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**Role of nucleic acid sensing in the pathogenesis of type 1 diabetes**

Badal D *et al*. Nucleic acid sensing in T1D

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**Abstract**

During infections, nucleic acids of pathogens are also engaged in recognition *via* several exogenous and cytosolic pattern recognition receptors, such as the toll-like receptors, retinoic acid inducible gene-I-like receptors, and nucleotide-binding and oligomerization domain-like receptors. The binding of the pathogen-derived nucleic acids to their corresponding sensors initiates certain downstream signaling cascades culminating in the release of type-I interferons (IFNs), especially IFN-α and other cytokines to induce proinflammatory responses towards invading pathogens leading to their clearance from the host. Although these sensors are hardwired to recognize pathogen associated molecular patterns, like viral and bacterial nucleic acids, under unusual physiological conditions, such as excessive cellular stress and increased apoptosis, endogenous self-nucleic acids like DNA, RNA, and mitochondrial DNA are also released. The presence of these self-nucleic acids in extranuclear compartments or extracellular spaces or their association with certain proteins sometimes leads to the failure of discriminating mechanisms of nucleic acid sensors leading to proinflammatory responses as seen in autoimmune disorders, like systemic lupus erythematosus, psoriasis and to some extent in type 1 diabetes (T1D). This review discusses the involvement of various nucleic acid sensors in autoimmunity and discusses how aberrant recognition of self-nucleic acids by their sensors activates the innate immune responses during the pathogenesis of T1D.

**Key Words:** Nucleic acid sensing; Type 1 diabetes; Pattern recognition receptors; Nucleic acid receptors; Type 1 interferon; Beta cells

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**Core Tip:** Under abnormal physiological conditions, such as excessive cellular stress or apoptosis, endogenous self-nucleic acids like DNA, RNA or mitochondrial DNA accumulate in extranuclear compartments or extracellular spaces or form complexes with host proteins. Such situations sometimes lead to the failure of discriminating mechanisms of nucleic acid sensors leading to proinflammatory responses as seen in autoimmune diseases like systemic lupus erythematosus, psoriasis and to some extent in type 1 diabetes (T1D). The understanding of the role of nucleic acid-sensing and their downstream signaling pathways is gradually evolving and provides another avenue in exploring therapeutic options for treating autoimmune diseases like T1D.

**INTRODUCTION**

Type 1 diabetes (T1D) is a complex autoimmune disorder that involves infiltration of innate and adaptive immune cells culminating in the killing of insulin producing beta (β)-cells, mainly through T-cell dependent mechanisms. Pathogenesis of T1D involves an initial infiltration of mononuclear cells consisting of neutrophils, dendritic cells (DCs) and macrophages[1] in the pancreatic islets[2] followed by lymphocytic infiltration[3]. Beta-cell death is mainly mediated by autoreactive CD8+ T cells that release cytolytic granules, perforins facilitating the entry of granzymes in target β-cells[4,5]. The innate immune cells carry a variety of specialized receptors known as pattern-recognition receptors (PRRs) whose main function is to detect well-conserved structural motifs that are indispensable to pathogen survival and are known as pathogen-associated molecular patterns (PAMPs)[6]. In addition to recognizing PAMPs, these receptors under certain circumstances can also recognize damage associated molecular patterns (DAMPs) released by dying autologous cells, including β-cells, and can activate signaling cascade in a fashion similar to PAMPs recognition[7]. This recognition initiates a canonical immune signaling cascade driven by type 1 interferons (IFNs), mainly IFN-α to induce IFN-stimulated genes (ISGs) which activate inflammatory mediators, release cytokines responsible for instituting an inflammatory state in the pancreatic islets, and overexpression of HLA class-1 molecules on β-cells that enhances uptake of autoantigens by antigen-presenting cells (APCs)[8-10]. Nucleic acids, like other PAMPs, are vital for the survival and propagation of pathogens, and hence, the PRRs of the human innate immune system were evolved to recognize and mount an appropriate response against the pathogens bearing them. In various autoimmune conditions, like systemic lupus erythematosus (SLE), psoriasis, *etc.* and to some extent in T1D, the nucleic acids released by self-cells under certain physiological conditions, such as inflammation, stress, apoptosis, necrosis, pyroptosis, necroptosis, and NETosis act as ligands of PRRs, leading to either initiation of these autoimmune conditions or worsening of their pathogenesis[1,11,12]. In this review, we have summarized the recent advances in understanding the role of self-nucleic acids, their sensors, and downstream signaling pathways involved in the pathogenesis of T1D and discussed the novel therapeutic approaches targeting autoimmune diseases, including T1D.

**Nucleic acid sensinG**

As a part of the innate immune system, PRRs are the primary sentinels against the microbes, and initiation of immune responses through PRR recognition is crucial for the host defenses. PAMPs, such as viral or bacterial nucleic acids, in addition to other bacterial or fungal cellular components, are commonly recognized by the host PRRs. Recognition of PAMPs by PRRs initiates a downstream signaling cascade resulting in the innate immune responses by promoting the expression of pro-inflammatory cytokines, IFNs, *etc.*[13]. These cytokines signal the adjacent cells to promote the expression of various ISG to impair replication of pathogens. Besides microbial infection, PRRs activation by nucleic acids can also be initiated by the host cells. Stress or cell-death induced release of self-nucleic acids, such as genomic DNA, mRNA, tRNA and mitochondrial DNA (mtDNA) can also be recognized by PRRs to trigger inflammatory cytokines and type-I IFN, leading to chronic inflammation. Inappropriate or prolonged detection of these nucleic acids has been shown to be associated with many autoimmune diseases[11]. Presently, PRRs are classified into 4 main categories as follows: Toll-like receptors (TLRs), retinoic acid inducible gene-I (RIG-I)-like receptors (RLRs), absent-in-melanoma (AIM)-Like Receptors (ALRs), nucleotide-binding and oligomerization domain (NOD)-like receptors (NLRs), and C-type lectins (CTLs). CTLs and most TLRs are located in the plasma membrane, while the NLRs, RLRs, ALRs and a few TLRs are located intracellularly[13].

