7-6-2023

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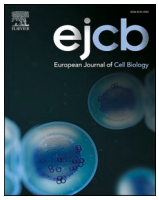
European Journal of Cell Biology 102 (2023) 151338

Contents lists available at ScienceDirect

European Journal of Cell Biology

journal homepage: www.elsevier.com/locate/ejcb



Cancer cell-specific cGAS/STING Signaling pathway in the era of advancing cancer cell biology

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ARTICLE INFO

Keywords:
Cancer
Inflammation
NF-κB
Tumor
TME
TIME
cGAS
STING
Type 1 IFNs

ABSTRACT

Pattern-recognition receptors (PRRs) are critical to recognizing endogenous and exogenous threats to mount a protective proinflammatory innate immune response. PRRs may be located on the outer cell membrane, cytosol, and nucleus. The cGAS/STING signaling pathway is a cytosolic PRR system. Notably, cGAS is also present in the nucleus. The cGAS-mediated recognition of cytosolic dsDNA and its cleavage into cGAMP activates STING. Furthermore, STING activation through its downstream signaling triggers different interferon-stimulating genes (ISGs), initiating the release of type 1 interferons (IFNs) and NF-κB-mediated release of proinflammatory cytokines and molecules. Activating cGAS/STING generates type 1 IFN, which may prevent cellular transformation and cancer development, growth, and metastasis. The current article delineates the impact of the cancer cell-specific cGAS/STING signaling pathway alteration in tumors and its impact on tumor growth and metastasis. This article further discusses different approaches to specifically target cGAS/STING signaling in cancer cells to inhibit tumor growth and metastasis in conjunction with existing anticancer therapies.

1. Introduction

Pattern recognition receptors (PRRs) recognize endogenous death/damage-associated molecular patterns (DAMPs) and exogenous microbe or pathogen-associated molecular patterns (MAMPs or PAMPs) to initiate a protective proinflammatory immune response (Kumar, 2022; V, 2018). Toll-like receptors (TLRs), nucleotide oligomerization domain (NOD) like receptors (NLRs), retinoic acid-inducible gene-1 (RIG-1)-like receptors (RLRs), C-type lectin receptors (CLRs), and absent in melanoma-2 (AIM2)-like receptors (ALRs) are some PRRs with crucial immunoregulatory functions (Li and Wu, 2021). In addition, PRRs are crucial to mount an anticancer proinflammatory innate immune response at early stages (Man and Jenkins, 2022). However, uncontrolled and polarized immune responses generate a cancer-supportive tumor immune microenvironment (TIME) by promoting immunosuppression.

The cyclic guanosine monophosphate (GMP)-adenosine monophosphate (AMP) synthase (cGAS or C6orf150 or MAB-21 domain-containing protein 1 or MB21D1)/stimulating interferon genes (STING) pathway also serves as a critical cytosolic PRR signaling event in cancer pathogenesis (Samson and Ablasser, 2022). Human cGAS (h-cGAS, a ~522 amino-acids protein) is a member of the nucleotidyltransferase (NTase, which transfer nucleoside monophosphate (NMP) from nucleoside triphosphate (NTP) to an acceptor hydroxyl (OH) group to proteins, nucleic acids, and other small molecules) enzyme family that works upstream of STING (Kuchta et al., 2009; Hopfner and Hornung, 2020; Sun et al., 2013). cGAS was initially recognized as an interferon-stimulated gene (ISG) (Schoggins et al., 2011). On the other hand, STING (a 42 kDa dimeric transmembrane protein (TMEM173) is predominantly expressed in macrophages, T cells, dendritic cells (DCs), endothelial cells, epithelial cells, and fibroblasts (Barber, 2014, 2015).

The cGAS/STING pathway detects DNA damage-induced

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https://doi.org/10.1016/j.ejcb.2023.151338
Received 17 March 2023; Received in revised form 27 June 2023; Accepted 4 July 2023
Available online 6 July 2023

micronuclei or cytoplasmic chromatin fragments and triggers a proinflammatory anticancer immune response through either cytotoxic activities or immune stimulation (Yum et al., 2020; Mackenzie et al., 2017; Harding et al., 2017; Motwani and Fitzgerald, 2017). cGAS-mediated micronuclei recognition involves chromothripsis (a complex process of chromosomal rearrangement)-induced rapid cGAS accumulation and subsequent STING-dependent ISG expression resulting in type 1 interferon (IFN) release and NF-κB activation (Mackenzie et al., 2017; Harding et al., 2017; Dewhurst, 2020). Thus, the cGAS/STING signaling pathway may serve as a cytosolic immune surveillance mechanism, recognizing a range of neoplasia-inducing processes, including micronuclei and cytosolic dsDNA in precancerous or premalignant cells. Hence, it is crucial to understand cGAS/STING signaling in cancer cells to delineate cancer pathogenesis and develop adjunct immunomodulatory approaches for enhancing the efficacies of currently available chemotherapies and radiotherapies and evolving immunotherapies, including DNA virus-based oncolytic virus therapies (OVTs).

2. cGAS/STING signaling pathway is crucial in maintaining cellular homeostasis

The cGAS/STING pathway can be classified into canonical and non-canonical signaling pathways (Fig. 2) (Kumar, 2019, 2021). Canonical cGAS/STING signaling governs IRF3-dependent type 1 IFN generation and NF-κB-dependent synthesis and release of proinflammatory molecules and cytokines (Fig. 1). The non-canonical cGAS/STING signaling induces cellular senescence (via STING-mediated senescence-associated secretory phenotype (SASP) production), autophagy (STING-dependent but TANK-binding kinase 1 (TBK1), and IFN-independent), and links to cell death/apoptosis and proliferation control (Fig. 1) (Dou et al., 2017; Glück et al., 2017; Yang et al., 2017; Gui et al., 2019; Liu et al., 2019; Wu et al., 2019; Cerboni et al., 2017). Also, cGAS/STING/PKR-like endoplasmic reticulum kinase (PERK)/ eukaryotic translation initiation factor 2alpha (eIF2α) pathway has recently been identified as another non-canonical signaling pathway that forms an inflammatory- and survival-preferred translation program that is evolutionarily primitive and physiologically critical to cellular senescence and fibrosis induction (Fig. 1). The activation of the cGAS/STING/PERK/eIF2α pathway induces a global mRNA translation arrest. It is independent of UPR transducers (serine/threonine-protein kinase/endoribonuclease inositol-requiring enzyme 1 α (IRE1α) and activating transcription factor 6 or ATF6) with marginal activation of canonical downstream targets of eIF2α (ATF4 and CCAAT/enhancer-binding protein (C/EBP) homologous protein or CHOP), suggesting that the STING/PERK/eIF2α axis is specific and largely independent of the classical endoplasmic reticulum (ER) stress response (Zhang et al., 2022; Hetz and Glimcher, 2009). Targeting cGAS/STING/PERK/eIF2 attenuates lung and kidney fibrosis which can also vitiate different cancers as fibrosis is a hallmark of cancer, and up to 20% of cancers are associated with chronic inflammation-related fibrosis (Chandler et al., 2019; Karampitsakos et al., 2017; Piersma et al., 2020; Hosein et al., 2020).

cGAS is not freely floating in the cytosol. Instead, it predominantly localizes to the inner plasma membrane leaflet through its N-terminal domain (Fig. 2) (Barnett et al., 2019). cGAS N-terminal domain interacts with the inner plasma membrane leaflet via phosphatidylinositol 4, 5-biphosphate (PIP2 or PtdIns(4,5)P2) in a steady state. The membrane-localized cGAS provides a fast way to detect invading DNA viruses or DNA released from dying cancer cells or DNA contained in exosomes or extracellular vesicles (EVs) entering through endocytosis (Fig. 2). For example, foreign DNA (pathogen-derived or dying cancer cell-derived) uptake via endocytosis induces spleen tyrosine kinase (SYK) and cGAS recruitment to the endosome.

