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[Review] Cyclic GMP-AMP synthase- Stimulator of Interferon Genes Signaling and their Agonistic / Antagonistic Values

Anju Kaushal

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Abstract

The cytosolic PRRs and Cyclic GMP-AMP synthase (cGAS) attain the capability to detect DNA viruses like, vaccinia virus, HSV1 and HSV2, cytomegalovirus, adenoviruses, human papilloma virus etc and clear them off via IFN I regulations. PRRs can recognize the pathogen associated molecular patterns- PAMPs and self-DNA in the form of damage associated molecular patterns- DAMPs under stressed conditions, when monocytes and macrophages with other immune cells release excessive proinflammatory cytokines. Cytotoxic ssDNA and dsDNA escape from endosome and rupture mitochondrial DNA as well. The cGAS-STING signaling also have the polymorphic role to increase the pathogenesis in case of positive sense RNA virus's infection (SARSCoV-2), retroviruses and bacterial pathogens. STING protein is primarily present on ER, mitochondrial and Golgi bodies and gets activated through ligands cGAS / or cGAMP (2'-3'-cGAMP). This specific molecular pathway triggers the innate immune response in the cytoplasm and consecutively develop the adaptive immune arm against the pathogens. Activation of cGAS-STING signaling also exerts the antitumor effects via activation of p53 and p16 proteins. TLR9 is expressed on the DCs and B-cells to detect CpG motif of DNA. PRR agonists activate the STING to work effectively on CD4+ and CD8+ cells to establish the sustainable innate & adaptive immune response. STING also harbours the adjuvant properties to release potent immune response in the development of novel therapeutics against cancer, autoimmune and infectious diseases.

Anju Kaushal (PhD)

(Orcid ID: 0000-0002-0902-5461)

Auckland, New Zealand

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Introduction

The immune response in a host is measured by the effective activity of T and B-cells against the pathogens and its nucleic

acids. The first line of host defense against the invading pathogen is covered by the innate immune response, which subsequently activates the adaptive response to work specifically against the pathogenic antigens and keep the information in the memory cells to combat the invasion of the same pathogen for future. The process of safe pathogen elimination in the body to normalize the inner cellular environment is known as homeostasis. The immune response is always initiated by pattern recognition receptors (PRRs) that acquire the attributes to sense the molecular patterns of invading pathogens through pathogen-associated molecular patterns -PAMPs. In case of the nucleic acids released due to massive tissue injury being referred as damage -associated molecular pattern-DAMPs are recognized by special PRRs. Toll-like receptors (TLRs), RIG-I like receptors (RLRs), Nod-like receptors (NLRs), C-type lectin receptors (CLRs), other cytosolic DNA sensor proteins are the different PRRs which facilitate the response against various molecular antigens. At the time of activation, PRRs react with specific patterns of foreign and self-antigens to produce interferons and proinflammatory cytokines. Interferon I-III and pro-inflammatory cytokines are the by-product of inflamed macrophages and monocytes, activated under stress/ normal conditions to provoke the antiviral or inflammatory response. These inflammatory reactions are the suggestive of leading to cause the autoimmune, inflammatory diseases and cancers, along with life-threatening events by permanent tissues and organs damage [1].

PAMPs/ or DAMPs, in viral, bacterial and self-nucleic acid, are released followed by the involvement of an adaptor protein “stimulator of interferon genes -STING”, which exerts immunity against various pathogens. TLR9 senses the endosomal and cytosolic DNA via sensors like cyclic GMP-AMP synthase (cGAS), IFN gamma-16 (IFI16), absent in melanoma (AIM2), and DNA-dependent activators of IRFs (DAI) to be involved in a signaling mechanisms pointing the physiological significance [2].

Other functional DNA sensors such as, DEAD-box helicases are involved in metabolic activities from biogenesis to decay, and DDX41 RNA helicases to activate the cGAS-STING assisting in post-translational regulation & function. They assemble in nuclei, mitochondria and ribosomes. RNA polymerase III transcribes DNA to synthesize tRNA, rRNA, small RNAs etc. & DNA dependent protein kinase (DNA-PK) involves in survival and proliferation of cells. Meiotic recombination 11 homolog A (MRE 11) gather the information on DNA damage to regulate the DNA stability. The studies on the mechanisms of these nucleic acid sensors could provide the insights to detect autoimmune, cancer and viral disease. Immunomodulation on them would be of great significance to develop essential therapeutics for the treatment against various diseases [2].