***TLRs***

TLRs are a conserved class of PRRs belonging to the family of type-I transmembrane receptor proteins consisting of an extracellular Leucine-Rich Repeat (LRR) domain and an intracellular C-terminal toll/IL-1 receptor (TIR) domain[14]. This domain is required for the interaction and recruitment of various adaptor molecules to activate downstream signaling pathways involving the transcription factors Activator Protein-1 (AP-1), Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells (NF-κB), and Interferon Regulatory Factor (IRF)[15]. To date, 13 different types of TLRs (TLR 1-13) have been identified. TLRs 1-9 are expressed by both humans and mice; whereas only humans, express TLR10, while mice are known to express TLR11-13[16]. TLRs are broadly expressed in both immune and non-immune cells in two distinct cellular compartments, extracellular and intracellular (mainly in endosomes)[17]. In T1D, upon recognition of pathogenic and/or foreign material, TLRs influence many immunologic mechanisms, including activation and maturation of APCs, antibody production, down regulating regulatory T cell (Treg) responses, and facilitating a pro-inflammatory environment through the secretion of a plethora of cytokines and chemokines[18].

TLR-TLR ligation and interaction transduces signals through MyD88 (Myeloid differentiation primary response 88)-dependent or independent pathways. Upon activation, MyD88 recruits Interleukin 1 Receptor Associated Kinase (IRAK-1), IRAK-4, and Tumor Necrosis Factor receptor (TNFR)-Associated Factor 6 (TRAF-6), which then activate c-Jun N-terminal Kinase (JNK), Ikβ Kinase (IKK), AP-1, and NF-κB. The MyD88-independent pathway is mediated by TIR-domain-containing adapter-inducing IFN-β (TRIF) and TRIF Related Adaptor Molecule (TRAM), leading to the activation of NF-κB, AP-1, or IRFs[19], while the TLR3 signaling is mediated through TRIF, TLR7, TLR8, and TLR9 signals through MyD88. It has also been demonstrated that TLR signaling can efficiently promote the uptake of autoantigens by APCs[8-10]. Under normal physiological conditions apoptotic cell derived antigens are not presented efficiently by MHC class II molecules. However, TLR ligand co-administration not only enhances antigen presentation but also promotes antigen specific responses by CD4+ T cells[8]. Thus, it means that TLRs not only acts as danger signal sensors but also regulators of self-and non-self-antigen discrimination[20,21]. In support of this fact, it has been demonstrated that stimulation of TLRs enhances antigen processing by up-regulating scavenger receptors *via* the MyD88-dependent pathway[22].

The role of TLRs especially those involved in the recognition of nucleic acids is also being recognized in autoimmune diabetes. TLRs can recognize various forms of endogenous DNA or RNA produced during virus infection induced cell death[23]. However, TLR3, TLR7, TLR8, and TLR9 specifically recognize viral-associated nucleic acids with comparatively higher affinity and have been implicated in the pathogenesis of T1D. TLR3-/- NOD mice have shown high mortality from Coxsackie B4 virus (CVB4) infections and the few that survived develop T1D[24]. Certain polymorphisms in the *TLR3* gene (rs3775291 and rs13126816) have also been shown to be related with a higher risk of T1D and a more aggressive pathology[25]. A double stranded RNA (dsRNA) mimetic polyinosinic: polycytidylic (poly I: C) has been reported to be recognized by TLR3, leading to induction and increase in the severity of T1D in mice, depending on dose and administration[25].

Stimulation of TLR7 (in addition to CD40 activation of DCs) can induce diabetogenic cytotoxic CD8+ T cells in the pancreatic lymph nodes of NOD mice to promote the onset of autoimmunity[26]. Repeated topical administration of a TLR7 agonist, imiquimod, is sufficient to promote T1D development while inhibition using IRS661 can significantly lower disease onset[26]. Similarly, TLR7 signaling in plasmacytoid DCs (pDCs) triggers B and T cell activation *via* IFN-I secretion in rotavirus infections, on the other hand, inhibition of TLR7 can block this process and prevent the acceleration of T1D following infection[27]. Zhang *et al*[28] have shown that TLR9 blockade can impede the activation of diabetogenic CD8+ T cells and, delay autoimmune diabetes in NOD mice. Liu *et al*[29] generated TLR9 knockout NOD mice and observed improvements in insulin secretion, glucose tolerance, and β-cell function. These improvements were partially mediated by the upregulation of CD140a on β-cells. Similar results have been observed by the use of TLR9 antagonists or by genetic targeting on ontogenesis and function of β-cells to protect NOD mice from T1D.

Hence, these and other reports further necessitate more research to understand and improve defects associated with self-nucleic acid recognition by TLRs associated with T1D pathology.

***RLRs***

RLRs are a group of intracellular receptors that recognize viral dsRNA and are comprised of 3 proteins: (1) RIG-1; (2) Melanoma differentiation-associated gene 5 (MDA5); and (3) Laboratory of genetics and physiology 2 (LGP2), which is composed of a DExD/H box RNA helicase domain and a C-terminal domain[30]. Both RIG-1 and MDA5 contain additional N-terminal caspase activation and recruitment domains (CARDs) that transmit downstream signaling. RIG-I and MDA5 have similar functions and they initiate antiviral signals to induce *IFN* gene activation, while LGP2 acts as a regulator of MDA5 and RIG-1[31]. Upon recognition of RNA, an ATP-dependent conformational change occurs in RLR[32] resulting in the activation of CARD and further activation of an adaptor molecule, mitochondrial antiviral signaling (MAVS) protein[33]. Activation of MAVS, in turn, triggers signaling cascades involving TRAF3/6, caspase 8/10, RIP-1, fas-associated death domain, and TNF receptor-associated death domain ultimately activating TANK binding kinase 1 (TBK1)/IKK-ε and IKKα/IKKβ to induce transcription of type-I IFNs and proinflammatory cytokines by activating IRF-3 and NF-κB.