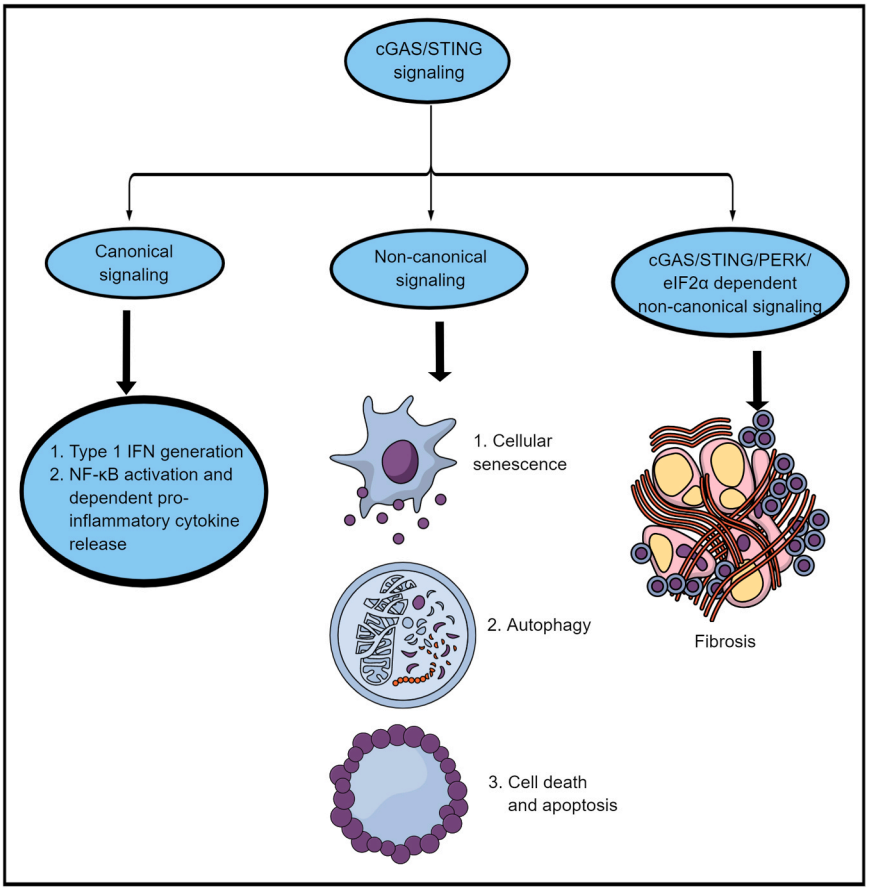

Fig. 1. A glance on the canonical and non-canonical cGAS/STING signaling pathway. Canonical cGAS/STING signaling pathway activation in response to the cytosolic dsDNA triggers type 1 IFN and NF-κB-mediated proinflammatory immune response. The non-canonical pathway is STING dependent but cGAS, TBK1, and IFN-independent that mediates cellular senescence, autophagy, and apoptotic cell death. Another recently discovered non-canonical cGAS/STING/PERK/eIF2α is crucial for inflammatory and survival translation programs that induces organ fibrosis. Kindly see the text for details.

The endosomal vacuolar H^+ pump (V-ATPase) activated SYK phosphorylates h-cGAS$^{Y214/215}$ or mouse or m-cGAS$^{Y200/201}$ to prime its activation (Yang et al., 2022a). Mutant cGAS cannot bind to the inner plasma membrane because the defective lipid binding is localized to the cytosol and nucleus (Fig. 2). Mislocalized cytosolic cGAS is a potent type 1 IFN inducer against self-DNA released into cytosol during genotoxic stress compared to the invading pathogen DNA (virus and bacteria) or dying cancer cell DNA. Also, the genotoxic stress-inducing DNA damage breaks the cGAS-linkage to the inner leaflet of the plasma membrane (Fig. 2). As a result, it induces its movement to the nucleus, suppressing cGAS activity to recognize cytosolic DNA acutely and suppressing cancer development at the initial stages (Fig. 2) (Liu et al., 2018). Hence, cytosolic cGAS localization is crucial for its PRR activity against different stimuli, including microbial DNA, cytosolic self-DNA, mitochondrial DNA, and nuclear chromatin, as discussed below (Fig. 2) (Hopfner and Hornung, 2020). Oxidized cytosolic DNAs (generated during ultraviolet (UV) rays' exposure and other chronic oxidative stress conditions) are resistant to digestion by cytosolic nucleases, including cytosolic DNase 3' repair exonuclease 1 (TREX1) (Fig. 2). They, therefore, are potent inducers of cGAS activation-mediated type 1 IFN release (Gehrke et al., 2013). For example, TREX1 and exonuclease 1 (having 5' flap endonuclease activity for Okazaki fragment processing and post-replicative ribonucleotide excision repair) continuously check on released immunogenic DNA waste generated during genomic replication by degrading them (Schubert et al., 2022). Hence, TREX1 and exonuclease 1 deficiency can generate the cGAS/STING-dependent type 1 IFN and associated chronic inflammation (Fig. 2).

cGAS recognizes and catalyzes cytosolic double-stranded DNA (dsDNA) with at least 36 base pairs (bp) long to generate 2',3'-cyclic GMP-AMP (2',3'-cGAMP) (Sun et al., 2013; Kumar, 2019; Kato et al., 2017; Gao et al., 2013; Xie et al., 2019). Adenosine triphosphate (ATP) and guanosine triphosphate (GTP) are required for *in vitro* cGAMP production from dsDNA via cGAS (Wu et al., 2013; O'Neill, 2013). Notably, cytosolic RNAs colocalize with phase-separated condensates of cGAS and dsDNA, promoting the formation of cGAS-containing phase separations and enhancing the cGAS activity at low cytosolic dsDNA level (Chen et al., 2023). Thus, although RNAs do not directly bind and activate cGAS, but promote the cGAS-condensate formation at low cytosolic dsDNA levels for generating a potent type-1 IFNs level. Interestingly, at a high cytosolic dsDNA level, RNA competes with it in phase-separated granules of cGAS to inhibit the cGAS activity. Therefore, at a low cytosolic dsDNA level, RNA promotes cGAS activity but inhibits the cGAS activity at a higher cytosolic dsDNA level. cGAS (structurally, a member of the second-messenger enzymes family in innate immunity) binds to the sugar-phosphate backbone of the cytosolic dsDNA without binding to any of its nitrogen bases, indicating cGAS-dsDNA binding is a sequence-independent process. For example, cGAS structurally resembles the antiviral cytosolic dsRNA sensor 2'− 5'oligoadenylate synthase 1 (OAS1) but contains a unique Zinc (Zn^{2+}) thumb to recognize the B form dsDNA (Civril et al., 2013). Zn^{2+} finger CCHC domain-containing protein 3 (ZCCHC3) directly binds to the dsDNA as a co-sensor and enhances its recognition by cGAS to generate cGAMP (Fig. 2) (Lian et al., 2018). ZCCHC3 deficiency inhibits dsDNA-cGAS interaction and thus cGAMP generation, the type 1 IFN synthesis, and the associated proinflammatory immune response. In addition, increased ZCCHC3 expression has been seen in osteosarcoma (Wang, 2021).

cGAMP serves as an endogenous second messenger or an immunotransmitter recognized by cytosolic STING, producing proinflammatory cytokines and type 1 IFN. The recognition of smaller cytosolic ds DNAs (15–35 bp) inhibits cGAS enzymatic activity to generate cGAMP, inhibiting the STING activation and type 1 IFN generation (Liu et al., 2022a; Chen et al., 2016a). Instead, small cytosolic dsDNAs induce cGAS interaction with Beclin-1 that removes Rubicon (it negatively regulates phosphatidylinositol 3-kinase class III (PI3KC3) from Beclin-1-PI3KC3 complex for initiating autophagy (Liu et al., 2022a). Thus, small cytosolic dsDNAs are endogenous molecular brakes for cGAS activation, which may be helpful to prevent acute inflammatory damage but help cancer growth and metastasis by supporting chronic low-grade inflammation. Longer dsDNAs induce allosteric cGAS dimerization and form 2:2 cGAS: DNA complex crucial to generating cGAMP and STING-dependent type 1 IFN and other NF-κB-dependent proinflammatory cytokines. The allosteric cGAS dimerization induced by its N-terminal domain is further promoted by clustering, forming a ladder-like network with the binding DNA (Andreeva et al., 2017; Hooy and Sohn, 2018). The high-mobility group box 1 protein (HMGB1) and mitochondrial transcription factor A (TFAM) sternly stimulate long DNA sensing by cGAS via inducing U-turns and bends in the DNA (Andreeva et al., 2017). Hence, cGAS preferentially binds to incomplete nucleoid-like structures or bent DNA.

Notably, longer single-stranded DNAs (ssDNAs) can weakly stimulate cGAS enzymatic activity as positively charged residues on cGAS recognize the cytosolic DNA's sugar-phosphate backbone. However, cytosolic RNAs (ssRNA and dsRNA) cannot activate cGAS (Kranzusch et al., 2013; Zhang et al., 2020a). The weaker cGAS activation by ssDNA may generate a chronic low type 1 IFN that supports cancer growth. It is important to note that h-cGAS has different DNA-length specificity than mice cGAS (m-cGAS) for enhanced immune surveillance (Andreeva et al., 2017; Luecke et al., 2017; Zhou et al., 2018). Also, cGAS activation may not need the cytosolic dsDNA as a nuclear RNA-cDNA hybrid intermediate called long interspersed nuclear element-1 (LINE-1, a retrotransposon) originating in the RNase-H2 deficiency could activate cGAS/STING signaling pathway (Fig. 2) (Benitez-Guijarro et al., 2018). The LINE-1 expression correlates well with p53 mutation, and most cancers either lack functional p53 due to mutation or completely lack p53 protein (McKerrow et al., 2022).

