Available online at **www.ijmrhs.com**

ISSN No: 2319-5886

International Journal of Medical Research & Health Sciences, 2018, 7(2): 102-109

Stimulator of Interferon Genes (STING): A Factor to Consider in Cellular Homeostasis

Justice Chidiebere Chima[1], Clerol Austrie[1], Alice Solomon[1], Iniubong Ukpe[1], Precious Anthony[1], Favour Anthony[1], Adeiza David Otohinoyi[1], Esther Olunu[2] and Adegbenro Omotuyi John Fakoya[3]*

[1] *Medical Student, All Saints University School of Medicine, Dominica*

[2] *Instructor, Department of Microbiology and Immunology, All Saints University School of Medicine, Dominica*

[3] *Associate Professor, Department of Anatomical Sciences, Histology and Cell Biology, All Saints University School of Medicine, Dominica*

**Corresponding e-mail: gbenrofakoya@gmail.com*

ABSTRACT

Interferon is a cellular response to infection, paraneoplastic event, and other biological entities. They are proteinous entities consisting of about 144-166 amino acids transcribed from 20-30 genes. They participate in autophagy and immune response to biological entities when stimulated. Biological or clinical states that affect the proper transcription of interferon genes to either downregulate or upregulate it, usually result in susceptibilities to infections, autoimmune diseases, as well as systemic inflammatory diseases. This review aims to briefly describe the stimulator of the interferon genes (a 379-amino acid protein), how it elicits its cellular homeostatic functions with the sole purpose of enhancing cell survival and reducing morbidities.

Keywords: Interferon, STING, Immunity, Inflammation, Autoimmune

INTRODUCTION

Interferons are protein-based molecules released by eukaryotic cells as a reaction to infection, paraneoplastic event, and other biological entities [1]. They attach on the receptors of target cells and prompt the transcription of nearly 20-30 genes, thus sensitizing the target cell to fight against the intruder [2]. They are beneficial in combating illness like hepatitis, various cancers, multiple sclerosis, and many other diseases [3]. Basically, they consist of 145-166 amino acids and are classified as either type I Interferon (alpha and beta), or type II Interferon (interferon-gamma or immune interferon) [3].

Alpha Interferons are synthesized by leukocytes; beta Interferons by fibroblasts. They are both encoded on chromosome 9 and bind to interferon cell receptors type 1 [4]. They share related functions but bind on different locus. Viral infection primarily stimulates their production. It mobilizes the first line of defense against invading organisms. They are the largest group of interferon secreted by almost all cell types [5], however, their exact mechanism is not fully understood [6]. Alpha and beta interferons attach on the heterodimeric receptor on cell surfaces. Alpha receptor is made up of at least 2 polypeptide chains: IFNaR1 and IFNa-R2 [7]. IFNa-R1 is for signal transduction; IFNa-R2 for ligand-binding chain and also helps in signal transduction. Ligation performed by these polypeptide chains initiate the oligomerization and initiation of the signal transduction pathway [8], and this causes the phosphorylation of signal transductors and activators, which is needed for transcription proteins as a trimeric complex, ISGF-3 [9].

On the other hand, type 2 interferon which binds to type 2 receptors is encoded on chromosome 12 and is synthesized by some activated T-cells and natural killer cells. It is formed in reaction to antigen or mitogen stimulus of lymphocytes [10]. B cells, natural killer T cells and professional antigen-presenting cells also secrete interferons [11]. Gamma production are usually stimulated by immune or inflammatory stimuli and not viral antigen and its production is controlled by interleukin 12 and 18 [12].

Interferon receptors are encoded by separate genes, namely, IFNGR1 and IFNGR2, and are located on chromosome 6 and chromosome 21, respectively [13]. When triggered, these receptors stimulate JAK1 and JAK2 pathway that involves the phosphorylation of a tyrosine residue on the intracellular domain of IFN-R1. This causes the phosphorylation of STAT1 that forms homodimers and translocate to the nucleus to activate a range of interferon-responsive genes [14]. After which the ligand-binding chains on the receptor are ingested and broken down to be recycled afterwards.

Stimulator of Interferon Genes (STING) Signal Pathway

STING is a signaling protein that is embedded in the endoplasmic reticulum of cells. It stimulates the transcription of host defense genes such as pro-inflammatory cytokines and Type 1 interferons in defense against aberrant genes and cyclic dinucleotides present in the cytosol of the host cell [14-16]. STING is a 379-amino acid protein (Figure 1) with several transmembrane portions. It is expressed in various epithelia, endothelial and hematopoietic cell types [15].