The replication products of nucleic acids in the form of capsid and glycoprotein-PAMPS are mainly present in lysosomes / or cytosol directly sensed by PRRs, TLRs, RLRs, and NLRs. cGAS or cGAMP is a newly emerged detector of immune sensing of cytosolic DNA and RNA could trigger inflammatory/ or anti-inflammatory cell mediated response in a unique way [2][3]. Cytotoxic ssDNA and dsDNA in the cytosol released from DNA in viral, retroviral, microbial infections and associated bacteriophages, escape from endosomes and a ubiquitous process the regulated cell death (RCD) ruptures the mitochondria releasing mitochondrial DNA (mt DNA) under stress conditions to accelerate the immune stimulation [2][4][5][6].

During radiation therapy the death of malignant and normal cells are induced, increasing the accumulation of cytosolic

DNA needs to be cleared off efficiently. This imbalance eventually detected by DNA sensors & binding proteins to set up the intracellular signaling cascade [2]. As a result, IFN type I initiates antiviral immunity and / or programmed cell death within the same cells, and inhibit the infection spread to the neighbour cells. TLR9, cGAS-STING, IFI16 and AIM2 also induce pyroptosis. It has been speculated that sequence of cytotoxic DNA, methylation, histone and non-histone chromatin-binding proteins etc. have the implications on the activity of various DNA sensors. TLRs harbour the Leucin rich repeats (LRRs) to transduce the signals through TIR-domain-containing adaptor-inducing interferon -β, TRIF and Myeloid differentiation primary response gene-MyD88 to activate NF-kB. TLR3,7,8,9 and 13 also recognise the pathogenic nucleic acids, mediate through MyD88 and TLR3 to induce TRIF [7][8][9]. TLR 9 translocates from ER to CpG containing lysosomes. Variety of TLRs and PRRs could sense HSV-1 and 2, varicella zoster virus, polyoma virus and cytomegalovirus, Kaposi's sarcoma -associated herpes virus (KSHV), ectomelia virus (ECTV), Epstein Barr virus, and HIV [2][9].

Some viruses like herpes are directly released into the nucleus and can only be detected by the sensor when broken/ or defective DNA leaks through nucleus to the cytoplasm. The leakage of mt DNA into the cytosol has also been reported in herpes virus infection due to the excessive cellular stress could lead to activate the cGAS-STING pathway [10]. Human coronaviruses HCoV-NL63 and SARSCoV papain like protease (PLP) antagonize the innate signaling via STING pathway, where IRF-3 induction and nuclear translocation does stop. Hence, it negatively regulates the STING-MAVS-TBK1/1KKE required to activate the IRF-3 & IFN. STING dimerization and ubiquitination was substantially reduced contributing to the disruption in IFN induction [11][12].

This review article explores the emerging mechanism of cGAS-STING signaling with the emphasis to play an important part in the innate immune mechanism induced via DNA-viruses, retroviruses and other viral infections including autoimmune and cancer like diseases. This signaling process does have a great implication in the pathogenesis of various diseases and is going to be a future method to mount the immune response for the targeted therapeutics against various respiratory diseases. The modulation of immunostimulatory effects produced via activated cGAS (cGAMP)- STING mechanism can also maintain the IFN I and proinflammatory cytokines regulation.

cyclic GMP-AMP synthase – Stimulator of Interferon Genes (cGAS-STING) Signaling Pathway

Cyclic GMP-AMP synthase (cGAS) is a nucleotidyl transferase enzyme. It is a cytosolic sensor to detect DNA viruses like vaccinia virus, HSV1 and HSV2, cytomegalovirus, adenovirus, human papilloma virus and murine gamma herpesvirus [2][13][14][15]. These viruses are seemingly cleared by regulation of IFN type I through this mechanism. cGAS can also sense other retroviruses like murine leukemia virus, SIV, HIV, West Nile virus, vesicular stomatitis virus (VSV), dengue virus and gram-positive and gram-negative bacteria.