When challenged with pathogenic stress, various single nucleotide polymorphism (SNP) in the *interferon induced with helicase C domain 1* (*IFIH1*) gene have been found to cause greater or reduced susceptibility in the pathogenesis of T1D *via* altering MDA5 activation and expression[34]. The *IFIH1* mutation A946T (rs1990760)has been involved in the pathogenesis and development of various autoimmune diseases like T1D, SLE, and multiple sclerosis (MS)[35,36]. Two independent studies conducted on subjects with diabetes showed that subjects with heterozygous A946T SNP have a more prominent immune response and ISG expression to Coxsackie virus challenge in comparison to healthy controls, suggesting greater IFNs and ISGs expression during infection[37,38]. In another study, Cinek *et al*[39] demonstrated a positive correlation between IFIH1 polymorphism (rs1990760), which is known to be strongly associated with T1D, and enteroviral RNA frequency in the blood of T1D subjects. The authors further suggested that rs1990760 can modify enteroviral frequency in the blood of healthy children harboring IFIH1 polymorphism, predisposing them towards T1D[39]. Gain-of-function mutations in *IFIH1* have been also found to be associated with overexpression of type 1 and type 3 IFN[40]. A study by Gorman *et al*[41] observed mice that were homozygous for *IFIH1* SNP (946T) or exhibiting IFIH1 risk alleles (843R and 946T) simultaneously, had enhanced expression of *IFIH1*-related genes, increased rate of autoimmunity development, and ability to recognize self-RNA. Such mutations may alter the expression of inflammatory molecules and the dynamics of target binding, and activation may also be altered, resulting in more potent/enhanced IFN response leading to the risk of T1D. For example, MDA5 mutation E627 causes loss of a portion of C-terminal region, resulting in loss of dsRNA ligand and binding[42]. Overall, these reports provide us with enough knowledge about the role of RLRs in the pathogenesis of T1D.

***ALRs***

A few PRRs also include some members of the family of proteins containing pyrin and hematopoietic interferon-inducible nuclear (HIN) domain[43]. The Pyrin and HIN domain (PHYIN) family of proteins comprises of ALR, which contains an N-terminal Pyrin domain and one or two C-terminal hematopoietic IFN-inducible nuclear proteins with 200 amino acids (HIN-200) domains, containing an oligonucleotide/oligosaccharide-Binding fold (OB fold), which is a common DNA-binding motif[44]. Of all ALRs, absent in melanoma 2 (AIM2) protein is the only one conserved in both humans and mice. AIM2 possesses the ability to sense DNA in the cytoplasm and as well as in the nucleus[44].

AIM2 is a cytosolic dsDNA receptor that oligomerizes on recognizing cytosolic foreign dsDNA and promotes the polymerization of the adaptor protein, Apoptosis-associated Speck-like (ASC) protein and eventually forming a caspase-1 activating inflammasome[44]. AIM2 binds to small DNA fragments up to 20bp; however, in order to initiate immune responses against longer DNA fragments, oligomerization of AIM2 is required~~.~~ ALRs can sense self-DNA through leakage from nuclear envelope and exosomes engulfed by phagocytes; however, the ability of ALRs to elicit type 1 IFN responses is questionable, as mice deficient in ALRs can mount effective type 1 IFN responses to DNA viruses and lentiviruses[45].

***NLRs***

NLRs are comprised of various cytosolic PRRs, which are characterized by the presence of a conserved NOD[46]. NLRs consist of an N-terminal effector binding region, which is further comprised of: (1) protein-protein interaction domain such as the: (a) CARD; (b) pyrin domain (PYD); and (c) Baculovirus inhibitor repeat domain; (2) NOD domain, which is needed for self-oligomerization and nucleotide binding; and (3) array of C-terminal LRR motifs to recognize the pathogenic pattern and regulate NLR activity.

Upon recognition of nucleic acids by the C-terminal LRR motifs, the downstream signaling gets initiated, involving conformational changes that result in oligomerization of NLR *via* the NOD domain. NLR exposes the effector domains to initiate CARD and PYD recruitment and activation by enhancing their oligomerization[47]. NLRs interact with receptor interacting serine/threonine protein kinase 2 to trigger mitogen-activated protein kinase (MAPK) and NF-κB[48]. The NLRs have a proven role in antiviral immunity; however, their role in sensing self-nucleic acids is gradually emerging[49]. NLRs also recognize oxidized forms of mitochondrial DNA, which could have important implications in inflammation and cancers[50].

***Role of ALRs and NLRs in the formation of inflammasomes***

Inflammasomes are a diverse class of cytosolic multiprotein complexes consisting of an adaptor protein containing CARD, a sensor protein and caspase-1 which is highly proinflammatory. Their assembly can be triggered by a variety of stimuli, ultimately leading to caspase-1 activation and synthesis of proinflammatory cytokines. Inflammasomes play a crucial role in the mobilization and activation of various immune cells in maintaining tissue homeostasis by initiating acute immune responses. Inflammasomes can also initiate chronic immune response leading to uncontrolled inflammation which eventually causes cell death *via* pyroptosis[51]. Among them, NLRP3 and NLRP1 inflammasomes are the most common subtypes[52]. ALRs and NLRs initiate the immune response by forming inflammasomes, thereby alleviating IL-1β and IL-18 maturation and release[53,54]. Activated caspase-1 then cleaves pro-IL-1β or pro-IL-18 ,enabling the release of the mature active cytokines IL-1β and IL-18[53,55].