Cytosolic DNA activates STING by binding to Cyclic AMP- GMP synthase (cGAS), which is a 522-amino acid protein. cGAS catalyzes the production of a type of CDN called cGAMP (cyclic GMP- AMP) in the presence of ATP and GTP. cGAMP contains one 2′,5′-phosphodiester linkage and a canonical 3′,5′ linkage (c[G(2′,5′) pA(3′,5′)p]) which activates STING [17]. When STING is activated, it signals the TANK binding kinase (TBK1) and interferon regulatory factor-3 (IRF-3) axis. This enables it to upregulate type 1 interferon production. TBK1 further relate with IκB kinases, inducing phosphorylation and degradation of IκB. This liberates NF-κB (nuclear factor kappa B) subunits, enabling their translocation which results in the upregulation of type 1 interferon and other pro-inflammatory cytokines [18].

RNA Induced Sting Activation

Some RNA viruses such as Human Immuno-deficiency virus, Influenza A virus, Sendai virus, and vesicular stomatitis virus have been observed to activate STING signaling through DNA detection dependent and independent mechanisms. Complementary DNA (cDNA) which is produced by the reverse transcription of negative stranded RNA in retroviruses can induce cGAS dependent DNA sensing pathway that will activate STING [19].

It is also observed that STING/TBK1 relocation can be induced by cationic liposomes and nucleic acid-free herpesvirus-derived virus-like particles regardless of DNA sensing pathways. This process is the membrane fusion mechanism. Also, Influenza A virus has been observed to release hemagglutinin fusion peptide, inducing STING without activating cGAS [19].

The RNA-inducing adaptor MAVS (mitochondrial antiviral signaling protein) can also induce STING. MAVS is the platform that enables the RLR dependent RNA sensing pathway that brings about a type 1 interferon response [19].

Regulation of the Signal Pathway of STING

To initiate immune responses elicited by DNA, STING relies on cytosolic sensors. IF116, a member of the PYHIN family of DNA sensors, regulates STING dimerization and phosphorylation, and subsequent TBK1/IRF3 activation [20]. IFI16 binds DNA and activates the STINGTBK1-IRF3/7 pathway leading to type I IFN response [21,22], while it also recognizes episomal double-stranded DNA (dsDNA) in the nucleus, resulting in the assembly of a cytosolic inflammasome [23]. Moreover, IFI16 contributes to enhanced cGAMP production by cGAS in human cells macrophages [24].

Nevertheless, the best characterized STING-related sensor is the cGAMP synthase cGAS (also known as Mb21d1) that belongs to the nucleotidyltransferase protein family [25]. cGAS presents structural similarities to OAS (20 -5′ oligoadenylate synthase) proteins that recognize dsRNA, while cGAS contains a unique zinc finger that detects B form dsDNA [26]. Interestingly, cGAS can contribute to IFI16 stabilization in fibroblasts and keratinocytes, improving DNA sensing and innate immune responses [27].

Reports have also indicated that STING is part of the ER-associated translocon-associated protein (TRAP) complex, however it is not clear whether TRAP is required for the autophagy-like signaling process [28]. Proteins for N-linked glycosylation and/or exocytosis are usually transported through the TRAP complex into the luminal region of the ER after translation, however, it is not understood if STING has a role in this [29,30].

