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dsRNA sensors and plasmacytoid dendritic cells in host defense and autoimmunity

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Summary

The innate immune system detects viruses through molecular sensors that trigger the production of type I interferons (IFN-I) and inflammatory cytokines. Because viruses vary tremendously in size, structure, genomic composition, and tissue tropism, multiple sensors are required to detect their presence in various cell types and tissues. In this review, we summarize current knowledge of the diversity, specificity, and signaling pathways downstream of viral sensors and ask whether two distinct sensors that recognize the same viral component are complementary, compensatory, or simply redundant. We also discuss why viral sensors are differentially distributed in distinct cell types and whether a particular cell type dominates the IFN-I response during viral infection. Finally, we review evidence suggesting that inappropriate signaling through viral sensors may induce autoimmunity. The picture emerging from these studies is that disparate viral sensors in different cell types form a dynamic and integrated molecular network that can be exploited for improving vaccination and therapeutic strategies for infectious and autoimmune diseases.

Keywords

dendritic cells; viral; systemic lupus erythematosus; autoimmunity; diabetes; Toll-like receptors/ pattern recognition receptors

The primary response to viral detection: type I interferons

Innate antiviral defense largely depends on type I interferons (IFN-I). These cytokines comprise IFNβ, multiple IFNα subtypes, as well as IFNκ and IFNω (called limitin in mouse) (1). IFN-I engage the IFNα receptor1/2 (IFNAR1/2) heterodimer on all cell types, inducing a signaling cascade that leads to the transcription of many IFN-stimulated genes (ISGs). ISG products block viral replication, establish an antiviral state in uninfected cells, and promote apoptosis of infected cells, ultimately limiting viral spreading. Key ISGs for blocking viral replication are the 2′-5′ oligoadenylate synthetases (2–5 OAS)/RNaseL system and RNA-activated protein kinase R (PKR). While the 2–5 OAS/RNaseL system induces RNA breakdown, preventing the translation of viral RNA (2, 3), PKR phosphorylates the eukaryotic translation initiation factor 2α (eIF2α), resulting in protein synthesis inhibition (4). IFN-I also enhance immune responses by inducing dendritic cell (DC) maturation, activation of monocytes and natural killer (NK) cells, as well as promoting T-cell responses and antibody production (5–7).

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IFN-I secretion is triggered by the recognition of invading viruses. Viruses very enormously in terms of size, structure, and nucleic acid composition, which can be single stranded (ss) RNA, double stranded (ds) RNA, or DNA. Moreover, during infection, virions tend to localize in distinct intracellular compartments, including endosomes, the cytosol, and nucleus. To cope with this overwhelming diversity, the innate immune system detects invading viruses through germ-line encoded pattern recognition receptors (PRRs), which recognize common molecular features of pathogens, known as pathogen-associated molecular patterns (PAMPs) (8). Originally discovered in *Drosophila* (9), Toll-like receptors (TLRs) are the first and best characterized family of PRRs implicated in the recognition of viruses (10, 11). Several other types of PRRs involved in viral recognition have been subsequently identified. The diversity of antiviral PRRs enables recognition of disparate viral PAMPs. Moreover, different PRRs are expressed in distinct cellular compartments, enabling viral detection in multiple cellular locations. Finally, antiviral PRRs utilize diverse signaling pathways to induce the synthesis of IFN-I or inflammatory cytokines, enabling flexibility of antiviral responses. Following is a detailed description of PRR sensors that induce antiviral IFN-I responses.

TLRs that sense viral nucleic acids

TLRs are transmembrane proteins that consist of a luminal domain of leucine-rich repeats (LRRs) for pathogen sensing and a cytoplasmic Toll/interleukin-1 receptor homology (TIR) domain for downstream signaling (8). TLRs involved primarily in antiviral responses include TLR2, TLR3, TLR7, TLR8, and TLR9. While TLR2 is expressed on the cell surface and detects viral hemagglutinin and other unknown viral components (12–20), TLR3, TLR7, TLR8, and TLR9 detect viral nucleic acids in endosomal compartments (11, 21, 22). Upon viral infection, these TLRs are transported from the endoplasmic reticulum (ER) to a specialized endosomal compartment through an ER-associated twelve-membrane-spanning protein, UNC93B1 (23, 24). Viral nucleic acids gain access to TLR-containing endosomes following phagocytosis of virions or virally infected apoptotic cells. Moreover, some viruses are assembled in the endosomes during viral replication.