The increased hypomethylated LINE-1 levels in normal cells of different tissues, including the colon and cervix, increase their predisposition to develop associated cancer via chronic cGAS activation without any external chronic inflammogen/mutagen exposure (Fig. 2) (Xiao-Jie et al., 2016; Zhang et al., 2020b). Also, human colorectal cancer cells from patients with low RNase-H2 show decreased survival, indicating an increased LINE-1 level is responsible for chronic low-grade cGAS/STING activation to promote cancer growth and metastasis (Aden et al., 2019). Similar findings have also been reported in mice lacking RNase-H2 in their epithelial cells (skin and gastrointestinal tract or GIT), which have increased DNA damage and spontaneously developed small intestine and colon carcinoma and squamous cell carcinoma of the skin (Aden et al., 2019; Hiller et al., 2018). Interestingly, RNase-H2 is crucial for genome integrity via removing ribonucleotides from DNA, and its expression decreases in senescent and cancer cells that drive inflammatory gene expression via genomic DNA fragmentation (Hiller et al., 2012; Sugawara et al., 2022). Thus, RNase-H2 deficiency via promoting genomic instability and LINE-1 levels promotes chronic low-grade cGAS/STING activation, possibly leading to inflammation-associated cancer (Fig. 2). Further studies are warranted in this direction.

The DNA mechanical flexibility, governed by DNA sequence, -damage, and -length, determine its potential to bind and activate cGAS (Wang et al., 2022). The conserved cGAS residue (mouse R222 and human R236) determines DNA flexibility and associated cGAS activation. The DNA binding to cGAS robustly forms liquid-like droplets in which cGAS becomes activated, and long DNAs are more efficient in this process than short DNA (Du and Chen, 2018; Ablasser, 2018). Hence, DNA binding to cGAS induces a phase transition (liquid-like droplet formation or liquid-like phase-separated condensates) to induce cGAMP formation and STING activation-dependent type 1 IFN release. The Zn^{2+} presence increases the formation of such condensates or liquid-like droplets *in vivo (* Du and Chen, 2018*)*. Also, nuclear cGAS is bound to intranuclear chromatin, specifically on centromeres and pericentric heterochromatic regions dense in nucleosomes (Gentili et al., 2019; Volkman et al., 2019). The non-enzymatic N-terminal domain of cGAS determines its nucleo-cytoplasmic localization, enrichment on

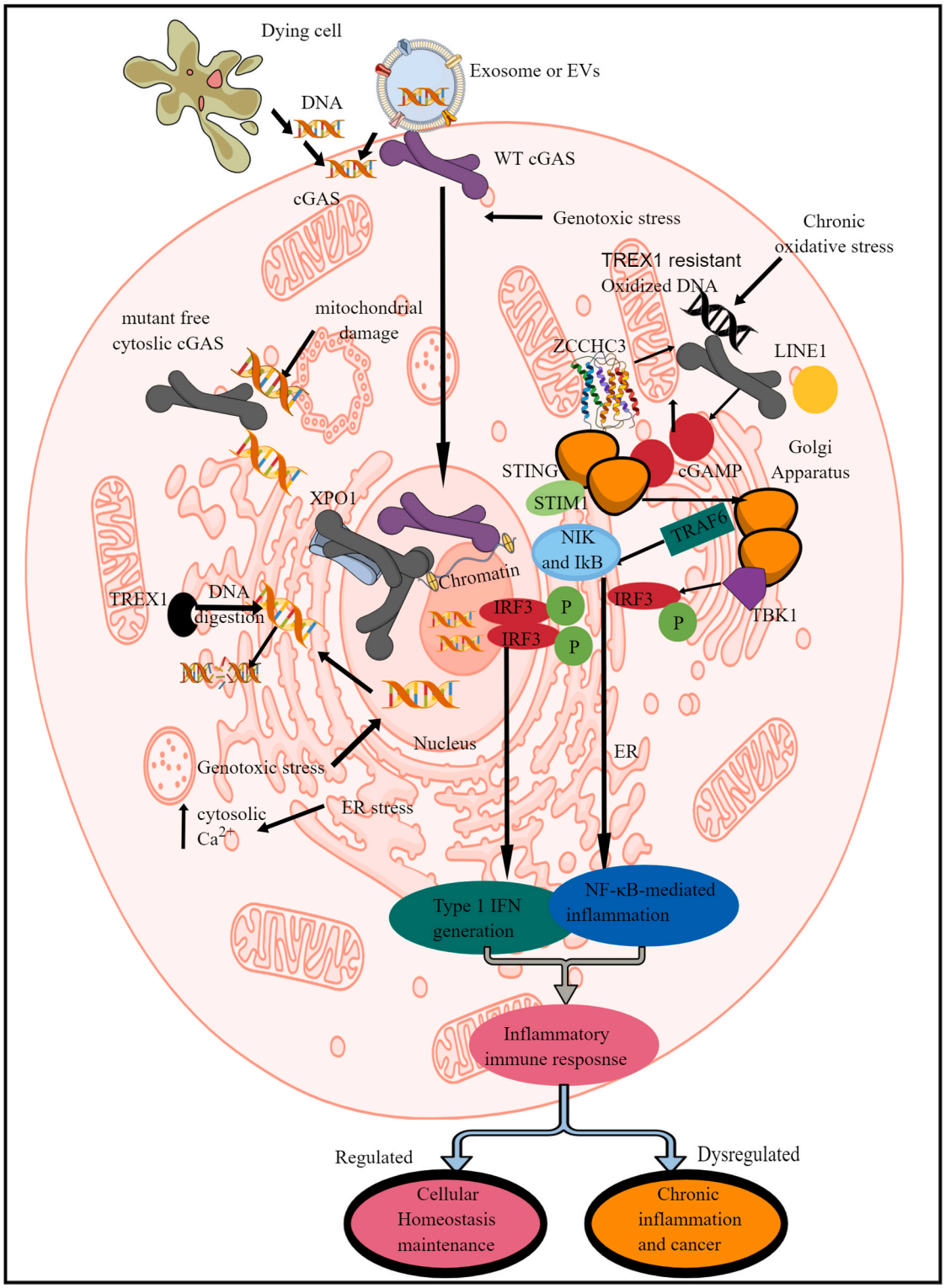

Fig. 2. cGAS/STING signaling is crucial in maintaining cellular homeostasis. cGAS is an intracellular PRR attached to the inner side of the cell membrane that helps to frequently recognize of the foreign dsDNA (host and pathogen-derived). The mutant cGAS fails to attach with cell membrane and resides in the cytosol and nucleus. Also, under genotoxic stress membrane bound cGAS moves to the nucleus that prevents/decreases its PRR activity for generating acute cell or tissue protective innate immune response. The cytosolic cGAS recognizes cytosolic dsDNA to generate 2'– 3'-cGAMP or cGAMP. cGAMP binds to the adaptor protein called STING located in the ER. The cellular or ER stress increases the cytosolic Ca^{2+} that frees the STING from STIM in the ER and STING shows ERGIC movement or moves to the Golgi apparatus from ER. In the Golgi apparatus cGAMP bound STING recruits TBK1 and IRF3. The downstream IRF3 activation is responsible for type 1 IFN generation. TRAF6 recruitment via NIK and IκB downstream signaling is responsible for NF-κB activation and generation of pro-inflammatory cytokines (TNF-α, IL-6, and IL-12). Acute inflammatory response is crucial in the danger removal and maintaining the cellular/tissue homeostasis. However, the chronic and low-grade type 1 IFN and NF-κB-dependent pro-inflammatory cytokines' generation creates a tumor supportive environment. TREX1 (a cytosolic nuclease) is an endogenous negative regulator of cGAS/STING signaling pathway. ZCCHC3 promotes cGAS activity by binding to the cytosolic dsDNA. The nuclear cGAS unresponsive to the

nuclear DNA comes out to the cytosol via XPO1 to act as PRR for the cytosolic dsDNA under genotoxic or other cellular stressful condition. *Details are mentioned in the text.*

centromeres, and activation of nuclear-localized cGAS (Gentili et al., 2019). The functional leucine-rich nuclear export signal (NES) between the N and C terminal of cGAS is crucial to sense cytosolic DNA and its nuclear export (Gentili et al., 2019; Sun et al., 2021). Notably, nuclear cGAS is 200 times less efficient at recognizing self-DNA as a DAMP than exogenous cytosolic DNA. The expulsion of nuclear cGAS to the cytosol occurs by an active mechanism involving exportin 1 (XPO1) or CRM1 (*c*hromosomal *r*egion *m*aintenance) (Fig. 2) (Sun et al., 2021; Stade et al., 1997). Nuclear cGAS does not recognize nuclear DNA as a DAMP because it is available as chromatin rather than naked DNA (Zierhut et al., 2019). However, the nuclear export signal (NES, 169LEKLKL174) is present in cGAS, which determines its translocation or export from the nucleus to the cytoplasm to sense cytosolic DNA as a DAMP or PAMP (Sun et al., 2021). Hence, recognizing six amino acid sequences, 169LEKLKL174 of the cGAS by CRM1, specifically L172 of the NES, determines cGAS translocation from the nucleus to the cytosol, where it acts as a PRR for cytosolic DNA. A mutation in this 6 NES removes its PRR activity for cytosolic DNA and the type 1 IFN generation.