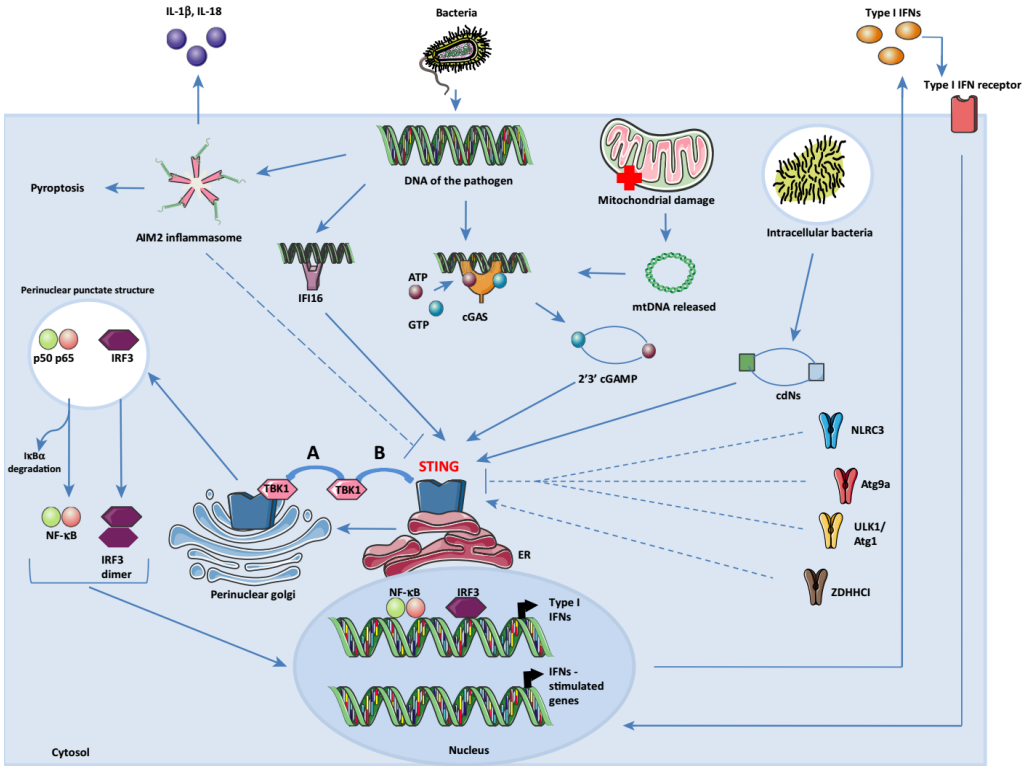

Figure 1. Diagrammatic model for STING (Adapted) [31]

The Role of STING in Inflammation

The activation of STING via NF-kB and IRF3, results in the production of type 1 interferons (IFNS) [31]. STING controls a signaling pathway important for the detection of cytosolic DNA and type I IFN expression [32]. Activation of STING leads to the production of IFN-B during bacterial infection, which may be beneficial or harmful for its host depending on the infection [33]. STING signaling is known to influence the expression of precursor proteins and may act in concert with the Absent in Melanoma 2 (AIM2) pathway [34]. Although AIM2 interacts with non-specific dsDNA species, it triggers caspase 1-mediated cleavage of pro-inflammatory cytokines IL-1beta and IL-18 from their precursor protein [34].

During *Francisella tularensis* infection, activation of STING induces the production of Type1 IFN, which is important for AIM2 inflammasome activation. AIM2 is able to detect intracellular dsDNA, secretes mature IL-1beta, IL-18, and causes pyroptosis cell death. IL-1B and IL-18 is important for antibacterial immune responses (Figure 1) [33,34]. Foreign DNA in the cytosol activates STING-mediated innate immune responses, and also inflammasome, leading to the maturation and secretion of IL-1b and IL-18 [35]. STING is also responsible for stimulating the formation of LC3 puncta involved in autophagosome formation [36].

STING is important in innate immune sensing which may help prevent dangerous bacterial infection and may also facilitate bacterial survival [34]. STING is also inhibited by some pathogens. *Shigella flexneri* type 3 effector invasion plasmid antigen J (IpaJ) inhibits STING-mediated IFN Beta activation by hindering STING translocation from endoplasmic reticulum to ER-Golgi intermediate compartments in mouse embryonic fibroblasts, this is important for the pathogenesis of Shigella. In contrast, some intracellular pathogens stimulate STING to inhibit the T-cell mediated immune response [33].

Intracellular Bacteria and STING

Bacteria such as *Listeria monocytogenes*, *Salmonella typhirium*, *Chlamydia trachomatis* and *Mycobacterium tuberculosis* have been linked with STING activation [34], which can force direct intracellular anti-pathogen activity and some cytokines with the release or production of type 1 IFN that protect the cells that are not infected and triggers the adaptive immune responses (Figure 1) [34].

Listeria monocytogenes

Listeria monocytogenes is a gram-positive, facultative intracellular, rod shaped bacterium, that replicates in the cytoplasm of myeloid cells [35]. It has been illustrated that *L. monocytogenes* stimulate a type I IFN response, which is due to cytosolic detection of c-di-AMP [35]. During the infection, *L. monocytogenes* leave the phagocytic vacuole into the cytosol of the host where it replicates [36]. Some immune pathways are triggered because of the cytosolic entry [37].