The DNA sensors such as, PRRs detect the viral nucleic acids and lead to the production of IFN type I cytokines and caspase 1-dependent secretions of IL-1β, however, strategically IFN I is the main defense mechanism for the clearance of

nucleic acids. DAI, RNA polymerase III, cGAS, AIM2, and IFI16, consequently, activate the IFN production in the STING-Pathway (Figure 1).

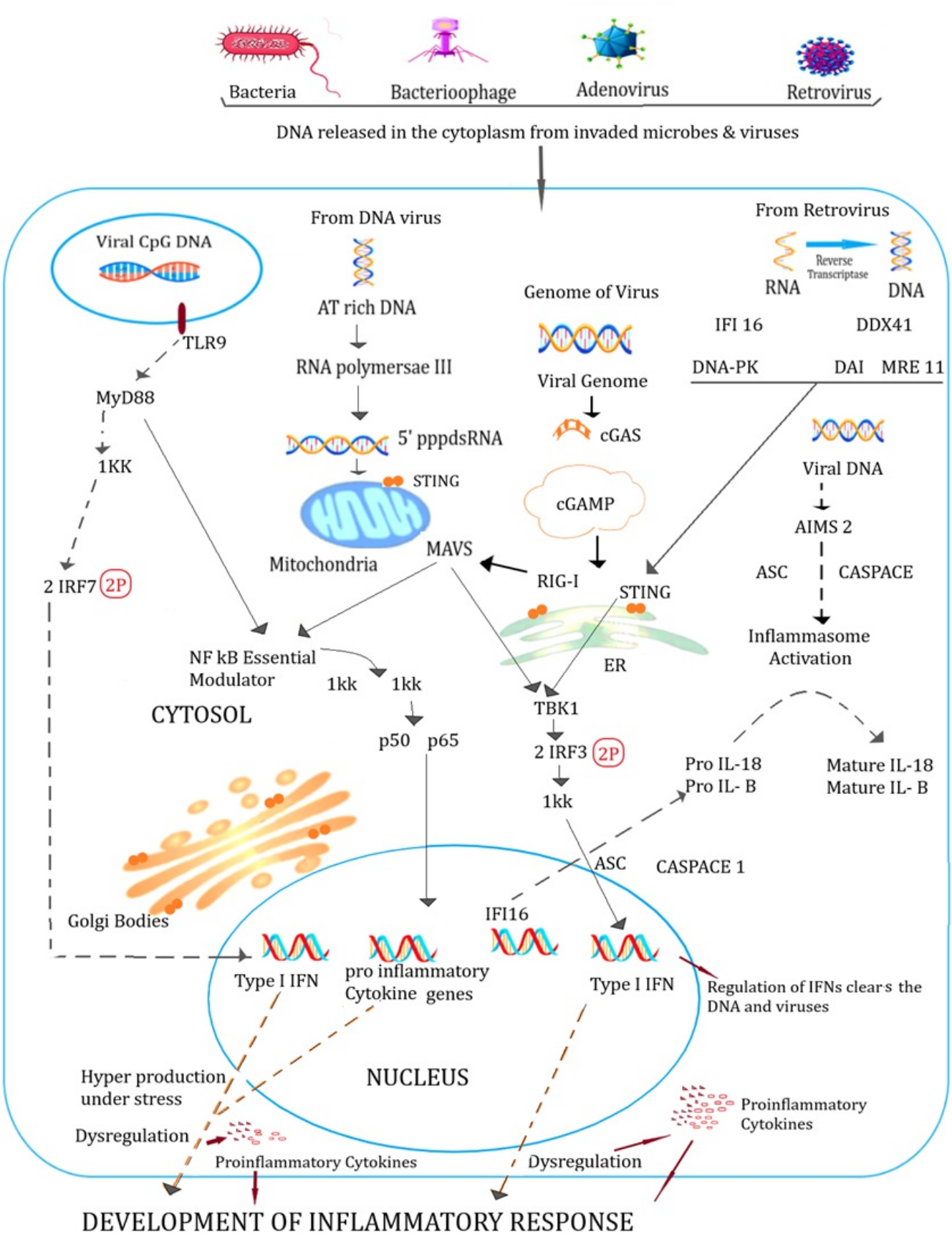

Figure 1. Representation of Cyclic GMP-AMP synthase – Stimulator of Interferon Genes Signaling pathway through viral and microbial infections and hyperproduction of Type I IFNs and pro-inflammatory cytokines exerting the inflammation.

TLR9 involves in DNA mediated immune signaling. It is emerged from endoplasmic reticulum (ER) and travel to the endosome mediated by UNC-93B protein which control the trafficking of TLR sensors regulate their function by controlling the autoimmune inflammatory response. Cytosine Guanine Dinucleotide (CpG) motif induced upon this procedure and a signaling cascade is established through MyD88, Interleukin-1 Receptor Associated Kinase 4 (IRAK4), and Tumor Necrosis Factor (TNF) Receptor Associated Factor 6 (TRAF6). TRAF-6 ultimately stimulate Transforming Growth Factor-β (TGF- β) Activated Kinase-1 (TAK1), which induce Mitogen Activated Protein Kinase (MAPK) and 1kB Kinase complex (1KK complex)- 1KKα, 1KKβ, and 1KKγ, to activate NF-kB. MAPK and NF-kB produce a pattern of releasing inflammatory cytokines. TLR9 builds affinity towards methylated CpG DNA to agonists it functions forming the active dimer of TLR9 and CpG DNA. However, viral DNA binds to TLR9 to overlap its agonistic site. IRAK4 activates TRAF3 and IRAK1 altogether phosphorylate the Interferon Regulatory Factor 7 (IRF7) and produces the I IFNs expression. The cytosolic DNA-mediated innate response is produced through cytosolic AT-rich dsDNA recognized by RNA Polymerase III (Pol III) and transcribed into 5'-triphosphate RNA, which stimulate the Retinoic Acid Inducible Gene I/ Interferon β promoter stimulator 1 (RIG-I/IPS-1) signaling. IPS1 