TLR3 detects dsRNA, which constitutes not only the genome of dsRNA viruses but also intermediates produced during replication of ssRNA and DNA viruses (25). Polyriboinosinic:polyribocytidylic acid [poly(I:C)], a synthetic dsRNA that mimics viral RNA, is often used as agonist of TLR3 (25, 26). TLR3 is expressed in macrophages, B cells and dendritic cells (DCs), particularly $CD8\alpha^+$ DCs, a conventional DC (cDC) subset that very effectively cross-presents antigens to $CD8^+$ T cells (27). TLR3 is also expressed in non-immune cells such as fibroblasts, liver stellate cells, myofibroblasts, as well as some epithelial cells and endothelial cells. TLR3 signals through the TIR-domain containing adapter-inducing IFN-β protein (TRIF) (28, 29). TRIF interacts with tumor necrosis factor (TNF) receptor-associated factor 3 (TRAF3) and TRAF6 through a TRAF-binding motif (30, 31). TRAF3 activates inhibitor of nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB) kinase ε (IKKε) and TANK-binding kinase 1 (TBK1), which induce the phosphorylation and nuclear translocation of interferon regulatory factor-3 (IRF3). IRF3 activates the transcription of IFN-β. TRAF6 triggers a downstream signaling pathway that ultimately activates NF-κB and mitogen-activated protein kinases (MAPKs), resulting in the production of inflammatory cytokines, such as TNFα, interleukin-6 (IL-6), IL-12, and chemokine (C-C motif) ligand 2 (CCL2) (32).

In laboratory settings, murine TLR3 has been implicated in IFN-I responses to multiple RNA viruses. These include West Nile virus (WNV) and encephalomyocarditis virus (EMCV), a small non-enveloped (+) sense ssRNA enterovirus with tropism for the brain and heart (Fig. 1). In humans, however, TLR3 is essential for eliciting IFN-I and

proinflammatory cytokines in response to the DNA virus herpes simplex virus 1 (HSV-1). Most likely, TLR3 detects RNA intermediates that are generated during HSV-1 replication (33). Genetically inherited mutations of UNC93B1, TLR3, or TRAF3 are associated with susceptibility to neonatal HSV-1 encephalitis (34–37). TLR3-deficient mice mount defective anti-HSV-1 $CD8^+$ T-cell responses and are more susceptible to HSV-1 infection than wildtype (WT) mice (38). In addition to inducing IFN-I, TLR3 signaling results in the production of inflammatory cytokines. However, excessive TLR3-mediated inflammation in response to certain viruses has been shown to be rather detrimental to the host (39, 40).

TLR7 and TLR8 recognize ssRNA viruses (Fig. 1) and synthetic oligoribonuleotides (ORNs) (41–43), while TLR9 detects DNA viruses containing unmethylated CpG-rich DNA sequences (Fig. 1) and synthetic CpG oligodexoyribonucleotides (CpG ODNs) (44). TLR7 and TLR9 expression is chiefly restricted to immune cells, especially antigen-presenting cells (APCs), including cDCs, plasmacytoid DCs (pDCs), macrophages, and B cells. TLR8 was initially shown to sense viral ssRNA in human monocytes, and its murine homolog was thought to be non-functional (41). However, a recent study demonstrated that vaccinia viral (VACV) DNA activates murine TLR8 in pDCs, suggesting the possible involvement of TLR8 in sensing viral ssRNA in mice (45). TLR7, TLR8, and TLR9 transmit intracellular signals through the adapter protein myeloid differentiation primary response gene 88 (MyD88), which leads to production of both IFN-I and inflammatory cytokines. To induce IFN-I, MyD88 associates with Interleukin-1 receptor-associated kinase 1/4 (IRAK1/4), TRAF3/6, IKKα, and osteopontin, leading to the phosphorylation and activation of IRF7 (10, 22, 46–48). Phosphorylated IRF7 translocates into the nucleus, where it induces the transcriptional activation of IFN-I genes (49, 50). The PI3K-mTOR-p70S6K pathway positively regulates IRF7 activation (51), while interactions with 4E-BPs repress it at the translational level (52). To induce inflammatory cytokines, MyD88 associates with IRAK1/4, activating the TRAF6-TAK1 pathway that ultimately activates NF-κB and MAPK. MyD88 also recruits IRF5, which cooperates with NF-κB to activate inflammatory cytokine and chemokine gene transcription (53).