The first pathway undergoes an inflammatory response that can result in the death of the host cell. It also triggers the expression of beta interferon by the cytosolic surveillance pathway (CSP) which is solely dependent on the cytosolic pattern recognition receptors [36,37]. C-di-AMP coordinates the stability of the cell wall, growth of bacteria, cell wall stability, and reaction to plays and stress a crucial role in bacterial pathogenesis [37].

Salmonella typhirium

This is a facultative intracellular bacterium that causes various illness ranging from gastroenteritis to typhoid fever. Focal Adhesion kinase deficiency (FAK) in macrophages promotes IFN-β production in response to Salmonella infection. This bacterium triggers an autophagic response in host cells during infection [38-40]. During this microbe-induced autophagy, portions of the cytoplasm that include invading bacteria or their products are confiscated in double-membrane autophagosomes before fusion with lysosomes to generate degradative autolysosomes [38-40]. The IFN-β response to autophagic killing of Salmonella is mediated by both TLR3 and TLR4.

Chlamydia trachomatis

Chlamydia trachomatis is a Gram-negative rod that synthesizes cyclic di-AMP, a nucleic acid metabolite. Chlamydia infection and c-di-AMP treatment induces type I IFN responses in cells that express STING. The inability to encourage a type I IFN response to Chlamydia and c-di-AMP will cause poor movement of STING from the endoplasmic reticulum to cytosol signaling complexes necessary for IFN activation. Studies done on Chlamydia have reported that it induces STING-mediated IFN responses by detecting c-di-AMP in the host cell cytosol, thus showing that the role of c-di-AMP is undisputable [41].

Chlamydia infection shows that caspase-1, type-1 interferons, caspase-11, and cytokine IL-1β is responsible for most of chlamydia pathogenesis [42]. Chlamydial infection also causes an increase in olfactomedin 4 (OLFM4), which potentially blocks NOD1-mediated signaling, cGAS, cGAMP synthase [43].

Mycobacterium tuberculosis

M. tuberculosis, induce type I IFNs but the mechanisms remain obscure. *M. tuberculosis* activates the STING/TBK1/IRF3 pathway which is activated by the pattern recognition receptors and the cytosolic DNA receptors [44]. The membrane is permeabilized early after infection occurs [44].

Extracellular Bacterial Activation of STING

While Stimulator of Interferon Genes (STING) are intracellular proteins embedded in the endoplasmic reticulum (ER) of the cell, extracellular bacteria play a role in their activation. The signaling of Type 1 INF by bacterial components is a critical component of the immune defense. The activation of type 1 IFN signaling can be achieved by Toll-Like Receptor (TLR) dependent mechanism due to the presence of lipopolysaccharides in Gram negative organisms, or via TLR-independent cytosolic receptors that respond to nucleic acid [45]. The induction of INF release may either aid in the host defense against the pathogen or be detrimental to the host. Cells infected by extracellular bacteria that affect the respiratory tract such as *Streptococcus pneumoniae* mediate type 1 IFN productions to heighten the mucosal immunity [46].

Macrophages and dendritic cells are known to produce type 1 IFN in response to nucleic acid using TLR 7 and 9. This nucleic acid acts as the bacterial ligand. In S. pneumococcal infection, autolysis causes the contents of the bacteria to be released and enters the host cell [46]. The free pneumococcal DNA then reaches the host cytoplasm where it is detected by STING. This has been proven by research done on STING null mice being incubated by *S. pneumoniae* which had a much less INF production as opposed to mice with STING. In addition, another study shows that stress on the endoplasmic reticulum causes the expression of Atg9a, a STING activation inhibitor, causing a reduced production of IFN and heightened susceptibility to *S. pneumoniae* [46].

The mechanism of interferon activation in *Streptococcus pyogenes* and Group A strep can be seen in macrophages using the GAMP-AMP Sequence (GAS). Macrophages sense GAS DNA of the pathogen and signals STING [31]. Extracellular bacteria activate both macrophages and dendritic cell. Macrophages play a role in IFN activation via STING, TBK1 and IRF3, while dendritic cells activate IFN via MyD88 and IRF5 [46].