cGAS activation stimulates more type 1 IFN (IFN-α and -β) production than other cytosolic PRRs (TLR7 and TLR9) that recognize cytosolic dsDNA. STING (a 379 amino acid protein in humans) recognizes cGAMP and activates IRF3 via TBK1 recruitment and NF-κB by kinase IKKβ (Iκ B kinase) (Barber, 2014, 2015; Ishikawa and Barber, 2008). The TBK1 recruitment and activation involve the conserved PLPLRT/SD motif within the C-terminal tail of STING (Zhao et al., 2019). The TBK1 recruitment to STING activates IRF3 and NF-κB-dependent immunity, including anticancer immune response (Yum et al., 2021). The calcium (Ca^{2+}) sensor stromal interaction molecule 1 (STIM1, an EF-hand-containing Ca^{2+}-binding protein) interaction with STING retains it in the ER compartment under normal conditions (high ER Ca^{2+} level) (Fig. 2). However, increased cytosolic Ca^{2+} levels during inflammatory signaling (ER stress) disrupt this association, leaving STING free to move from the ER to the ER-Golgi intermediate compartment (ERGIC) and Golgi apparatus (Fig. 2) (Srikanth et al., 2019; Chaudhari et al., 2014; Smith, 2020; Harapas et al., 2022; Dobbs et al., 2015). STING trafficking is a crucial cGAS/STING signaling-dependent function, including autophagy, type 1 IFN generation, and NF-κB-dependent cytokine release (Fig. 2) (Jeltema et al., 2023). TBK1-mediated IRF3 phosphorylation and dimerization work with the myeloid-specific transcription factor (TF) IRF8 to produce IFN-β in specific human monocytes (Kato et al., 2017; Balka et al., 2020a; Li et al., 2011). It is important to note that human cells may have natural STING variants, which are poorly responsive to cGAMP. However, a response to DNA and cGAS signaling may have evolved to discriminate between pathogen-derived and self-DNA-generated CDNs. These STING variants in cancer cells may alter anticancer immunity in the tumor microenvironment (TME) or TIME.

Blocking STING-dependent TBK1 phosphorylation prevents IRF3 activation and dependent ISGs, including type 1 IFNs, thereby demonstrating TBK1's importance in the cGAS/STING signaling-mediated immune response (Yum et al., 2021). Although STING can work independently of type 1 IFN generation and autophagy, recruitment of TBK1 to STING is critical for its immunological functions. Notably, TBK1 alone is not essential for the STING-induced NF-κB-dependent immune response, and it works redundantly with IKK-ε to induce NF-κB activation (Balka et al., 2020b). Hence, cGAS/STING signaling activation produces type 1 IFNs and NF-κB-dependent proinflammatory cytokines, crucial for immune cell recruitment, function, and polarization.

Chronic inflammatory conditions that induce DNA damage and its leakage to the cytosol also chronically activate the cGAS/STING signaling pathway to support molecular carcinogenesis and metastasis (Fig. 2) (Ahn et al., 2014; Zheng et al., 2020a; Khoo and Chen, 2018; Chen et al., 2016b; Bakhoum et al., 2018). Furthermore, the chronic ER stress that occurs in the setting of chronic STING activation-mediated intracellular calcium (Ca^{2+}) impairment primes T cell death, thereby creating a cancer-supportive immunosuppressive TIME that is independent of type 1 IFN signaling (Wu et al., 2019; Ritchie et al., 2022; Larkin et al., 2017; Wu et al., 2020). Also, the vertebrate STING C-terminal tail (CTT) serves as a linear signaling hub that determines the type 1 IFN and NF-κB-mediated immune response generation in macrophages and T cells (de de de Oliveira Mann et al., 2019). Thus, STING-mediated chronic IRF3, NF-κB-dependent type 1 IFN, proinflammatory cytokine release, and independent signaling events regulating TME are critical for chronic inflammation-associated cancer development and metastasis (Fig. 2).

3. cGAS/STING signaling in cancer cells

cGAS phosphorylation at Ser305 in humans and Ser291 in mice by Akt/protein kinase B (PKB) serine/threonine protein kinase inhibits its enzymatic activity to catalyze cytosolic DNA to cGAMP and STING activation-dependent type 1 IFN production (Seo et al., 2015). The expression of intracellular phosphorylation-resistant cGAS S291A mutant in mice increases the type 1 IFN production upon cytosolic DNA stimulation. The increased Akt expression in cancer cells is associated with increased survival via preventing their apoptosis and rapid disease progression via different mechanisms (increasing aerobic glycolysis, epithelial to mesenchymal transition in squamous cell carcinoma) described elsewhere (Mundi et al., 2016; Toker and Yoeli-Lerner, 2006; Grille et al., 2003; Elstrom et al., 2004; Vivanco et al., 2014). Furthermore, the increased glycolysis in cancer cells is associated with decreased anticancer immune cell infiltration in the TME of solid human cancers (Cohen et al., 2022). Thus increased Akt expression in cancer cells by phosphorylating cGAS inhibits its potential to activate STING-dependent acute type 1 IFN to generate an anticancer immune response (Th1 immune response) at the earliest. Furthermore, cancer cells express Akt isoforms (Akt1 and Akt2) differently with different phosphorylation statuses (Wang et al., 2018). Hence, only cancer cells with higher active Akt expression will show phosphorylated or inactive cGAS.

Additionally, tubulin-tyrosine-like ligases 4 and 6 (TTLL4 and TTLL6) induce cGAS glutamylation to inhibit its cytosolic DNA cleaving activity required for STING-dependent type 1 IFN generation (Table 1) (Xia et al., 2016a). Cytosolic carboxypeptidases (CCPs) called CCP5 and CCP6 check cGAS inactivation by removing TTLL4 and TTLL6-induced mono and polyglutamylation (Xia et al., 2016a). The increased TTLL4 and TTLL6 expression in different cancer cells, including breast cancer (BC) and esophageal carcinoma, can also induce cGAS glutamylation/inactivity to prevent the type 1 IFN generation-mediated anticancer immune signaling, supporting cancer growth and metastasis (Qiu et al., 2020; Arnold et al., 2020). Thus, the cGAS/STING signaling pathway in different cancer cells depends on different factors, including cancer cell type, stage, and TIME.

For example, hepatocellular carcinoma (HCC) patients with elevated cGAS/STING signaling have high immune cell infiltration (Qi et al., 2020). However, regular mouse and human hepatocytes do not express STING and lack cGAS/STING-mediated type 1 IFN generation. Interestingly, Kupffer cells (liver macrophages) have intact cGAS/STING signaling pathways and can respond to cytosolic DNA to generate a potent anticancer immune response (Thomsen et al., 2016). Similarly, active or intact cGAS/STING signaling in pancreatic ductal adenocarcinoma (PDAC) cells increases cytotoxic anticancer $CD8^{+}$T cell infiltration along with other anticancer immunocompetent dendritic cells (DCs) and natural killer (NK) cells in TIME and increases patient survival

Table 1
cGAS/STING signaling activity in different tumor cell types along with their modifiers and mechanisms. ↓ and ↑ indicate decreased and increased levels/activity of cGAS and STING in different cancer cells. For details, please refer to the text.

Cancer Cell Type	cGAS activity	STING activity	cGAS/STING activity modifiers and mechanisms
Breast Cancer cells, excluding TNBC	↓ via Mono or polyglutamylation and its condensation	↓ via Demethylation	↑ H3K4 lysine demethylases (KDM5B and KDM5C) suppress STING activity (Wu et al., 2018), ↑ PCPB2 induces cGAS condensation (Gu et al., 2022), ↑ TTL4 and TTL6 induce cGAS glutamylation (Arnold et al., 2020)
TNBC cells	↓	↓	↑ Myc suppresses cGAS/STING via increasing DNMT1 transcription (Wu et al., 2021), ↑ ATAD3A (indirect action via controlling mitochondrial DNA release in the cytosol) (Teng et al., 2019)
Esophageal Carcinoma	↓	↓	↑ TTL4 and TTL6 (Qiu et al., 2020)
CRC cells	↓	↓	↑ H3K4 lysine demethylase, ↑ATAD3A (Teng et al., 2019; Huang et al., 2021)
Melanoma cells	↓	↓	↑ H3K4 lysine demethylase (Xia et al., 2016a)
Glioma cells	↓	↓	↑ H3K4 lysine demethylase (Low et al., 2022b), ↑ PCPB2 (Han et al., 2013; Mao et al., 2020)
Gastric Cancer cells	↓	↓	↑ PCPB2 (Chen et al., 2018b)
LUAD cells	↓ cGAS dimerization and cGAMP production	↓	↓ TRIM56 expression increases vimentin level that suppresses downstream TBK1-IKK-ε-IRF3 axis crucial for type 1 IFN generation (Lu et al., 2021) ↑ H3K4 lysine demethylase expression (Wu et al., 2018; lin et al., 2022)
Ovarian Cancer cells	↑ cGAS dimerization and cGAMP production	↑	↑ TRIM56 expression decreases vimentin level and activates downstream TBK1-IKK-ε-IRF3 axis crucial for type 1 IFN generation (Zhao et al., 2018)
Head & Neck cancer cells	↓	↓	↑ ATAD3A (Lang et al., 2022)