interacts with Fas- Associated Death domain / Receptor Interacting Serine/Threonine Protein Kinase 1 (FADD/RIP1), which activates NF-kB. IPS-1 also activates TRAF Activator NF kB (TANK) Binding Kinase 1 (TBK1), which phosphorylate IRF3 and stimulate the production of I IFN. AT-rich dsDNA or non-AT-rich dsDNA both have capability to activate STING. STING present in ER with translocons like, Translocon Associated Protein complex (TRAP)-β & membrane protein Sec 61 to activate Sec5/ TBK1 inducing the IFN. STING can also activate NF-kB inducing pro-inflammatory cytokines. dsDNA also activates AIM2/ Apoptosis Associated Spek Like protein i.e., ASC/ Caspase-1 inflammasome pathway to activate IL -β (Figure 1) (18). Leucin Rich Repeat Protein (LRR) domain also recognize the DNA and which also help mature TLR9 activity [16]. The transmembrane protein STING is also expressed on the mitochondrial membrane along with endoplasmic reticulum, where it connects with TANK-binding kinase 1(TBK1) which causes the phosphorylation of IRF3 and IRF7 [2][17][18].

The glycolipid receptors help transport the microbial toxins and viruses, presumably, through the activated cytosolic mechanism called as 'ER trafficking'. These products have low lysin contents, so they ought not to be the active substrates for ubiquitination and subsequent proteasomal degradation in the cytosol. Hence, these proteins could lead to the ER-associated protein degradation (ERAD) pathway, where the proteins are treated in ER lumen and delivered to the cytosol for final destruction [19]. Thereafter, the DNA is finally released along with unfolded proteins in the cytosol for further processing. *In-vivo* DNA sensing against ectromelia virus (Mousepox virus) acts in two pathways. The first pathway is TLR9-MyD88-IRF7, necessary to express proinflammatory cytokines in CD11 c (+) cells and for the further recruitment of monocytes. In the second one, the DNA sensors and adaptors of STING are induced in monocytes to activate IRF7 and nuclear factor NF-kB producing IFN-α and IFN-β [20][21].