The STING adaptor has been proven by many studies to facilitate TBK1-mediated IFN-β induction. It has a shorter half-life than TBK1 and this may be the reason silencing STING shows a more significant effect as compared to silencing TBK1. A significant effect when silenced is also seen when IRF3 is activated by another kinase other than TBK1 [45]. From this we determine that the TBK1/STING pathway is essential for induction of IFN-β by S. pyogenes. However, there was no detection of signaling factors (TLRs) for TBK.

Streptococcus agalactiae is major cause of neonatal invasive infection. It's activation of STING is dependent on its virulence [47]. Live *S. agalactiae* bacteria activates the GAS-STING pathway while heat killed strains activate IFN response via TLR pathway [31].

In some extracellular pathogens such as Neisseria Gonorrhea and gonococcal lipooligosaccharide, the combination of STING and the TLR pathway induce a full blown IFN type 1 induction response to DNA [29]. This excessive IFN production is detrimental to the host because it impairs the *N. Gonorrhea* killing and creates an environment that sustains the bacteria by increasing the host intracellular iron pool [46].

STING in Viral Immunity

STING promotes immunity to DNA viruses and retroviruses. Endogenous retroviruses (ERVS) stimulates T cell-independent B cell activity in reaction to bacterial capsular polysaccharides or viral capsid [18]. The activation of both RIG-I and STING signaling pathways by reactivated ERVS are known to elicit the B cell response [18].

STING plays an important role during the 5'pppRNA (5'triphosphate) protection against Herpes simplex virus 1 (HSV-1) infection both *in vitro* and *in vivo*. 5'pppRNA stimulates RIG-I which induces the expression of STING at both MRNA and protein levels. The activation of RIG-I-MAVS pathway suppresses infection by the DNA virus HSV-1 both *in vivo* and *in vitro* in a STING-dependent way. STING deficient mice are less likely to survive HSV-1 infection [48]. STING may not only be crucial to dsDNA dependent or CDN (cyclic dinucleotide) dependent innate immune signaling but may facilitate innate immune responses by negative-stranded and positive-stranded RNA viruses. Mice lacking STING are highly sensitive to Vesicular stomatitis virus (VSV) and Simian virus (SV) infection. However, in the absence of STING, the ability of synthetic dsDNA (poly IC) to produce type 1 interferon is not affected [49].

Dengue virus (DENV) expresses the NS2B3 protease complex in order to evade the type 1 interferon response. NS2B3 protease complex cleaves STING in human dendritic cells thus inhibiting the production of type I IFN in human but not mouse cells, since it does not degrade murine STING. STING restrict DENV replication in mouse cells [18]. STING also suppresses RNA virus replication [18].

STING in Autoimmunity and Systemic Inflammation

The suppression of STING can limit the functionality of regulatory T cell activation factor IDO-1 and TLR negative regulators like SOCS1, A20, and SOCS3, instigating hysterical systemic inflammation [19].

STING variants as well as dysregulated STING signaling are associated with amplified vulnerability to certain infections and autoimmune illnesses. Patients with these irregularities can display early on-set of severe and chronic systemic inflammation of organs and blood vessels, with similar pathologies to SLE (systemic lupus erythematous) and AGS (Aicardi-Goutières Syndrome) [19]. Below is a brief review of these conditions.

STING and SLE

STING is defective in conditions such as SLE and deficiency of STING leads to increased autoantibody production. Patients with SLE showed a lower expression level of STING in B cells due to the downregulation of the expression of STING in B cells. STING can inhibit dsDNA-triggered activation of JAK1-STAT1 signaling by inducing SHP-1 and SHP-2 phosphorylation. JAK1-STAT1 signaling promotes B cells activation and antibody responses [50].

STING and Vascular and Pulmonary Syndrome (VAPS)

STING is encoded by TMEM173. Alternative polymorphism in human TMEM173 gene has been identified to have a gain of function phenotype and are likely to contribute to severe inflammatory disorders. Patients with VAPS exhibit three mutations in exon 5 of TMEM173 (N154S, V155M, and V147L) resulting in STING hyperactivity [18].

STING and AGS

AGS is a genetically based autoimmune disease characterized by Type I interferonopathy. This Type I interferonopathy is cGAs-STING dependent and its reaction can be repressed by the down regulation of DNA sensor or STING in cells or animals with mutated TREX1 or SAMHD [19].