NLRP3 inflammasomes have been reported to play crucial roles in the pathogenesis of various autoimmune disorders, including T1D[56,57]. In 2019, Sun *et al*[58], showed the association of SNPs with T1D pathogenesis and diabetes onset in the *NLRP1* gene of T1D patients of Chinese Han origin. Increased susceptibility to T1D and celiac disease have been reported to be associated with SNPs within the *NLRP3* gene. A study by Hu *et al*[59] showed an important role of NLRP3 in the pathogenesis of T1D in NOD mice. Elimination of NLRP3 altered T cell maturation *via* regulation of CCR5 and CXCR3 expression, as well as pathogenic T cell mobilization to the pancreatic islets, which is a crucial process leading to β-cell death and disease progression. Also, knockout of NLRP3 downregulated C-C motif chemokine ligand 5 (CCL-5) and C-X-C motif chemokine ligand 10 (CXCL10) expression in the pancreatic islets *via* IRF-1 signaling[59]. Furthermore, in STZ induced diabetic mice model, NLRP3 activation *via* mtDNA initiated IL-1β production in caspase-1 dependent manner, suggesting a direct role of NLRP3-caspase1 signaling in T1D[60]. Pereira *et al*[61] recently highlighted the role of mtDNA in the involvement of vascular endothelial dysfunction in human subjects with T1D and asserted on the connection between NLRP3 inflammasomes and T1D complications. In this study, mtDNA isolated from diabetic mice promoted NLRP3 inflammasome activation *via* mechanisms involving mitochondrial ROS and Ca2+ influx, which was abrogated in NLRP3 knockout mice.

***Cyclic GMP-AMP synthase-stimulator of IFN***

The cyclic GMP-AMP synthase-stimulator of IFN genes (cGAS-STING) is a DNA sensing receptor present in the cytoplasm that recognizes host/pathogenic DNA[62]. When DNA binds on the active site of cGAS, its C-terminal containing the catalytic unit undergoes a variety of conformational changes, resulting in cyclic guanosine monophosphate–adenosine monophosphate (cGAMP) formation from ATP and GTP[63,64]. cGAMP formation results in STING activation by inducing conformational changes upon binding to its active site and also facilitates STING transportation from the endoplasmic reticulum to the Golgi apparatus[65,66]. Upon activation, STING further forms a complex with TBK1, which further phosphorylates IRF3 in endolysosomes[67,68]. Phosphorylated IRF3 translocates into the nucleus undergoing dimerization, and thus inducing the expression of ISG[69,70]. However, STING is also involved in the stimulation of IFN-β by interacting with the Translocon-Associated Protein (TRAP)[65,71].

The role of cGAS-STING in various autoimmune disorders is being widely explored, while its role in T1D has not been reported earlier. Lemos *et al*[72] reported that the activation of STING resulted in suppression of T1D onset and progression when NOD mice were administered with DNA nanoparticles, which promoted indoleamine 2,3 dioxygenase (IDO) activity, thus modulating T cell immunity in pancreatic lymph nodes and pancreas.

Overall, many studies have yielded important information on how the nucleic acid sensors lead to the activation of downstream signaling pathways (Figure 1). These sensors and their signaling mediators have been implicated in different autoimmune diseases including T1D (Table 1)[73-84].

**Type 1 IFN signaling: An important converging point**

Most of the nucleic acid recognition pathways culminate in the release of type 1 IFN, especially IFN-α, via mediators like IRFs, which makes them one of the most crucial part of the nucleic acid sensing pathway. IFN-α has multiple roles, including upregulation of human leukocyte antigen (HLA) class I and HLA class II to enhance antigenic presentation, increase in immunoproteasome activity, induce ER stress and cellular inflammation through TYK2 activation, induction of transcription factors, and signal transducer and activator of transcription 2 and IRF9. It also acts synergistically with IL-1β and induces β-cell apoptosis[85]. Heightened IFN-α secretion in peripheral blood mononuclear cells of T1D subjects by stimulation with influenza viruses has been attributed to the recognition of viral nucleic acids by endosomal TLRs of pDCs. Additionally, *in vitro* studies have demonstrated that pDCs secreted IFN-α enhances Th1 responses[86]. Another study observed higher levels of secreted IFN-α by pDCs obtained from the relatives of T1D subjects following their stimulation with CpG 2216[87]. The transition of prediabetic stage to full-blown diabetes is also found to be controlled by IFN-α signaling. The study demonstrated that the infiltration of autoreactive T cells and β-cell killing can be prevented by blocking IFN-α signaling by sphingosine-1 receptor agonist prior to the clinical onset of disease[88]. Rodrigues *et al*[89] in a recent study revealed IFN-1 hyper-responsiveness in T1D after innate immune stimulation of whole blood cells with CpG DNA. They observed higher induced IFN-1-associated gene expression in monocytes from NOD mice. Similarly, in human participants, *ex vivo* whole blood stimulation showed higher induced IFN-1 responses in participants with T1D compared with healthy controls. In our recent study, we, too, observed increased secretion of IFN-α by the peripheral pDCs from T1D subjects compared to non-diabetic controls. Enhanced IFN-α secretion was also observed after stimulation with DNA-LL37 complexes indicating the inflammatory nature of pDCs derived from T1D subjects. Collectively, these data support the notion that IFN-α mediated effects play an important role in the early pathogenic events during initiation of autoimmune diabetes, and the presence of early type 1 IFN signature in susceptible individuals and animal models suggests the role of viral nucleic acids, and to some extent, the self-nucleic acids in T1D pathogenesis.