(Kabashima et al., 2022). The anticancer immune cell infiltration in PDACs with intact cGAS/STING signaling was also accompanied by the decrease in cancer-supportive cancer-associated fibroblasts (CAFs). Thus, cGAS/STING activation in PDACs decreases CAFs that support anticancer immune cell infiltration to kill PDAC cells. This study indicates that not all CAFs reduce the anticancer immune cells infiltration in the TIME but cGAS/STING signaling determines pro- and anti-tumor function of CAFs. Furthermore, the cGAS/STING signaling activation in the PDAC cells depends on polymerase theta (Polθ or POLQ, which is undetectable in normal cells and tissues) that affects the cytosolic micronuclei formation (Oh et al., 2023; Kawamura et al., 2004). For example, Polθ or POLQ deficiency in breast cancer gene 2 (BRCA2) negative PDAC cells increases cytosolic micronuclei formation, promoting cGAS/STING activation and anti-tumor $CD8^{+}$T cell infiltration in their TIME. Polθ regulates microhomology-mediated end-joining (MMEJ, also called alternative nonhomologous end joining) pathway of double-strand break (DSB) repair and its deficiency dysregulates cellular DNA repair mechanism, increasing the cytosolic dsDNA, which activates cGAS/STING signaling. Further studies are required for cGAS/STING signaling in context to different PDAC types as Polθ or POLQ, which have emerged as a new cGAS/STING regulator in BRCA2 negative PDACs. Hence, it will be interesting to observe Polθ or POLQ expression in other cancer types to-specifically determine and target cGAS/STING signaling in different cancer cell types.

cGAS/STING expression is lower in the peripheral blood mononuclear cells (PBMCs) of patients with metastatic non-small cell lung cancer (NSCLC) compared to patients with localized NSCLC (Raaby Gammelgaard et al., 2021). However, a recent study encompassing 18 cancer types has demonstrated an inverse correlation between cGAS/STING expression, immune cell infiltration in some cancers, and prognosis (An et al., 2019). Given these conflicting data, it is critical to understand the cancer-specific differences in cGAS/STING to utilize it as a biomarker. cGAS/STING signaling alteration in cancer cells may be due to many factors discussed below depending on the cancer type and stage.

Epigenetic silencing or loss-of-function mutation of cGAS or STING is responsible for decreased anticancer immunity in different cancers, including colorectal cancer (CRC), BC, melanoma, and gliomas (Zheng et al., 2023; Konno et al., 2018; Xia et al., 2016a; Low et al., 2022a; Xia et al., 2016b). Histone H3K4 lysine demethylases KDM5B and KDM5C epigenetically suppress STING, and HRK4 methyltransferase activates STING (Table 1) (Wu et al., 2018). Therefore, KDM5 (Lysine demethylase 5) family histone demethylase inhibition can potentiate STING signaling by inhibiting its epigenetic silencing (Konno et al., 2018; Wu et al., 2018). The decreased STING expression is associated with poor prognosis in gastric cancer and lung adenocarcinoma (LUAD) but not in lung squamous cell carcinoma (LUSC) (Song et al., 2017; lin et al., 2022). STING hypermethylation in LUAD cells compared to adjacent non-cancer lung cells correlates with an unfavorable outcome.

Tripartite Motif 56 (TRIM56, an E3 ligase) interacts with the amino-terminal regulatory domain of the cGAS to induce Lys335 mono-ubiquitination. The Lys335 monoubiquitination of the cGAS increases its dimerization, a crucial step in recognizing the cytosolic DNA to generate cGAMP that activates STING-dependent type 1 IFN generation (Seo et al., 2018). In ovarian cancer, TRIM56 prevents the cancer progression by degrading vimentin (a type III intermediate filament, and its overexpression in solid tumors drives epithelial to mesenchymal cell transition or EMT) (Table 1) (Zhao et al., 2018; You et al., 2021; Kidd et al., 2014; Satelli and Li, 2011). Vimentin also inhibits type 1 IFN generation by disrupting the TBK1-IKK-ε-IRF3 axis (Liu et al., 2022b). The decreased TRIM56 has also been reported in LUAD (Table 1). It is responsible for poor prognosis, which can be directly correlated with decreased STING levels due to low cGAS activity to generate cGAMP (Lu et al., 2021). Hence, overexpressing TRIM56 in cancer cells can directly (cGAS monoubiquitination promoting its dimerization) or indirectly (via targeting vimentin-mediated TBK1-IKK-ε-IRF3 axis) stimulate

cGAS/STING signaling-mediated protective anticancer immune response. For example, increased vimentin expression in butyrate/histone deacetylase inhibitor (HDACi)-resistant CRC cells further supports the cGAS/STING signaling alteration due to the defective TBK1-IKK-ε-IRF3 axis responsible for type 1 IFN generation for generating the anticancer immune response (Lazarova and Bordonaro, 2016).

It is important to note that increased TRIM56 expression in glioblastoma (GBM) decreases the radiosensitization in humans via promoting the DNA repair by inducing Forkhead box protein 1 (FOXM1) expression via STAT3 activation and promotes GBM malignant progression in animal xenograft model by stabilizing the inhibitor of apoptosis protein (IAP), clAP1 (a caspase 3 inhibitor) (Dong et al., 2022; Yang et al., 2022b; Maachani et al., 2016). The TRIM56-mediated decreased radiosensitization in GBM patients can be attributed to the epigenetic STING silencing by cg16983159 methylation in glioma and normal brain cells (Ishikawa and Barber, 2008; Low et al., 2022b; Qiu et al., 2022). The cg16983159 methylation-mediated STING silencing in GBM can be reversed by DNA methyltransferase (DNMT) inhibition (Decitabine, a DNMT inhibitor) to transform the cold GBM TME to hot GBM TME. Therefore, we can speculate that TRIM56 overexpression during GBM radiotherapy tries to protect from cell death due to over-accumulation of the damaged DNA in the cytosol in the presence of a defective cGAS/STING signaling in these patients. First, however, it is crucial to investigate a specific mechanism. Interestingly, murine GBM models established with murine glioma cell lines (GL261 and CT-2A) are responsive to STING agonists and promote robust immune response and NK-cell-based GBM regression (Berger et al., 2022; Ohkuri et al., 2014). The sensitivity of murine GBM to STING agonists indicates that GL261 and CT-2A glioma cells have intact cGAS/STING signaling, including the presence of WT p53 in CT-2A cells (Martínez-Murillo and Martínez, 2007). Therefore, results of murine glioma cell lines-based GBM studies investigating the impact of cGAS/STING therapy cannot be directly translated to human GBM patients.

The Ariadne RING-in-between-RING (RBR) E3 ubiquitin ligase (ARIH1 or HHRAI) also induces cGAS oligomerization via mono-ISGylation to promote cGAS/STING signaling-dependent type I IFN generation in MICs, including DCs (Xiong et al., 2022a). ARIH1 induces cGAS ISGylation at its K187 residue, potentiating its dimerization in cytosolic DNA. Another, cGAS-interacting protein Poly(rC)-binding protein 2 (PCBP2) inhibits cGAS enzymatic activity via promoting its condensation (Table 1) (Gu et al., 2022). Thus, an increased expression of PCPB2 suppresses cGAS activation. For example, the PCPB2 overexpression in different cancer cells, including BC, gastric cancer, and glioma cells, increases their viability, progression, metastasis, and poor outcome, which can be attributed to the lack of cGAS activation and STING-mediated anticancer action (Table 1). However, further studies are needed in this direction. However, PCPB1 enhances the cGAS activity by directly binding to DNA. As a result, it increases its interaction with cGAS (Liao et al., 2021), and its expression in different cancers, including LUAD, BC, ovarian, and prostate, decreases cancer growth and metastasis (Zheng et al., 2022; Shi et al., 2018; Woosley et al., 2019; Chen et al., 2021).