STING AND Vasculopathy with Onset in Infant (SAVI)

STING-associated SAVI is linked to gain-of-functions of STING. STING mutants V147L, N1545, V155M and V155R were identified to guide SAVI to an active conformation enhancing dimerization and prompting TBK1-IRF3 signaling. This leads to an elevated IFN-I response in keratinocytes, fibroblasts, and immune cells to draw and assemble proinflammatory cells and regulators in tissues and capillaries. SAVI is also a result of STING hyperactivity [19].

STING and Familial Chilblain Lupus (FCL)

There is a gain of function mutations of STING in the autoimmune disease FCL. It is a rare genetic form of SLE linked with cytoplasmic DNA build-up in monogenic alterations of exonucleases TREX1 or SAMHD [19].

CONCLUSION

The cellular homeostatic role of STING is undisputable. Their interaction with either intracellular or extracellular antigen determines the fate of a cell and ultimately the heath of an individual. Conditions that lead to a decrease or an increase in the transcription of interferon genes have been associated with increased susceptibility to infections, and some autoimmune and systemic inflammatory diseases respectively. However, its interface with biomolecules is still not properly understood, hence, researchers are still tasked with providing proper elucidation on its pathways.

DECLARATIONS

Acknowledgement

The authors wish to appreciate the administration of All Saints University school of Medicine, Dominica for their financial support.

Conflict of Interest

The authors declare that there is no conflict of interest.

REFERENCES

[1] De Andrea, Marco, et al. “The interferon system: an overview.” *European Journal of Paediatric Neurology,* Vol. 6, 2002, pp. A41-A46.

[2] Pittock, Sean J. “Interferon beta in multiple sclerosis: How much benefit?” *The Lancet,* Vol. 370, No. 9585, 2007, pp. 363-64.

[3] Knight, E., et al. “Human fibroblast interferon: Amino acid analysis and amino terminal amino acid sequence.” *Science,* Vol. 207, No. 4430, 1980, pp. 525-26.

[4] Richter, Marc F., et al. “Specific contribution of Tyk2 JH regions to the binding and the expression of the interferon α/β receptor component IFNAR1.” *Journal of Biological Chemistry,* Vol. 273, No. 38, 1998, pp. 24723-29.

[5] Kalie, Eyal, et al. “The stability of the ternary interferon-receptor complex rather than the affinity to the individual subunits dictates differential biological activities.” *Journal of Biological Chemistry,* Vol. 283, No. 47, 2008, pp. 32925-36.

[6] De Libero, Gennaro, and Lucia Mori. “Recognition of lipid antigens by T cells.” *Nature Reviews Immunology,* Vol. 5, No. 6, 2005, p. 485.

[7] de Weerd, Nicole A., Shamith A. Samarajiwa, and Paul J. Hertzog. “Type I interferon receptors: biochemistry and biological functions.” *Journal of Biological Chemistry,* Vol. 282, No. 28, 2007, pp. 20053-57.

[8] NCBI. " IFNAR1 interferon alpha and beta receptor subunit 1 [*Homo sapiens* (human)] Gene ID: 3454". *Name of website*. National Center for Biotechnology Information, U.S. National Library of Medicine, updated on 4 Feb. 2018, https://www.ncbi.nlm.nih.gov/gene/3454.

[9] Schneider, William M., Meike Dittmann Chevillotte, and Charles M. Rice. "Interferon-stimulated genes: a complex web of host defenses." *Annual Review of Immunology,* Vol. 32, 2014, pp. 513-45.

[10] Hermant, Pascale, and Thomas Michiels. "Interferon-λ in the context of viral infections: production, response and therapeutic implications." *Journal of Innate Immunity,* Vol. 6, No. 5, 2014, pp. 563-74.

[11] Ochiai, K., et al. "Effect of IL-4 and interferon-gamma (IFN-γ) on IL-3-and IL-5-induced eosinophil differentiation from human cord blood mononuclear cells." *Clinical & Experimental Immunology,* Vol. 99, No. 1, 1995, pp. 124-28.

[12] Udagawa, Nobuyuki, et al. "Interleukin-18 (interferon-γ–inducing factor) is produced by osteoblasts and acts via granulocyte/macrophage colony-stimulating factor and not via interferon-γ to inhibit osteoclast formation." *Journal of Experimental Medicine,* Vol. 185, No. 6, 1997, pp. 1005-12.