**Self-nucleic acids: Role in pathogenesis of type 1 diabetes**

During the initial phase of T1D, innate immune cells, like DCs, neutrophils and macrophages, infiltrate the islets much before the infiltration of T and B cells[2,90-92]. This buildup of innate immune cells is persistent during the later β-cell destructive insulitis as well[93]. Therefore, the entry of DCs and macrophages/monocytes can be considered an initial sign of the autoimmune process during the pathogenesis of T1D[1,20,94].

Although there is ambiguity regarding the exact role of innate immune cells and other initial triggers involved in the loss of β-cell tolerance, certain factors, like viral infection and ER stress are known to provoke an immune response in β-cells leading to the activation of pro-inflammatory pathways. Additionally, β-cells themselves might also participate in their demise by invoking apoptosis rather than being an innocent victim of autoimmune attack as previously thought [95]. One of the outcomes of β-cell destruction is the release of self-nucleic acids along with other cellular debris. Among the nucleic acids, the role of self-DNA in the development of T1D is highlighted by few studies, Diana *et al*[1] demonstrated that neutrophils, B-1a cells, and plasmacytoid dendritic cells are recruited to islets during physiological periods of β-cell death. Activated B-1a cells secrete dsDNA specific IgGs, which activate neutrophils to release DNA-binding cathelicidin-related antimicrobial peptide (CRAMP), which binds self-DNA, and along with DNA-specific IgG, activating pDCs through the TLR9–MyD88 pathway, leading to IFN-α production in pancreatic islets and initiation autoimmune diabetes in NOD mice. Mollah *et al*[96] observed increased incidence of diabetes associated with increased accumulation of ssDNA in the immune cells of granzyme A (protease degrading intracellular DNA) deficient NOD mouse due to induction of IFN response in pancreatic islets. The study identified DNA as a novel endogenous trigger of autoimmune diabetes and an *in vivo* role for granzyme A in maintaining immune tolerance. Earlier, Zentsova *et al*[97] had also observed that monocytes contribute to DNA sensing in patients with T1D *via* the TBK1 and STING pathways by recognizing CpG-DNA leading to the release of IFN-α and proinflammatory cytokines. These studies highlight the importance of investigating the interaction of DNA sensors of innate immune cells during the early pathogenesis of T1D. However, limitations in obtaining pancreatic tissues pose a big challenge in assessing such interactions.

Besides DNA, the role of self-RNA in the progression of T1D is also being speculated. A study by Kocic *et al*[98] demonstrated that accumulation of circulating self-RNA can lead to the progression of autoimmune or inflammatory conditions in subjects with juvenile T1D. Recently, studies from several groups suggested that adenosine deaminase acting on RNA (Adar1) deficiency leads to the accumulation of retroelements, such as Alu:Alu hybrids, in the cytoplasm, which are then recognized by MDA5, resulting in excessive proinflammatory response[99,100]. Furthermore, mouse models deficient in Adar1 established that dysregulated RNA editing caused MDA5-driven autoimmunity[101,102]. The role of mtDNA acting as a ligand for nucleic acid sensors is also being observed by various research groups. When mtDNA is released into extracellular space and cytoplasm, it activates a variety of innate immune responses. West *et al*[103] showed that the mitochondrial transcription factor A (TFAM) deficiency leads to mis-packaged mtDNA, resulting into its cytoplasmic release where it bound and activated cGAS initiating a type-I IFN response. mtDNA has also been involved in the activation of inflammasome[104]. Carlos *et al*[105] shown that mtDNA activates NLRP3 to trigger IL-1β secretion *via* caspase-1-dependent pathway to precipitate the onset of streptozotocin (STZ) induced T1D in C57BL/6 mice. In 2020, Pereira *et al*[61] observed that mtDNA promoted NLRP3 inflammasome activation that contributed to inflammation and endothelial dysfunction in patients with T1D.

**Nucleic acid sensing: What leads to the dysregulation?**

The role of nucleic acids and their signaling has been explored by several studies in many autoimmune diseases, yet there is very little data on the aberrations in nucleic acid sensing mechanisms in autoimmune *vs* non-autoimmune conditions. Parallels are drawn from those autoimmune diseases, like psoriasis and SLE, where nucleic acids are targeted by the immune cells. During the pathogenesis of SLE, the pDCs get activated due to facilitated recognition of autoantibodies against nucleic acids by TLR7 and TLR9 leading to increased secretion of type 1 IFNs[106,107]. A similar role of self-DNA complexes and specific antibodies was also suggested by Diana *et al*[1] during the initial stages of T1D in the activation of TLR9 in pancreatic pDCs, which release IFN-α in NOD mice, as explained earlier.

An important study by Revelo *et al*[108], explored the possible role of different types of nucleic acids contributing to glucose intolerance during diet induced obesity (DIO). The study concluded that oxidized mtDNA derived from abnormal formation of extracellular traps (ets) can promote inflammation of metabolic tissues *via* TLR7 and TLR9 in pDCs. The same study has also explored the possible role of exogenous sources of nucleic acids like CpG-ODN, which worsened glucose tolerance in lean mice, possibly by the recognition of CpG DNA by TLR9. A similar study has also shown that increased levels of circulating cell free DNA are involved in the activation of macrophages *via* TLR9 during DIO[109]. A recent study by Zentsova *et al*[97] demonstrated altered DNA sensing in subjects with T1D in response to microbial DNA. Prominent proinflammatory responses were observed in pDCs and monocytes of T1D patients compared to healthy controls. Furthermore, monocytes isolated from T1D subjects were shown to bind and internalize DNA and responded by releasing higher levels of proinflammatory cytokines as compared to control subjects. Surprisingly, this cytokine production was independent of the TLR9 signaling pathway but dependent on other intracellular receptors like, TBK1 and STING for recognition of CpG-DNA and NETs, which were used to mimic self-DNA in the study. During our study on the role of self-DNA in T1D, we have also observed that the pDCs and monocytes of T1D subjects behave differently from those of healthy subjects. We observed that the pDCs and monocytes of T1D subjects were more prompt on acquiring an inflammatory phenotype upon stimulation with molecules like DNA-LL37 complexes by initiating inflammation through IFN-α and augmenting autoimmunity by activating CD4+ T cells[110]. Therefore, it appears that either altered forms of nucleic acids or alterations in their sensors underlie the dysregulations in nucleic acid sensing in autoimmunity.