The extract of cytoplasm, *in-vitro,* from mammalian cells contain cyclic GMP-AMP or cGAMP from ATP and GTP in presence of DNA, but not RNA. So, the DNA transfection also trigger the production of cGAMP bound to STING leading to the formation of IRF3 and IFN-β [22]. cGAMP is also recognized as secondary messenger activated via multivalent

interactions accelerated by the presence of Zn to enhance the STING dependent response [23].

Ablasser A et al. 2013, described the catalytic reaction of cGAMP (cGAS)*in -vivo* and *in-vitro* to produce cyclic GMP-AMP dinucleotide with 2'-5' (first catalytic-form) and 3'-5' (second catalytic-form) phosphodiester linkage. The 2'-5' linkage increase the antiviral efficacy of STING by producing type I IFNs and NF-kB-dependent proinflammatory cytokines [24][25][26]. Mutations in cGAS which binds to dsDNA or catalytic pocket can diminish the activity of this enzyme. Moreover, the 2',5'- cyclic hetero-dinucleotide second messenger in metazoan, belongs to c [G (2',5') pA (3',5') p] is different from bacterial 3'-5 cyclic dinucleotide [27].

The enzyme CD-Ntase (cGAS/DncV – nucleotidyltransferase) produce c-di-GMP sensed by bacterial STING protecting against phage growth inside the bacteria. Therefore, it is speculated that STING is originated from bacteria. A model has been prepared to show the transition from c-di-GMP-dependent signaling in bacteria to 2'3'-cGAMP-depepndent signaling in eukaryotes [28].

Autoactivity of cGAS to self and active DNA is controlled by histones are embedded the cGAS DNA binding sites. cGAS protein can directly halt the DNA repair at the time of its attachment to chromatin increasing the production of micronucleus with genome instability, promoting the cell apoptosis under the condition of genomic stress [29][30][31]. This binding inhibits the cGAS oligomerization.

STING also induce autophagy through a pathway which is independent of TBK1 activation and interferon induction. Four transmembrane helices of STING, keeps in ER binding to Ca2+ sensor stromal interaction molecule (STIM1), once it has bound with cGAMP mediates its movements from ER to ER-Golgi intermediate compartments (ERGIC) through COP II and ADP-ribosylation factor (ARF) GTPases [32]. There is another important point for STING activation, which binds to TBK1 (Phosphorylates the C-terminal tail region which is a docking site for IRF3). IRF3 gets induced and dimerize to translocate to the nucleus to regulate the transcription of IFN-β. IFN-β activates IFNAR 1 &2 receptors to activate Junas kinase (JAK)-Signal transducer and STAT signaling pathway to stimulate the ISGs transcription which in turn stop the viral replication [33].

The PYHIN, IF16 and nucleotidyltransferase cGAS, both bind to DNA which stimulate the interferon genes via STING to localize in ER. cGAS undergoes conformational changes and activates the secondary messenger cyclic GMP-AMP (2'-3'-cGAMP) from ATP and GTP, which is a known ligand for STING. These cyclic dinucleotides contain a conventional 3'-5'-linkages. cGAS produce 2'-3'-cGAMP a highly potent stimulator of both murine and human STING [12].

STING binds directly to cyclic diguanylate monophosphate (c-di-GMP), but not other nucleic acids/ or nucleotides. STING acts as a direct sensor to c-di-GMP, besides its role as signaling adaptor. Cyclic nucleotide has shown promise to be used a novel vaccine adjuvant and immunotherapeutics to be sensed by innate immune system [34]. This pathway can induce apoptosis and necroptosis.

Control of STING activity by DNase to eliminate the Self-DNA

During infection the pathogen DNA present in the cytoplasm could trigger innate response through cGAS-STING pathway. But, on the other hand the DNA accumulation due to cell damage could also activate the cGAS-STING pathway is mainly caused under the stressed conditions.