Whether engagement of TLR7/8/9 engenders IFN-I or inflammatory cytokines is dictated by the endosomal compartmentalization of the TLRs and their ligands (54, 55). Trafficking of DNA/RNA to specific compartments is regulated by physical-chemical properties, such that aggregated DNA/RNA localize in early endosomes, eliciting the production of IFN-I, while other DNA/RNA forms reach late endosomes, resulting in cytokine secretion and pDC maturation. To elicit IFN-I, TLR7 and TLR9 must translocate from the ER to a specialized lysosome-related organelle. This process requires AP-3 as well as Slc15a4, BLOC-1, and BLOC-2 (56, 57). TLR9 activation also requires proteolytic cleavage in the endosome and the presence of granulin as a cofactor (58–61). Initially it was thought that IFN-I induction via co-localization of TLR7/9 with their ligands in specialized endosomes occurred primarily in pDCs, whereas TLR7/9 signaling in non-pDCs resulted in the production of inflammatory cytokines. However, there is increasing data suggesting that cDCs are also capable of producing IFN-I in a TLR7/9 dependent manner (62, 63).

RIG-I like receptors

Retinoic acid inducible gene I (RIG-I)-like receptors (RLRs) are the cytosolic sensors for viral RNA (Fig. 1). There are currently three known family members: RIG-I, melanoma differentiation-associated gene 5 (MDA5), and laboratory of genetics and physiology-2 (LGP2) (8, 64). All three RLRs contain a conserved DExD/H box-containing RNA helicase domain that binds to RNA. MDA5 and RIG-I also contain two N-terminal caspase recruitment domains (CARD) involved in signaling (65–68). Both RIG-I and LGP2 contain an additional C-terminal repressor domain that inhibits signaling in the absence of ligands

(68). RLRs recognize RNA structures that are highly specific to viral RNAs and distinct from endogenous 5′ capped mRNA. RIG-I preferentially binds to 5′-triphosphorylated ssRNA as well as short dsRNA (69). MDA5 recognizes long dsRNA like poly(I:C) and does not require 5′-triphosphorylation (69–73). The distinct ligand preference of each these two molecules enables recognition of disparate viruses (Fig. 1). For instance, MDA5 preferentially detects picornaviruses, such as EMCV, Theiler virus, and Mengo virus (71, 72). RIG-I detects a series of ssRNA viruses, including flaviviruses and orthomyxovirus (71, 74). Both MDA5 and RIG-I detect vesicular stomatitis virus (VSV) and Sendai virus (71, 75, 76). Recent evidence indicates that RIG-I can also detect certain DNA viruses with a genome rich in AT sequences. The RNA polymerase III transcribes AT-rich DNA into uncapped 5′-triphosphorylated ssRNA that triggers RIG-I pathway (77, 78).

Ligand binding to RLRs induces conformational changes leading to association with mitochondrial-associated interferon-β promoter stimulator 1 (IPS-1) (also known as MAVS, VISA, or Cardif) through card-card domain interactions (79–82). IPS-1 then recruits TRAF3, which activates TBK1 and IKKε (83). This leads to the phosphorylation and nuclear translocation of IRF3 and IRF7 resulting in the transcription of IFN-I genes (84, 85). IPS-1 also interacts with FAS-associated death domain protein (FADD) and receptor-interacting protein-1 (RIP-1) (79), which activate caspase-8 and caspase-10, resulting in NF-κB activation and production of inflammatory cytokines (86, 87). LGP2 lacks a CARD domain and was first thought to be a negative regulator for RIG-I and MDA5 (88). Accordingly, it was shown that LGP2-deficient mice produce more IFN-I in response to poly(I:C) stimulation and VSV infection than WT mice (89). However, a recent study provided evidence that LPG2 plays a positive role in antiviral responses: both RIG-I- and MDA5-mediated IFN-I responses to viral infections were impaired in mice lacking either LGP2 or the LGP2 ATP-binding site (90). Thus, the role of LGP2 in viral recognition and antiviral signaling remains unclear.