***Formation of nucleic acid-protein complexes***

In normal circumstances, the self-nucleic acids are considered non-immunogenic in nature and in the extracellular environment, they undergo rapid degradation by various extracellular nucleases[111]. However, their binding to peptides like, LL37 and HMGB1 (released by neutrophils and monocytes, respectively)[112,113] can lead to the formation of complexes that are resistant to nuclease degradation. These complexes are transported to endosomal compartments of pDCs and monocytes, which are recognized by TLR9[114]. In the case of NOD mice, CRAMP (mouse equivalent of LL37) is known to form complexes with self-DNA and DNA-specific IgG to induce IFN-α production *via* the TLR9 and MyD88 pathways. In T1D, we have also observed that LL37 forms stable complexes with self-DNA to protect it from DNase degradation and, at the same time, it increases the efficiency by which pDCs and monocytes engulf DNA complexes in their cytosol[110]. Moreover, delayed clearance of apoptotic cells and other cellular debris by the macrophages also causes their accumulation, which in turn results in increased uptake of nucleic acids by innate immune cells, like pDCs and DCs that express abundant nucleic acid sensors. Apart from self-DNA, self-RNA is also capable of forming stable immune complexes with LL37, which was first observed by some researchers where they observed stable formation of complexes that readily enter endosomes of both pDCs and mDCs to induce TLR7 activation that finally triggers IFN-α secretion. Taking cue from these aforementioned studies it can be concluded that self-nucleic acids, like RNA, DNA and mtDNA, that are released from the dying β cells can form complexes with certain peptides and activate innate immune cells like pDCs, DCs and macrophages, and tilting the local immune homeostasis towards proinflammation.

However, the main unanswered question that remains is how does the uptake of self-nucleic acids or their complexes with proteins confer a proinflammatory phenotype to innate immune cells like the uptake of nucleic acids of viral and bacterial origin. Comparative studies done in past have shed some light and indicated that self-nucleic acids can induce similar if not heightened immune responses during the progression of autoimmune diseases, including T1D, although this hypothesis is still in its nascent stages and require some solid comparative studies, especially in T1D pathogenesis. The role of molecular mimicry by self-nucleic acids cannot be denied as they share similar motifs to pathogenic genomes like that of viruses and bacteria, a very good example of which is the presence of CpG islands in mtDNA. The role of nucleic acid induced innate immune inflammation also becomes particularly important, especially when viral infections alone cannot explain the initial infiltration and activation of innate immune cells, like pDCs, DCs, and monocytes, during the initial stages of T1D.

**Targeting nucleic acid sensing pathways: Therapeutic strategies**

With the increasing understanding of their roles and the signaling cascades in initiating inflammatory responses, novel therapies involving PRRs, have been attempted to target autoimmune diseases (Table 2).

Historically, targeting of downstream TLR signaling pathways using antimalarial drugs like chloroquine, quinacrine, and hydroxyl-chloroquine (HCQ) have been used in the treatment of autoimmune diseases since the 1940s, suggesting the effectiveness and importance of blocking endosomal TLR signaling rather than blocking TLR ligand themselves[115]. Compared to HCQ, CpG-52364, a quinacrine derivative and small-molecule antagonist of TLR7/8/9 is therapeutically more effective and has fewer side effects in animal studies. A phase I clinical trial for treatment of SLE (NCT00547014) showed inhibition of disease development without causing general immunosuppression[116]. Next, the idea of reducing exogenous DNA and RNA associated DAMPs has also been tried as an alternative and broader approach to suppress non-TLR dependent pathways of IFN production for the treatment of autoimmune diseases. Pulmozyme, a recombinant human DNase, has been in use since 1994 for the treatment of cystic fibrosis[117]. Additionally, Macanovic *et al*[118] showed that murine DNase can improve renal histology in NZB/NZW F1 Lupus-prone mice. A bovine DNase preparation also had initial success in improving clinical outcomes in a patient trial of SLE, but further studies were precluded due to the development of antibodies to the bovine DNase[119].

Oligodeoxynucleotides (ODNs) were first designed for direct binding and for antagonizing endosomal TLRs as an alternate strategy to treat SLE, which despite showing initial success the therapy, failed to garner support due to several reports of adverse effects like thrombocytopenia and neutropenia. Although greater promise was shown by ODNs, like immunomodulatory oligonucleotides (IMO)-8400 in psoriasis that target TLR7, TLR8, and TLR9 to reduce the expression of IL-17 signaling associated genes[120,121]. A phase 2a clinical trial, sponsored by Idera Pharmaceuticals, involving use of IMO-8400 for the treatment of plaque psoriasis exhibited reduced psoriasis severity with good tolerance in the recruited subjects (NCT01899729)[122]. A preclinical study on INH-ODN-24888, a guanine modified oligonucleotide was initiated for the treatment of lupus patients based on its activity as a TLR7 and TLR9 antagonist, and it was observed to be more efficient than the unmodified oligonucleotide (INH-ODN-2088)[123,124].

