cellular senescence

Cellular senescence is a state of essentially irreversible cell cycle arrest, induced by an array of internal or external stress such as telomere attrition, oxidative insults, oncogenic activation and various types of chemical stimuli. Although the causes and consequences of cellular senescence can vary, persistent DDR seems to be the common mechanism biologically critical for the establishment and maintenance of senescence phenotypes (42).

Senescent cells synthesize and secrete a wide variety of inflammatory factors, collectively referred to as the senescence-associated secretory phenotype (SASP) (43-45). Molecular mechanisms underlying the SASP formation and development remains incompletely understood, although increasingly lines of studies have revealed critical molecules and key pathways implicated in the SASP expression. Data from recent investigations defined a role for innate DNA sensing in the regulation of cellular senescence and the SASP. Specifically, cGAS recognizes cytosolic chromatin fragments in senescent mouse embryonic fibroblasts (MEFs) and triggers the production of SASP factors via stimulator of STING, thereby promoting paracrine senescence (46).

The activation of cGAS takes place following its recognition of aberrant cytoplasmic chromatin fragments (CCFs), which emerge in senescent cells because of nuclear lamin B1 degradation (47). CCFs usually carry genomic DNA, γH2AX and heterochromatin markers including H3K9me3 and H3K27me3, but miss certain euchromatin markers such as H3K9ac, suggesting that CCFs originally derive from transcriptionally repressed heterochromatin structures after DDR events (47, 48). Further, diverse triggers of cellular senescence, including oncogene signaling, oxidative stress and ionizing irradiation depend on cGAS-STING signaling to drive the production of inflammatory SASP factors, a feature that was also observed in vivo of experimental mice injected with transposons encoding oncogene NRasG12V (46), thus establishing endogenous DNA sensing through the cGAS-STING pathway as an important modulator of senescence and the SASP.

Interestingly, cellular senescence is associated with robust induction of CCF and pro-inflammatory factors, but not interferons (49). The failure to induce expression of interferons may be attributed to activation of the p38 mitogen-activated protein kinase (p38MAPK) in senescent cells, as p38MAPK inhibits STING-mediated interferon production (50, 51). To the contrary, SB203580, a p38MAPK inhibitor, potentiated interferon-β expression in senescent cells (49). The suppression of interferon upon cellular senescence is consistent with the observation that chronic interferon synthesis leads to immune checkpoint activation (52).

Upon elimination of cGAS or STING in human diploid fibroblasts (HDFs), several markers of senescence such as p16 upregulation and lamin B1 loss still appeared when cellular senescence was induced, but expression of key SASP factors including IL-1α and IL-9 essentially diminished. Following RNA sequencing (RNA-seq) in control and cGAS-deficient cells undergoing DNA damage-induced senescence, gene ontology analysis of the top downregulated genes revealed marked enrichment of the SASP program, a distinct pattern that was reproduced at the secreted protein level in conditioned media (49). Taken together, these results substantiated that cGAS-STING is functionally required for both induction and maintenance of the SASP program in senescent cells.

Concluding remarks and future perspectives

For years, cGAS is understood as a major cytosol sensor of microbial pathogens that contain nucleic acids, here mainly referred to DNA, or generate DNA in their life cycles. However, intensive studies have recently discovered a novel but equally critical role of cGAS in the surveillance of self-DNA that mislocalizes to the cytosol in pathological conditions. It is now evident that cGAS is well tuned to connect genomic DNA damage to inflammatory responses, as cGAS can be activated by dissegregated dsDNA that enters the cytoplasm in the case of multiple forms of stress including but not limited to chemical and physical insults to DNA, or more frequently, aberrant biological processes such as oncogene activation, telomere shortening and cell division accidents, events that all impinge on the structural integrity of genomic DNA.

Some components of the SASP are not only biomarkers of cellular senescence, but also active in driving paracrine senescence, such as Interleukin 6 (IL-6) and IL-8, two hallmark SASP factors that can initiate and orchestrate the senescence phenotype in neighboring cells via paracrine pathways (53). In addition, the SASP can attract immune cells in the microenvironment to eliminate the senescent cells (54). Besides these unique features, SASP is regulated at both transcriptional and epigenetic levels, such as modulation by NF-κB, c/EBPβ, BRD4, MLL1, G9A, GATA4, and Zscan4 (44, 45, 55-60). However, the precise intracellular mechanism directly linking the cGAS-STING pathway components to above regulators of the SASP remains unknown yet, which represents an intriguing but challenging topic in both senescent biology and immune research.

Our knowledge regarding the role of cGAS-STING pathway in cases of DDRs may be translated into clinical therapies against multiple human pathologies. Antagonists of cGAS or STING are potentially useful in blocking uncontrolled cytokine production in DNA-damaged cells, a cue that can lead to inflammation and auto-immune diseases. Since these antagonistic agents may inhibit cellular senescence, they may also be used for treating age-associated disorders. A few waves of attempts have been made to find compounds that inhibit the cGAS-STING pathway. To date, the pilot molecules are active against cGAS in vitro, but their potency in vivo remains largely unexplored, and STING-specific inhibitors are even lacking (61-64). A concern about employing cGAS or STING antagonists to treat inflammation or aging-related diseases is a potential increase of susceptibility to infectious pathogens as well as enhanced incidence of cancer. However, functional redundancy in human immune system and appropriate selection of drug doses to suppress the cGAS-STING pathway would allow these agents to provide sufficient therapeutic benefits while sustaining the innate immunity of patients against microbial infections and carcinogenesis.

Declarations

1) ***Consent to publication***
   We declare that all authors agreed to publish the manuscript at this journal based on the signed Copyright Transfer Agreement and followed publication ethics.
2) ***Ethical approval and consent to participants***
   Not applicable.
3) ***Disclosure of conflict of interests***
   We declare that no conflict of interest exists.
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5) ***Availability of data and material***

We declare that the data supporting the results reported in the article are available in the published article.

6) Authors' Contributions

Authors contributed to this paper with the design (YS), literature search (QX, CY, YS), drafting (QX, CY, YS), revision (YS), editing (YS) and final approval (YS).

7) *Acknowledgement*

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8) Authors' biography

None

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