RLRs are expressed in virtually all cell types during an antiviral response. This ubiquitous expression enables both immune and non-immune cells to detect replicating viruses, produce IFN-I, and upregulate ISGs to block viral spreading. Importantly, MDA5 and RIG-I are themselves ISGs, as they are induced by IFN-I. Thus, their antiviral function is most likely delayed in comparison with other sensors that are constitutively expressed. The upregulation and activation of MDA5 and RIG-I also lead to the production of inflammatory cytokines and chemokines that recruit immune cells to sites of infection, as well as activating endothelium. The RLR signaling pathway is also tightly regulated. RIG-I activation requires ubiquitination of its CARD domains by an E3 ubiquitin ligase TRIM25 in a caspase-12 dependent manner (91, 92). Caspase-8 cleaves RIP-1 and negatively regulates RIG-I activation (93). A microRNA, mir-146a, has also been shown to negatively regulate RIG-I-mediated IFN-I production by macrophages in response to VSV (94). Moreover, viruses can counter RIG-I and MDA5 via multiple mechanisms. Ebola virus VP35 protein serves as competitor for dsRNA and disrupts RIG-I-mediated IFN-I production (95). Sendai virus V protein selectively binds to MDA5 and inhibits dsRNA-induced activation of the IFN-I genes (96).

Other viral sensors

The presence of viral DNA in the cytosol also leads to IFN-I production through cytoplasmic DNA sensors (97, 98). DNA-dependent activator of IFN-regulatory factors (DAI) (also known as ZBP1 or DLM-1) was the first DNA-binding protein shown to respond to cytosolic DNA (99, 100). However, the role of DAI in DNA sensing is highly cell type-specific and DAI-deficient mice respond normally to DNA-based vaccines (100–102). These data suggest that DAI is not solely responsible for the recognition of foreign

DNA. IFI16 (p204 in mice), a member of PYHIN protein family, detects non-AT rich dsDNA like VACV DNA *in vitro* (103). The physiological importance of IFI16 is unclear at this point, due to the lack of any *in vivo* evidence for its impact on antiviral responses. An ER-associated protein, stimulator of interferon genes (STING), is required for the cytosolic DNA sensing pathway (104–106). HSV-1 and *L. monocytogenes* fail to induce IFN-I in DCs lacking STING and STING-deficient mice succumb to lethal HSV-1 infection due to abrogation of IFN-I responses (105, 106). Additionally, STING-deficient mice are exquisitely sensitive to VSV, which is normally detected by RIG-I, suggesting that STING is also involved in RIG-I signaling (105, 106). Given the close proximity between mitochondria and ER, it has been proposed that STING facilitates RIG-I recognition of viral RNA from ER-attached ribosomes and association with IPS-1 (97). High mobility group box (HMGB) proteins also have a role in sensing nucleic acids. Both intracellular DNA and poly(I:C)-mediated IFN-I production are impaired in cells lacking HMGB1, while only intracellular DNA mediated IFN-I production is defective in cells lacking HMGB2 (107). Moreover, a recent study suggested that a DExD/H box-containing helicase, DHX36, selectively binds to CpG-A and elicits IFN-I production in human pDCs (108). Finally, two cytosolic inflammasomes, AIM2 and NALP3, also detect viral DNA and RNA (109–118). These molecules are not involved in IFN-I production but trigger activation of caspase 1 and subsequent maturation of IL-1β (reviewed in 119–121).

Redundancy versus specialization of dsRNA sensors

TLR3 and MDA5 detect similar dsRNA structures, like poly(I:C), triggering IFN-I responses. This functional overlap may reflect molecular redundancy, so that one can substitute for the loss of the other. This redundancy may protect the organism from the deleterious effects of mutations that could otherwise abrogate detection of RNA viruses. However, there is increasing evidence that MDA5 and TLR3 only partially overlap and, in fact, may have distinct specialized functions.