Other peptide compounds designed to inhibit TLR signaling pathways in autoimmune diseases include SM934 (b-aminoarteether maleate). It targets TLR7 and TLR9 signaling cascades, thereby promoting their downregulation along with regulation of MyD88 expression and NF-kB activation through an unknown mechanism. Finally, it inhibits TLR-induced activation of B cells leading to a decrease in proliferation and antibody secretion in MRL/Lpr mice (animal model of SLE)[125]. Another peptide ST-2825 that blocks the dimerization of MyD88[126] by interfering with the recruitment of IRAK1 and IRAK4 to TLR7- and TLR9-MyD88 complexes was found to be of therapeutic importance in inhibiting TLR-mediated inflammatory responses. Recently, PF-06650833, a small molecule inhibitor of IRAK4 has been reported to be effective in ameliorating some symptoms in patients with moderate to severe rheumatoid disease[127]. Another molecule, reported as “Compound II” in the study by Hasan *et al*[128], was shown to inhibit TBK1 and consequently douse the hyper-inflammatory responses in Trex-/- mice. Another novel inhibitor, TJ-M2010-6, has also shown the ability to suppress homo-dimerization of MyD88 by interacting with amino acid residues of its TIR domain, thereby preventing and treating T1D in NOD mice. Upon deducing the mechanistic pathways, it was observed that TJ-M2010-6 treatment prevents insulitis *in vivo*, whereas *in vitro* experiments showed inhibition of DCs maturation, leading to suppression of T cell activation and production of inflammatory cytokines[129]. To directly target the interaction of TLRs with their corresponding ligands, several antibodies have been designed, including Sifalimumab (NCT00979654, NCT01283139) and AGS-009 (NCT00960362). Both of the antibodies showed significant reduction of the IFN-α signature in the clinical trials aimed at SLE treatment[130-132]. However, despite the indispensable role of endosomal TLRs in the pathology of several type 1 IFN-driven autoimmune diseases, the therapeutic strategies against TLR7, TLR8, and TLR9 have yet to see appreciable success in various clinical trials.

Recent data on the involvement of molecular pathways leading to NETosis, and the components of NETs, like myeloperoxidase MPO, neutrophil elastase NE, and nucleic acids, have made them an attractive target for therapeutic strategies in autoimmune diseases, including T1D[133]. The best studied and the viable target is PAD4, which is a nuclear enzyme mediating NET formation by chromatin de-condensation[134], several inhibitors against NETs have been tried, of which GSK484 has shown persistent activity in animal models of inflammatory disease[135]. Additionally, an enzyme, staphylococcal nuclease, has shown some promise by degrading intestinal NETs and ameliorating both intestine and pancreatic islet inflammation to effectively regulate the blood glucose homeostasis in NOD mice[136]. Keeping in view the important roles played by nucleic acid sensing in shaping immune responses, specifically *via* modulation of innate immunity, researchers are actively exploring the nucleic acid-based nanoparticles that can be designed and functionalized with known therapeutic immunomodulatory domains and motifs, for the treatment of various nucleic acid centered autoimmune diseases[137,138]. Collectively, these studies emphasize the scope of further exploration of novel approaches to targeting key checkpoints in nucleic acid recognition and their downstream signaling pathways.

**CONCLUSION**

There are ample studies on T1D pathogenesis in both humans and animal models, and significant progress has been made in understanding the role of various cellular mechanisms involved in the initiation of the disease. Emerging data on the contribution of nucleic acids and their receptors on innate immune cells is challenging the current dogmatic and historical view of T1D as being a T cell driven disease.

The evolving view, that we have tried to support in this review, is that the initiation of autoimmune diabetes and its etiopathogenesis is much more complex and might involve aberrant recognition of self-nucleic acids at a very early stage. Recent findings from several groups have suggested the role of self-nucleic acids in elevating IFN induced responses by involving several PRRs in various autoimmune disorders including T1D. We would further like to propose that recognition of these self-nucleic acids by various innate immune cell subsets may have a similar outcome as in other autoimmune diseases, like SLE and psoriasis, where DAMPs like self-nucleic acids play a crucial role in the precipitation of the disease. However, despite this growing knowledge, further insights are required on the role of various nucleic acids and their sensors particularly in the context of the regulation of their downstream signaling mediators during the pathogenesis of T1D. Thus, it becomes necessary to search for novel inhibitors or receptor antagonists as a way of modulating dysregulated nucleic acid sensing, which might be useful in preventing or delaying the progression of T1D and similar autoimmune diseases.