Under normal conditions, however, the self-DNA accumulation takes place due to cell damage is largely controlled by DNase enzymes, which automatically stop the unnecessary activation of cGAS-STING signaling. The four types of DNases have been described in literature to clear the accumulated DNA in and out of the cytosol and finally eliminating it from the body. Any mutations occur in the enzymes could lead to the autoimmune disorders at various levels [35]. A heterozygous nonsense mutation in the axon of human DNASE I can cause systemic lupus erythematosus -SLE, collectively affecting the various organs in the system [36][37]. DNASE IL3 dysfunction can cause polygenic SLE in mice [38]. However, GAS-STING should not be a part in this process. Biallelic functional inhibition caused a mutation in endonuclease DNase II, lead to cause the hyper increased type I interferon response to increase the process of phagocytosis and apoptosis.

DNase II deficient mice die of severe pneumonia, which are rescued by the STING deletion, but not GAS deletion [39][40][41]. This field could be needed to explore the exact function of STING and cGAS and how they intervene in clearing the aberrant DNA, while modulating their activities in the drug development.

Endogenous accumulated DNA is cleared by exogenous TREX1 (DNase III)[42][43]. Mutation in DNase III can cause Retinal vasculopathy & cerebral leukodystrophy (RVCL), systemic lupus erythematosus (SLE), familial chilblain lupus (FCL) and Aicardi-Goutieres syndrome (AGS)- related to myelin destruction [44][45]. TREX1 mutation activated the cGAS in TREX 1 deficient mice to produce excessive interferon leading to inflammatory myocarditis, lymphoid hyperplasia, vasculitis, and kidney disease. cGAS deletion could help increase the recovery in mice [46][47][48].

Conclusion

The epigenetic involvement of the disease pathogenesis, in COPD, asthma and pulmonary arterial hypertension (PAH), are significantly induced by the associated environmental factors. There is need to develop molecular assays along with epigenomic studies to learn more on the ‘pre-disease state’ to ‘disease state’ for the effective management of the pulmonary disease and associated disorders [49].

The normal epigenome changes assist in reprogramming the immune cells to combat the relative infection, especially by administering the attenuated vaccines, could modulate the immunostimulatory response and lower the impacts of longitudinal disease risk. Induction of aberrant methylation in DNA during epigenetic modifications could be a primary method leads to the development of cancer like disorders [50][51]. However, the functions of cGAS enzyme altering the activity through STING is yet to be revealed on this front.

Christensen MH et al. 2017, described that DNA is a highly stimulatory molecule producing the immune response to evoke the antiviral activity. Viral evasion through DNA sensing mechanism would need to verified *in-vivo*. It’ll provide a better

understanding to develop the target therapeutics which could be immunomodulatory with no side effects. The activation of cGAS- STING pathway plays an antitumor role in cancer cells i.e., activation of p53 and p16 proteins including carcinogenic stress inhibit the cell proliferation. It also promotes cell apoptosis via activating the mitochondrial apoptotic pathway [52]. PRRs belong to PYHIN family such as, AIMS 2, IFI 16, Myeloid cell nuclear differentiation antigen (MNDA), Pyrin and HIN domain family member 1 (PYHIN1) and Pyrin domain only protein 3 (POP3) and these are present on chromosomes 1q23 to induce interferons. These proteins do play an important role in transcriptional and cell cycle regulation including tumour suppression. IFI16 and AIMS2 recognize nonself DNA to upregulate the type I interferons and inflammasomes. POP3 acts a negative regulator for IFI16 and AIMS2. Therefore, PYHIN proteins largely involved with the function of innate immune responses, could raise the possibilities of therapeutic interests [53].

Finally, it is concluded that the cGAS & STING have a special involvement to manifest various diseases, ranged from infectious diseases to autoimmune disorders, with many human health implications could increase the opportunities to develop novel therapeutics.

Declarations

Author Contributions

Author has made the final approval for this manuscript.

Conflict of Interests

Author claims no conflict of interests.

Ethical Approval

Not applicable

Consent to Participate

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