Myc is dysfunctional in more than half of human cancers and is associated with poor prognosis, given its intense involvement in numerous cancer processes (Chen et al., 2018a). Myc is also an epigenetic regulator of the cGAS/STING pathway. For example, Myc is overexpressed in triple-negative breast cancer (TNBC) cells and binds to the *DNMT1* gene promotor, thus activating *DNMT1* transcription in TNBC cells and suppressing the cGAS/STING pathways (Table 1) (Wu et al., 2021). ATPase family AAA domain-containing protein 3 A (ATAD3A) is a nuclear-encoded mitochondrial enzyme. Different cancers (CRC, TNBC, and head and neck cancer cells) overexpress ATAD3A, indicating its crucial role in cancer development, progression, metastasis, and chemoresistance via dysregulating mitochondrial-ER connection through different mechanisms, including increasing the PD-L1 expression by ATAD3A-PTEN-induced kinase 1 (PINK1) axis (Teng et al., 2019; Lang et al., 2022; Teng et al., 2016; Lang et al., 2020; Huang et al., 2021). However, ATAD3A overexpression negatively controls cGAS/STING signaling-mediated type 1 IFN release and anticancer immunity (Table 1) (Lepelley et al., 2021). Conversely, deleting ATAD3A or its inhibition increases cGAS/STING signaling mediated type 1 IFN release in response to the cytosolic dsDNA, including mitochondrial DNA (mtDNA), T cell infiltration, cancer cell death, supports chemotherapy-induced ER stress for anticancer immunity, cancer cell death, and delays cancer regrowth *in vitro* and in vivo (Huang et al., 2021; Lepelley et al., 2021; Xie et al., 2023).

p53, a cancer suppressor TF considered the "guardian of the genome," is suppressed in most, if not all, human cancers (Marei et al., 2021). Wild-type p53 engages the cGAS/STING signaling pathway to exert its anticancer action by inhibiting the TREX1. The inhibition of TREX1 results in the accumulation of cytosolic dsDNA and subsequent activation of IFN-stimulatory pathways (Ghosh et al., 2022). However, p53 mutations result in unchecked TREX1 activation, which diminishes cGAS/STING-dependent recognition of DNA damage and cytosolic dsDNA, inhibiting anticancer immunity. Furthermore, the unchecked TREX1 is also associated with an increased mTORC1 (a cellular nutrient sensor) activity promoting cancer cell survival and growth by inhibiting autophagy and upregulating HIF-1α and MYC levels and activity, promoting aerobic glycolysis by upregulating different glycolytic enzymes (Hasan et al., 2017; Tian et al., 2019; Guertin and Sabatini, 2007; Sabatini, 2006). In addition, mutant p53 also suppresses cGAS/STING signaling via binding to TBK1, preventing the STING, IRF3, and TBK1 trimer formation to activate type 1 IFN and proinflammatory cytokine generation. Thus, loss of p53 and accumulation of mutant p53 in cancer cells suppresses cGAS/STING signaling via two mechanisms detrimental to the host.

Dynamin-related protein 1 (Drp1) is a critical GTPase for mitochondrial fission and is upregulated in different cancers. Drp1 upregulation induces mitochondrial dysregulation and cytosolic mtDNA stress, activating cGAS/STING signaling to induce autophagy and promoting cancer growth (Li et al., 2022). Hence, the mtDNA in the cytosol activates non-canonical cGAS/STING signaling-mediated tumor progression via promoting autophagy and tumor-associated macrophage (TAM) infiltration (Bao et al., 2019; Guo et al., 2020a). AMP-activated protein kinase (AMPK) or mammalian target of rapamycin (mTOR) signaling increases the STING expression in CRC cells, which increases tumor-node-metastasis (TNM) and drug resistance (Yao et al., 2022). In the absence of STING-dependent type 1 IFN generation that depends on TBK1 phosphorylation and its recruitment and binding to the STING, activated TBK1 regulates cancer cell metabolism (aerobic glycolysis by regulating glucose transporter 1 or GLUT1 expression), survival, and proliferation via regulating mTOR (mTOC1 and mTORC2)-dependent signaling events downstream to AKT activation (Bodur et al., 2018; Tooley et al., 2021; Zhou et al., 2022; Runde et al., 2022; Antonia et al., 2019). Also, CRC cells have a defective polyamine metabolism that increases the spermidine level, that with elevated MYC, increases their growth, development, and survival in human patients (Guo et al., 2020b). These CRC cells have low levels of spermine that regulate cGAS/STING signaling pathway activation via condensing cytosolic dsDNA to increase and stabilize cGAS-DNA binding required to generate cGAMP for STING activation-dependent type 1 IFN release (Wang et al., 2023). In addition, increased extracellular spermine level promotes hypoxia-induced cancer cell migration and immunosuppression (Tsujinaka et al., 2011; Holbert et al., 2022; Shi et al., 2022). Thus, CRC cells control intra- and extracellular spermine levels to maintain their growth, survival, and metastasis.

Furthermore, methionine accumulation in the CRC TME increases its uptake by CRC cells that induces cGAS methylation via S-adenosylmethionine (SAM) formation catalyzed by methionine adenosyltransferase II alpha (MAT2A) (Fang et al., 2023). SAM-mediated cGAS methylation at mK350 and hK362 involves SUV39H1, a H3K9 methyltransferase (Fang et al., 2023). Notably, SUV39H1 could not methylate

K-to-R mutated cGAS but directly methylates cGAS *in vitro*. The methylated cGAS accumulates in the insoluble nuclear fraction and tethers to the chromatin promoting its chromatin sequestration, which blocks its DNA binding capacity. The methylated cGAS binds to the Ubiquitin-like PHD and ring finger domain protein 1 (UHRF1) protein via a Tudor domain in a methylation-dependent manner that promotes it chromatin tethering property and blocks its DNA binding activity required to activate cGAS/STING signaling-dependent anticancer activity (Fang et al., 2023). The intracellular SAM or methionine deprivation by blocking the SAM production with MAT2A inhibitor FIDAS-5 enhances cGAS/STING activation against cytosolic dsDNA to activate anticancer immune response (Fang et al., 2023). The increased methionine uptake by cancer cells due to SLC43A2 (a methionine transporter) overexpression of and its uptake by cancer cells and UHRF1 overexpression have been associated with different cancers and therefore its critical to explore the cGAS methylation status, localization to the nucleus, and its tethering to the chromatin (Pan et al., 2022; Sidhu and Capalash, 2017; Kong et al., 2019; Ashraf et al., 2017; Bian et al., 2020; Pandit et al., 2023; Sedillo and Cryns, 2022). Therefore, it's interesting to understand that how cGAS and STING differently affect various cancers depending on tissue type and downstream signaling pathway activation for developing cancer-cell-specific cGAS/STING signaling-based therapies. Furthermore, the defective STING signaling also decreases the efficacy of oncolytic DNA virus therapy (ODVT) in CRC. cGAS dysregulation is associated with STAT3 activation, intratumoral myeloid-derived suppressor cell (MDSC) accumulation, decreased IL-10 production and increased Th17 differentiation (Hu et al., 2021a).

STING is also significant to cancer advancement in colon cancer (CC). The impaired DNA repair due to overactivated SH2-containing protein tyrosine phosphatase-2 (SHP2)-mediated poly (ADP-ribose) polymerase 1 (PARP1) inhibition causes dsDNA accumulation in CC cells, which activates cGAS/STING signaling-dependent immune response (Wei et al., 2021). Similarly, in patients with estrogen receptor-positive (ER^+) BC, the perinuclear STING (pnSTING) increases immune cell infiltration and alters immune checkpoint activity, leading to an improved prognosis. On the other hand, ER^-BC with low pnSTING expression has an increased number of immunosuppressive M2 macrophages in their TIME (Parkes et al., 2021). Furthermore, increased TAM infiltration in the BC TIME predominates with M2 macrophages supporting cancer development (Tariq et al., 2017).

Additionally, the STING expression in BC and OC cells' inner nuclear membrane (INM) protects them from DNA-damage-induced genotoxic stress by increasing the DNA Damage Response (DDR) 53BP1 foci formation and DNA stability (Cheradame et al., 2021). Thus, STING may have an immune or non-immune-mediated function depending on the tumor type and stage. cGAS/STING signaling also promotes chromosome stability in cancer cells via maintaining levels of the cyclin-dependent kinase inhibitor p21, which increases their survival (Basit et al., 2020; Abbas and Dutta, 2009). However, the nuclear translocation of cGAS in response to the DNA damage through importin-α suppresses DNA repair to promote tumorigenesis (Liu et al., 2018). Also, the nuclear cGAS recruited to double-stranded breaks interacts with poly [ADP-ribose] polymerase 1 (PARP1) via poly-ADP ribosylation, which prevents PARP1–Timeless complex formation to avert the homologous recombination. Thus, cancer cell-specific cGAS knockdown inhibits tumor growth, but STING-independently of cGAS supports tumor growth and survival. Hence, the anticancer and protumor activity of tumor cell-specific cGAS/STING signaling is multifactorial and potentially affects chemotherapies and radiotherapies along with TIME or vice versa. Therefore, other tumor types and stage-specific studies are warranted. The following section discusses the indirect impact of different therapeutics affecting cGAS/STING signaling in tumor cells.