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**Figure Legends**



**Figure 1 Nucleic acid sensors and their signaling pathways involved in autoimmune diseases including type 1 diabetes.** A: Toll-like receptor (TLR) signaling: Priming of nucleic acid sensing is mediated by the activation of several TLRs, which are located in endosomes. For *e.g.,* TLR3 recognizes double stranded RNA initiating downstream TIR-domain-containing adapter-inducing interferon (IFN)-β dependent signaling cascade *via* activation of IRF3 and IRF7, resulting in the induction of IFN-stimulated genes (ISGs). On the other hand, TLR7, TLR8 and TLR9 recognize ssRNA and dsDNA to trigger downstream signaling *via* Myd88, resulting in higher expression of either type1 IFNs or NF-κB *via* IRF7 and IκB phosphorylation, respectively. NF-κB activation further stimulates the production of pro interleukin (IL)-1β and pro IL-18, which get cleaved by caspase 1 into mature IL-1β and IL-18, respectively; B: Inflammasome complexes: Following recognition of nucleic acids, recruitment of various adaptor proteins occurs to form mature inflammasome complexes, which further cleave pro-caspase 1 and gasdermin D (GSDMD) into active caspase 1 and GSDMDn (GSDMD n-terminal), respectively. GSDMD gets inserted into the plasma membrane and helps in the release of inflammatory cytokines;C: Cytosolic Receptors: cGAS is another DNA sensor localized close to the plasma membrane. It recognizes and forms complexes with dsDNA. cGAS-dsDNA binding induces the catalytic synthesis of cGAMP from ATP and GTP, which further culminates in the stimulation of STING. Other DNA binding proteins (or sensors) like IFI16 and DDX41 also recognize DNA and activate STING, which further facilitates NLRP inflammasome activation. STING also activates the battery of IFN genes *via* IRF phosphorylation. Different forms of RNA originating from wide sources, like viral RNA, degraded self-RNA, *etc*. are recognized by RLRs, including RIG-1 and MDA5, following which they are imported to mitochondrial antiviral signaling (MAVS). MAVS further activates ISGs *via* IRF3-IRF7 activation. IFNs also work in an autocrine fashion and stimulate more production of different nucleic acid sensors and other ISGs. AIM2: Absent in melanoma; ASC: Apoptosis-associated speck-like protein containing a CARD (Caspase activation and recruitment domain*)* Domain; BAX: Bcl-2-associated X protein; cGAS: Cyclic GMP-AMP synthase; DDX41: DEAD-Box helicase 41; DHX: DEXH-box helicase; GBP: Guanylate-binding proteins; GSDMD: Gasdermin D; GSDMDn: Gasdermin D (N-Terminal); HIN: Hematopoietic IFN-inducible nuclear protein; IFI16: Interferon gamma inducible 16; IFIT1: Interferon induced p*rotein* with tetratricopeptide repeats 1; IFN: Interferon; IFNR: IFN receptor; IGRB10: Immunity-related GTPase family member B10; IKK: Iκb (Inhibitor of Nuclear Factor Kappa B) Kinase; IL: Interleukin; IL-1R1: IL-1 receptor 1; IRAK: Interleukin-1 receptor associated kinase; IRF: Interferon-regulatory factors; ISG: Interferon stimulated genes; JAK: Janus kinase; MAVS: Mitochondrial antiviral-signaling protein; MDA5: Melanoma differentiation-associated protein 5; Myd88: Myeloid differentiation primary response 88; NLRP: NLR (NOD-like receptor) family pyrin domain; NOD: Nucleotide binding and oligomerization domain; PKR: Protein kinase R; PYD: PYRIN Domain; RIG1: Retinoic acid-inducible gene I; STAT: Signal transducer and activator of transcription; STING: Stimulator of interferon genes; TBK1: TANK (TRAF family member-associated NF-kappa-B activator)-binding kinase 1, TLR: Toll-like receptor; TRAF: TNF (Tumor necrosis factor) receptor associated factors; TRIF: TIR [toll/interleukin-1 (IL-1) receptor] domain containing adapter inducing interferon-β.

 **Table 1 Nucleic acid sensors involved in various autoimmune diseases including type 1 diabetes**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **No.** | **Nucleic acid sensor** | **Downstream signaling molecule** | **Autoimmune disease** | **Ref**. |
| 1 | TLR9 | Myd88/ IRF3/7 | SLE | [73,74] |
| 2 | TLR7 | Myd88 | T1D | [27] |
| 3 | TLR3 | TRIF | T1D | [25,75] |
| 4 | RLR | IRF3 | Singleton-Merton Syndrome, | [76,77] |
| AGS and T1D | [34,78] |
| 5 | cGAS-STING | cGMP | SLE and AGS | [79,80] |
| 6 | NLR | Inflammasome activation | T1D and SLE | [58,81] |
| 7 | AIM | SLE | [81] |
| 8 | IFI16 | Inflammasome | Primary Sjogren’s Syndrome | [82] |
| Activation | Rheumatoid Arthritis | [83] |
| 9 | CTL | Bcl10/CARD9 | Multiple Sclerosis | [84] |

AIM: absent-in-melanoma; cGAS-STING: cyclic GMP-AMP synthase-stimulator of interferon genes; CTL: C-type lectin; NLR: nucleotide-binding and oligomerization domain-like receptor; RLR: retinoic acid inducible gene-I-like receptors; TLR: Toll-like receptor; TRIF: TIR-domain-containing adapter-inducing IFN-β.

**Table 2 Studies and trials with antagonists/inhibitors of nucleic acid sensors and their signaling mediators in various autoimmune diseases**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **No.** | **Inhibitor** | **Disease**  | **Target** | **Phase (Preclinical/Clinical-trial ID)** | **Ref.** |
| 1 | Hydroxychloroquine  | Rheumatoid arthritis and SLE | TLR7, TLR9, cGAS-STING  | NCT0380218 (Ongoing Trial) | [139] |
| 2 | SM934 | SLE | TLR7 and TLR9 | NCT03951259 (Phase II) | [125] |
| 3 | Amlexanox | T2D | TBK1 and IKKε  | NCT01975935 (Phase II) | [140] |
| 4 | TJ-M2010-6 | T1D | Myd88 | Preclinical | [129] |
| 5 | ST-2825 | SLE | IRAK1 and IRAK4 | Preclinical | [126] |
| 6 | Aspirin | AGS | cGAS | Preclinical | [141] |
| 7 | ODN-1411 | Rheumatoid Arthritis | TLR8 | Preclinical | [142] |
| 8 | INH-ODNs | SLE | TLR3 and TLR9 | Preclinical | [143] |
| 9 | X6 | Autoimmune myocarditis | cGAS | Preclinical | [144] |
| 10 | PF-06650833 | Rheumatoid Arthritis | IRAK4 | NCT02996500 (Phase II) | [127] |
| 11 | Compound II | SLE and AGS | TBK1 | Preclinical | [128] |
| 12 | Sifalimumab (MEDI-545) | SLE | IFN-α | NCT00979654(Phase II) | [145] |
| 13 | AGS-009 | SLE and Rheumatoid Arthritis | IFN-α | NCT00960362 (Phase I) | [132] |
| 14 | IMO-8400 | Plaque Psoriasis | TLR-7, 8, and 9 | NCT01899729(Phase IIa) | [122] |
| 15 | CpG-52364 | SLE | TLR-7, 8, and 9 | NCT00547014(Phase I) | [116] |

SLE: systemic lupus erythematosus; T2D: type 2 diabetes; TID: type 1 diabetes.



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