[13] Bach, Erika A., Michel Aguet, and Robert D. Schreiber. "The IFNγ receptor: A paradigm for cytokine receptor signaling." *Annual Review of Immunology,* Vol. 15, No. 1, 1997, pp. 563-91.

[14] Koettnitz, Karl, and Frank S. Kalthoff. "Human interleukin-4 receptor signaling requires sequences contained within two cytoplasmic regions." *European Journal of Immunology,* Vol. 23, No. 4, 1993, pp. 988-91.

[15] Ishikawa, Hiroki, and Glen N. Barber. "STING is an endoplasmic reticulum adaptor that facilitates innate immune signalling." *Nature,* Vol. 455, No. 7213, 2008, p. 674.

[16] Ishikawa, Hiroki, Zhe Ma, and Glen N. Barber. "STING regulates intracellular DNA-mediated, type I interferon-dependent innate immunity." *Nature,* Vol. 461, No. 7265, 2009, p. 788.

[17] Burdette, Dara L., et al. "STING is a direct innate immune sensor of cyclic di-GMP." *Nature,* Vol. 478, No. 7370, 2011, p. 515.

[18] Barber, Glen N. "STING: Infection, inflammation and cancer." *Nature Reviews Immunology,* Vol. 15, No. 12, 2015, p. 760.

[19] Li, Yang, Heather L. Wilson, and Endre Kiss-Toth. "Regulating STING in health and disease." *Journal of Inflammation,* Vol. 14, No. 1, 2017, p. 11.

[20] Jønsson, K. L., et al. "IFI16 is required for DNA sensing in human macrophages by promoting production and function of cGAMP." *Nature Communications,* Vol. 8, 2017, p. 14391.

[21] Unterholzner, Leonie, et al. "IFI16 is an innate immune sensor for intracellular DNA." *Nature Immunology,* Vol. 11, No. 11, 2010, p. 997.

[22] Jakobsen, Martin R., et al. "IFI16 senses DNA forms of the lentiviral replication cycle and controls HIV-1 replication." *Proceedings of the National Academy of Sciences,* Vol. 110, No. 48, 2013, pp. E4571-E4580.

[23] Dutta, Dipanjan, et al. "BRCA1 regulates IFI16 mediated nuclear innate sensing of herpes viral DNA and subsequent induction of the innate inflammasome and interferon-β responses." *PLoS Pathogens,* Vol. 11, No. 6, 2015, p. e1005030.

[24] Sun, Lijun, et al. "Cyclic GMP-AMP synthase is a cytosolic DNA sensor that activates the type I interferon pathway." *Science,* Vol. 339, No. 6121, 2013, pp. 786-91.

[25] Civril, Filiz, et al. "Structural mechanism of cytosolic DNA sensing by cGAS." *Nature,* Vol. 498, No. 7454, 2013, p. 332.

[26] Orzalli, Megan H., et al. "cGAS-mediated stabilization of IFI16 promotes innate signaling during herpes simplex virus infection." *Proceedings of the National Academy of Sciences,* Vol. 112, No. 14, 2015, pp. E1773-E1781.

[27] Konno, Hiroyasu, Keiko Konno, and Glen N. Barber. "Cyclic dinucleotides trigger ULK1 (ATG1) phosphorylation of STING to prevent sustained innate immune signaling." *Cell,* Vol. 155, No. 3, 2013, pp. 688-98.

[28] Nyathi, Yvonne, Barrie M. Wilkinson, and Martin R. Pool. "Co-translational targeting and translocation of proteins to the endoplasmic reticulum." *Biochimica et Biophysica Acta (BBA)-Molecular Cell Research,* Vol. 1833, No. 11, 2013, pp. 2392-2402.

[29] Makris, Spyridon, Michelle Paulsen, and Cecilia Johansson. "Type I interferons as regulators of lung inflammation." *Frontiers in Immunology,* Vol. 8, 2017, p. 259.

[30] Kopitar-Jerala, Nataša. "The role of interferons in inflammation and inflammasome Activation." *Frontiers in Immunology,* Vol. 8, 2017, p. 873.

[31] Marinho, Fabio V., et al. "The emerging roles of STING in bacterial infections." *Trends in Microbiology,* 2017.