4. Current cancer therapies indirectly affect cGAS/STING in cancer cells

Cancer therapies can disrupt the cGAS/STING pathway, stunting essential anticancer immune activities. Chemotherapy and radiotherapy-induced DNA damage alter the ability of the cGAS-dependent production of type I IFNs via STING activation (Mekers et al., 2022). The altered cGAS/STING activation may be due to changes in DNA flexibility, which is crucial to mount cGAS-mediated acute immune surveillance (AIS) via repairable (reusable) DNAs in hours (Wang et al., 2022). Thus, radiation therapy dose is crucial to determine the cGAS/STING-induced type 1 IFN-mediated AIS in the TME. Highly aggressive cancers reprogram the cGAS/STING pathway to promote their growth by suppressing the type 1 IFN release and simultaneously upregulating NF-κB activation to trigger their metastasis (Kwon and Bakhoum, 2020). However, the cGAMP produced in cancer cells by cGAS activation can be transferred to tumor-associated DCs (TADCs) and TAMs through gap junctions (connexin-43 or CX43 and CX45) expressed by cancer cells of TME or TIME to initiate the type I IFN production (Schadt et al., 2019; Pépin et al., 2020). Notably, the extracellular cGAMP in TME or TIME depends on ectonucleotide pyrophosphatase/phosphodiesterase (ENPP1 or CD203a), a ubiquitous STING signaling attenuator (Carozza et al., 2022; Li et al., 2014). ENPP1/CD203a degrades extracellular cGAMP that promotes cancer metastasis and immune escape, and ENPP1 expression correlates well with the resistance of immune checkpoint inhibitors (ICIs) targeting the PD-1/PDL-1 axis in chromosomally unstable tumors (Li et al., 2021). The ENPP1/CD203a and haptoglobin axis are also crucial for the local recurrence of cancer post-radiotherapy via exploiting MDSCs and metastasis (Ruiz-Fernández de Córdoba et al., 2022; Lau et al., 2013). ENPP1 or CD203a inhibitors activate STING in TIME to exert anticancer action and synergize the efficacy of radiotherapy to delay tumor growth (Peng et al., 2021; Carozza et al., 2020). Nevertheless, the TIME alters cGAS/STING function through changes in gene expression, mutations, or interaction between the pathway and tumoral proteins (Mekers et al., 2022).

In some cases (cancer cells with intact cGAS/STING signaling but not inhibited due to endogenous upregulation of negative regulators), traditional therapies can leverage the anticancer properties of the cGAS/STING pathway for improved prognosis. For example, among patients with TNBC, paclitaxel reprograms M2 macrophages to M1s by activating cGAS. cGAS activation increases anticancer lymphocytes' recruitment and patient survival when coupled with ICIs (Hu et al., 2021b). ICI-mediated PD-1/PD-L1 axis inhibition in lung cancer also depends on STING activation through IFN-γ activation that induces DNA damage by increasing the inducible nitric oxide synthase (iNOS) activity, producing nitric oxide ($NO^{\cdot}$) (Xiong et al., 2022b). The increased cytosolic dsDNA, in turn, activates cGAS/STING signaling-mediated type 1 IFN release from cancer cells to increase anticancer immunity. Additionally, etoposide inclusion increases IFN-γ-induced type 1 IFN production and chemokine ligand 5 (CCL5) expression.

The T cell activation via CD3 activation and PD-1/PD-L1 axis blockage in the LUAD TIME activates STING-dependent type 1 IFN production and CCL5 expression (Xiong et al., 2022b). Notably, blocking IFN-γ activity abrogates STING-dependent anticancer effects induced by PD-1/PD-L1 axis inhibition. INF-γ activation by ICIs targeting the PD-1/PD-L1 axis in LUAD may also activate cGAS activation via inhibiting PI3K-AKT signaling and lowering the PD-L1 expression in lung cancer cells. Notably, IFN-γ released from TIME macrophages can increase the PD-L1 expression in LUAD cells (A549 cells) to enhance lung cancer progression and metastasis (Zhang et al., 2017). Thus, IFN-γ released during ICI (PD-1/PD-L1) therapy activates cGAS/STING signaling in the cancer cells to exert anticancer effects, but macrophages-mediated IFN-γ in the absence of ICI therapy exerts protumor action. Similar findings are valid in BC, where a more robust anticancer immune response has been seen to neoadjuvant

chemotherapy due to the strong activation of the cGAS/STING pathway-dependent type 1 IFN release (Parkes et al., 2022). Conversely, chromosomal instability (CIN) in TNBC cells increases the cytosolic dsDNA, triggering the cGAS/STING-mediated inflammatory pathways (IL-6 release), and its inhibition increases survival among patients with TNBC (Hong et al., 2022). Also, the CIN or DNA damage induces the IL-6-STAT3 survival pathway in TNBC cells (Vasiyani et al., 2022; Bakhoum, 2022). Hence, the cGAS/STING signaling pathway-mediated IL-6 release increases cancer cell survival. Therefore, blocking IL-6/IL-6R signaling or inhibiting cGAS/STING signaling in cancers (TNBC) with high IL-6 and IL-6R expression and CIN has a great potential to inhibit cancer growth. Therefore, tocilizumab can be repurposed in TNBC and other cancers with CIN overexpressing IL-6R. The details of CIN in cancer and TME are discussed elsewhere (Bakhoum and Cantley, 2018).

cGAS/STING pathway is also a prognostic biomarker in metastatic lung cancer. For example, in a metastatic lung cancer mouse model of transplanted 4T1 BC cells, ionization radiation therapy activates cGAS/STING signaling, which activates type 1 IFN genes and CCL5 in mesenchymal stem cells (MSCs) (Zheng et al., 2020b). Disrupting cGAS/STING in MSCs prevents their metastasis, suggesting a significant link between radiation and cGAS/STING activation in BC metastasis to the lungs (Zheng et al., 2020b). Furthermore, deleting essential autophagy genes in BC cells increases their sensitivity to radiation therapy due to increased type 1 IFN secretion through cGAS/STING signaling pathway activation in response to the increased mtDNA due to increased mitochondrial outer membrane permeabilization (Yamazaki et al., 2020; Vera-Ramirez et al., 2018). This improves control of distant non-irradiated lesions via systemic cGAS/STING-dependent type I IFN signaling. Thus, radiation therapy increases mitochondrial outer membrane permeabilization that increases cytosolic mtDNA for cGAS/STING signaling pathway-dependent type IFN release to boosting irradiation therapy-induced immunogenicity, including the abscopal effects in BC patients (Yamazaki et al., 2020; Galluzzi et al., 2023).

Macrophage presence is crucial for the lung pro-metastatic effect of irradiated MSCs with activated cGAS/STING signaling. In addition, the cGAS/STING pathway activation improves the anticancer action of radiotherapy in NSCLC by increasing apoptosis (Xue et al., 2022). For example, anlotinib is a novel tyrosine kinase inhibitor that targets VEGFR, FGFR, platelet-derived growth factor receptors (PDGFR), and c-kit, increases the radiosensitivity and efficacy of radiotherapy and radioimmunotherapy (radiotherapy plus anti-PD-L1 drugs) by increasing the cGAS/STING signaling in NSCLC (Han et al., 2022; Shen et al., 2018).

Additionally, chemotherapy induces IFN lambda 1 (IFNλ1) in NSCLC via STING activation that primes a more comprehensive immune response through macrophages expressing IFNλ1R (Gammelgaard et al., 2022). The IFNλ1 binding to the IFNλ1R on TME macrophages induces the expression of different ISGs, including CXCL10 and CXCL11, activates autologous anticancer $CD8^{+}$T cells expressing higher amounts of granzyme B (GzmB) and IFN-γ. Additionally, IFNλ1-IFNλ1R interaction in NSCLC organoids suppresses the phagocytosis-inhibitory receptor called signal regulatory protein-α (SIRP-α) expression to increase the phagocytosis of cancer cells (Gammelgaard et al., 2022). Hence, type III IFN induction via STING activation in NSCLC exerts potent anticancer immunity during chemotherapy. Type III IFN activation via STING activation requires further exploration in other cancers, including BC and CRC.

Also, necroptosis of cancer cells increases the radiotherapy efficacy via Z-DNA-binding protein 1 (ZBP1)-mediated mixed-lineage kinase domain-like pseudokinase (MLKL) activation, inducing caspase 8 (CASP8)-dependent STING-mediated type 1 IFN release (Yang et al., 2021; Baik et al., 2021; Jiao et al., 2020). The phase transition from a solid-like to a liquid-like state, known as unjamming, promotes the locally confined epithelial malignancies to invasive cancers, including BC (Kim et al., 2020; Park et al., 2016). In cancer growth due to uncontrolled cell proliferation in a confined space, mechanical compressive stress develops that also causes epithelial cell unjamming without inducing EMT (Cai et al., 2022). The continuous chronic stress during mechanical compressive stress inducing unjamming reduces Lamin B1 level causing DNA damage and nuclear envelope rupture, releasing nuclear DNA into the cytosol (Frittoli et al., 2022). Irradiation therapy also promotes unjamming through DNA damage, which differs from EMT (O'Sullivan et al., 2020; Mitchel et al., 2020). This damaged cytosolic DNA induces cGAS/STING signaling in invasive BC cells that alter their solid-like state to a liquid-like state to promote tumor invasiveness and metastasis through EMT and generate chemoresistance in invasive BC (Frittoli et al., 2022). Notably, epithelial unjamming is an energetically expensive process and depends more on glycolysis than the solid-like non-migratory state of normal epithelia. TME supports this process efficiently due to its high dependence on glycolysis. Hence, cGAS/STING signaling is crucial in maintaining cellular homeostasis. Depending on cancer type and CIN, its alteration predisposes the cell to transform to a precancerous stage, leading to increased tumor growth, survival, invasiveness, and metastasis.