[32] Radoshevich, Lilliana, and Olivier Dussurget. "Cytosolic innate immune sensing and signaling upon infection." *Frontiers in Microbiology,* Vol. 7, 2016, p. 313.

[33] Margolis, Shally R., Stephen C. Wilson, and Russell E. Vance. "Evolutionary origins of cGAS-STING signaling." *Trends in immunology,* Vol. 38, No. 10, 2017, pp. 733-43.

[34] Manzanillo, Paolo S., et al. "*Mycobacterium tuberculosis* activates the DNA-dependent cytosolic surveillance pathway within macrophages." *Cell Host & Microbe,* Vol. 11, No. 5, 2012, pp. 469-80.

[35] Vázquez-Boland, José A., et al. "*Listeria* pathogenesis and molecular virulence determinants." *Clinical Microbiology Reviews,* Vol. 14, No. 3, 2001, pp. 584-640.

[36] Hamon, Mélanie, Hélène Bierne, and Pascale Cossart. "Listeria monocytogenes: A multifaceted model." *Nature Reviews Microbiology,* Vol. 4, No. 6, 2006, p. 423.

[37] Sauer, John-Demian, et al. "*Listeria monocytogenes* triggers AIM2-mediated pyroptosis upon infrequent bacteriolysis in the macrophage cytosol." *Cell Host & Microbe,* Vol. 7, No. 5, 2010, pp. 412-19.

[38] Delgado, M. A., and V. Deretic. "Toll-like receptors in control of immunological autophagy." *Cell Death and Differentiation,* Vol. 16, No. 7, 2009, p. 976.

[39] Deretic, Vojo, Tatsuya Saitoh, and Shizuo Akira. "Autophagy in infection, inflammation and immunity." *Nature Reviews Immunology,* Vol. 13, No. 10, 2013, p. 722.

[40] Cemma, Marija, and John H. Brumell. "Interactions of pathogenic bacteria with autophagy systems." *Current Biology,* Vol. 22, No. 13, 2012, pp. R540-R545.

[41] Nagarajan, Uma M., et al. "Type I interferon signaling exacerbates *Chlamydia muridarum* genital infection in a murine model." *Infection and Immunity,* Vol. 76, No. 10, 2008, pp. 4642-48.

[42] Prantner, Daniel, et al. "Critical role for interleukin-1β (IL-1β) during *Chlamydia muridarum* genital infection and bacterial replication-independent secretion of IL-1β in mouse macrophages." *Infection and Immunity,* Vol. 77, No. 12, 2009, pp. 5334-46.

[43] Elwell, Cherilyn, Kathleen Mirrashidi, and Joanne Engel. "Chlamydia cell biology and pathogenesis." *Nature Reviews Microbiology* Vol. 14, No. 6, 2016, p. 385.

[44] Russell, David G. "Mycobacterium tuberculosis and the intimate discourse of a chronic infection." *Immunological Reviews,* Vol. 240, No. 1, 2011, pp. 252-68.

[45] Gratz, Nina, et al. "Type I interferon production induced by *Streptococcus pyogenes*-derived nucleic acids is required for host protection." *PLOS Pathogens,* Vol. 7, No. 5, 2011, p. e1001345.

[46] Parker, Dane, and Alice Prince. "Type I interferon response to extracellular bacteria in the airway epithelium." *Trends in Immunology,* Vol. 32, No. 12, 2011, pp. 582-88.

[47] Andrade, Warrison A., et al. "Group B *Streptococcus* degrades cyclic-di-AMP to modulate STING-dependent type I interferon production." *Cell Host & Microbe,* Vol. 20, No. 1, 2016, pp. 49-59.

[48] Liu, Yiliu, Rongtuan Lin, and David Olagnier. "RIGulation of STING expression: At the crossroads of viral RNA and DNA sensing pathways." *Inflammation and Cell Signaling,* Vol. 4, No. 1, 2017.

[49] Woo, Seng-Ryong, et al. "STING-dependent cytosolic DNA sensing mediates innate immune recognition of immunogenic tumors." *Immunity,* Vol. 41, No. 5, 2014, pp. 830-42.

[50] Dong, Guanjun, et al. "STING negatively regulates double-stranded DNA-activated JAK1-STAT1 signaling via SHP-1/2 in B cells." *Molecules and Cells,* Vol. 38, No. 5, 2015, p. 441.