5. Future perspective and conclusion

cGAS evolved 600 million years ago (MYA) in a choanoflagellate called *Monosiga brevicollis*. For example, cGAS resembles the enzyme called nvA7SFB5.1 or nvcGAS of a sea anemone called *Nematostella vectensi* in function. Also, the crystal structure of human STING is identical to the nvSTING. However, we do not know about nvcGAS/nvSTING's role in pathogen defense, but it is involved in autophagy induction without involving the TBK1 activation (Kumar, 2021). In mammals, including humans, non-canonical cGAS/STING activation induces autophagy without involving TBK1 activation and type 1 IFN generating. Autophagy plays a significant role in cancer pathogenesis by inhibiting tumor initiation and growth and promoting tumor survival in established tumors where tumor cells are under metabolic stress by different mechanisms (Mathew et al., 2007; White, 2015). However, we do not know the role of cGAS/STING-dependent autophagy in cancer pathogenesis, and defective cGAS/STING signaling through different mechanisms could prevent autophagy of the precancerous and pre-metastatic cells before the induction of type 1 IFN signaling needing complex molecular signaling events. Notably, cGAS/STING-mediated type 1 IFN has evolved only in vertebrates (exceptions are amphibians, including *Xenopus tropicalis* and *X. laevis*) as their STING have CTT, crucial for type 1 IFN production via TBK1 and IRF3 recruitment. The type 1 IFN production evolution in vertebrates, including humans, may be due to increased pressure of infectious diseases, including DNA viral infections and tumorigenic transformation of cells to generate an antiviral and anticancer immune response. For example, a recent study has shown that autophagy induction is a primordial function of cGAS/STING signaling that acquired type 1 IFN production property later in time due to increased pathogen exposure load or other stressful conditions (genotoxic, mitochondrial, and ER stress) responsible for cellular transformation to the precancerous stage (Gui et al., 2019). The elevated circulating myristic acid (MA, a 14-carbon straight-chain saturated fatty acid) increases the BC risk that may be associated with MA-induced enhanced N-myristoylation of the GTPase ADP-ribosylation factor 1 (ARF1). This master regulator controls STING membrane trafficking (Gui et al., 2019; Matta et al., 2022). The ARF1 myristoylation inhibits the cGAMP-mediated ARF1 activation and STING ERGIC trafficking, which is crucial for type 1 IFN generation (Gui et al., 2019). However, ARF1 myristoylation promotes STING activation-triggered autophagy and degradation (Jia et al., 2023). Thus, women with high circulating MA levels have defective cGAS/STING signaling due to elevated STING autophagy signaling that promotes BC without cGAS/STING signaling-dependent type 1 IFN generation.

The ERGIC STING transfer upon cGAMP binding is crucial for its autophagy function and type 1 IFN generation that depends on coat

protein complex-II (COP-II complex) coated vesicles (Kumar, 2021). The COP-II vesicle formation needs the ordered coat assembly built from the cytosolic components Sar1p, Sec23p/Sec24p, and Sec13p/Sec31p. Unfortunately, HeLa cells (a human cervical cancer cell line) have a defective Sec13 recruitment and Sec31 to ER exit sites, indicating the defective cGAS/STING-dependent anticancer function (autophagy and type 1 IFN generation) in these cancer cells (Wang and Lucocq, 2005). Hence, we must target the COPII defect in other cancer cells to preserve the typical cGAS/STING signaling as an adjunct chemotherapeutic approach. For example, broad-spectrum protein kinase inhibitor staurosporine has ultimately rescued that COP-II defect in HeLa cells *in vitro*.

Conversely, the deletion of COP-I (involved in Golgi to ER transport of STING or post-Golgi STING trafficking) pancreatic cancer and osteosarcoma cells (having deregulated cGAS/STING signaling) increases cell death via inducing autophagy and apoptotic cell death (Gasparian et al., 2022). The autophagy induction in response to the COP-I deletion may be due to not complete loss of cGAS/STING signaling but to the activation and maintenance of tonic IFN signaling without instigating any pathogenic trigger (Tu et al., 2022). People without chromosome 9p, harboring IFN gene cluster (defective or no type 1 IFN and ω-IFN production), frequently develop different cancers, including malignant glioma and melanoma (Einhorn and Heyman, 1993; Josefa Bello et al., 1994). Thus, it will be interesting to identify this mutation in cancer patients with intact cGAS/STING signaling without type 1 IFN production but abnormally producing NF-κB-dependent proinflammatory cytokines chronically to create a tumorigenic niche.

NLRP12 exerts anti-inflammatory action through different mechanisms, including the cGAS/STING signaling pathway-mediated type 1 IFN generation via inhibiting TBK1 and IRF3 activation (Tuladhar and Kanneganti, 2020; Tsao et al., 2023). NLRP12's high expression in malignant prostate cancer tissues further supports the anticancer cGAS/STING signaling suppression but the increase in pro-tumorigenic NF-κB-dependent cytokines in these patients (Karan et al., 2017). Further study has indicated the increased IL-6 production through TBK1-independent cGAS/STING-dependent NF-κB activation (non-canonical signaling) in prostate cancer cells (Al-Asmari et al., 2022). The increased TBK1-independent cGAS/STING-dependent NF-κB activation (non-canonical signaling)-mediated IL-6 release in BC and osteosarcoma have also been discovered, indicating an indirect role of NLRP12 along with other negative regulators of cGAS/STING-dependent anticancer type 1 IFNs. Furthermore, treatment with type 1 IFN inhibits NLRP12 transcription by runt-related transcription factor 1–dependent (RUNX1-dependent) epigenetic regulation (Tsao et al., 2023). Hence, identifying cGAS/STING signaling mediators/regulators in specific cancer types provides an excellent opportunity to develop personalized cancer therapy with available anticancer approaches. However, non-human primate data has suggested the age-dependent safety and efficacy of STING-ligands *in vivo* that decreases in older macaques (Takahama et al., 2023). Therefore, patient age could be a prognostic factor for STING ligands.

Furthermore, ataxia telangiectasia mutated (ATM, resides primarily in the nucleus in the dividing cells and is a member of phosphoinositide 3-kinase (PI3K)-related protein kinase (PIKK) family of protein kinases) protein responds swiftly and vigorously to double stranded breaks (DSBs) in the DNA to coordinate DNA repair by targeting serine or threonine residues followed by glutamine (the 'SQ/TQ' motif) of its different substrates to activate different DNA repair genes, including p53, breast cancer antigen 1 (BRCA1) as discussed elsewhere (Shiloh, 2003; Wang et al., 2000; Lee and Paull, 2021; Canman et al., 1998; Lavin, 2008). The ATM inhibition/deletion has a potential to promote anticancer efficacy of different ICIs by promoting the cytosolic leakage of mtDNA to activating the cGAS/STING signaling pathway that enhances anticancer lymphocyte infiltration into the TME (Hu et al., 2021c). Furthermore, ATM deletion/inhibition downregulates TFAM causing mtDNA leakage into the cytosol for the cGAS-dependent recognition to initiate the anticancer immunity to enhance ICIs efficacy. However, the nonsense ATM mutations in human patients with different cancers determine the clinical benefits of ICIs (Hu et al., 2021c). Thus, ATM-mediated regulation of cGAS/STING signaling is also a critical factor for the efficacy of ICIs in patients with different cancers. Further studies will explore the associated regulatory ATM-cGAS/STING signaling axis mechanisms.

In conclusion, the cGAS/STING signaling pathway helps to maintain cellular homeostasis by recognizing cytosolic self-dsDNA as a foreign invader. Typical cGAS/STING signaling works acutely to clear cytosolic threat (dsDNA) and resolves by sending protective signals (type 1 IFNs) to adjacent cells. However, dysregulated cGAS/STING signaling via chronic activation supports cancer growth that increases with aging. Hence, understanding cGAS/STING in cancer cell types at different stages will potentially add adjunct therapies for existing chemo and radiotherapies and emerging immunotherapies and OVTs.

Informed Consent Statement

Not Applicable.

Funding

This research received no external funding.

CRediT authorship contribution statement

Conceptualization, VK; Writing, review, and editing, VK; Writing the first draft, CB; Final editing and proofreading, JH Stewart IV. All authors have read and agreed to the published version of the article.

Declaration of Competing Interest

All authors declare no conflict of interest.

Data Availability

No data was used for the research described in the article.

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