A strain of EMCV, called EMCV-D, has tropism not only for the brain and heart but also replicates in the pancreas of mice causing extensive tissue damage and diabetes (122). Since EMCV replication generates dsRNA intermediates that trigger IFN-I responses through both MDA5 (71, 72) and TLR3 (123), this virus has been used to study the relationship between TLR3 and MDA5 in viral sensing *in vivo*. Both TLR3 and MDA5 are required for protection against EMCV-D infection (124). However, EMCV-D infection has very distinct pathological consequences in MDA5- and TLR3-deficient mice. MDA5-deficient mice have severe heart pathology marked by increased viral load in the heart and elevated troponin levels in the serum. In contrast, TLR3-deficient mice have only modestly augmented viral titers in the heart, suggesting that MDA5 plays a dominant role in protecting against EMCV-D induced myocarditis. In the pancreas, early IFN-I production mediated by TLR3 is essential for protecting insulin-producing β-cells from EMCV-D, as TLR3-deficient mice develop diabetes due to uncontrolled viral replication in the islets. MDA5 also functions in the pancreas, as $MDA5^{+/-}$ mice develop transient hyperglycemia. However, mice completely deficient for MDA5 succumbed to severe myocarditis and death before the development of diabetic symptoms. Finally, MDA5 and TLR3 seem to provide host anti-EMCV-D defense in different cell types. Bone marrow chimera experiments have shown that MDA5 acts predominantly in the radio-resistant ‘stromal’ compartment, whereas TLR3 acts predominantly in the radio-sensitive ‘hematopoietic’ cell compartment (124).

Coxsackievirus B (CVB), like EMCV, is a small non-enveloped (+) sense ssRNA enterovirus that has tropism for the heart and pancreas (125, 126, 127). TLR3 signaling in macrophages is required for the survival of mice following CVB infection; lack of TLR3 results in increased cardiac and liver damage during acute CVB infection (128). On the other

hand, MDA-5 is not absolutely required for the induction of IFN-I in response to CVB but is essential for the production of maximal levels of systemic IFN-α after infection (129). Loss of MDA-5 enables the virus to replicate faster, resulting in increased liver and pancreas damage and heightened mortality. Taken together, these studies show that by acting in different tissues, cell types (hematopoietic cells vs. stromal), and cellular compartments (endosomes vs. cytosol), TLR3 and MDA5 play non-redundant but complementary roles in controlling infection by ssRNA viruses.

dsRNA as adjuvant in vaccination and immunotherapy

Poly(I:C) is a synthetic dsRNA that has long been recognized as a potential adjuvant for vaccination and anti-tumor immmunotherapy (130–132). Understanding how poly(I:C) promotes innate and adaptive immune responses has been the focus of recent investigations aimed at developing adjuvants that potentiate the immunogenicity of vaccines. Poly(I:C) chiefly engages two dsRNA sensors, MDA5 and TLR3, inducing robust production of both IFN-I and inflammatory cytokines (25, 71, 72, 133). Which of the dsRNA sensors and cytokine responses are essential for the adjuvant activity of poly(I:C)? These questions were recently addressed using a vaccination strategy where TLR ligands were administered in combination with antigen targeted to DC by conjugation with an anti-DC antibody. In these settings, poly(I:C) was a superior adjuvant compared to other TLR agonists in inducing $CD4^+$ T-cell immunity (134, 135). Poly(I:C)-induced IFN-I was the predominant cytokine responsible for enhancing $CD4^+$ T-cell immunity since the adjuvant effect of poly(I:C) was abrogated in mice lacking IFNAR1/2 (136). Bone marrow chimera experiments indicated that the adjuvant function of poly(I:C) on $CD4^+$ T-cell responses relies primarily on MDA5 expression in both stromal and hematopoietic cells (Fig. 2A).

Poly(I:C) also enhances $CD8^+$ T-cell responses to antigens. It was first shown that poly(I:C) triggers the TLR3 pathway in $CD8\alpha^+$ DCs, promoting the ability of these cells to cross-present antigens to $CD8^+$ T cells (26). Subsequently, it was shown that poly(I:C) enhances $CD8^+$ T-cell responses by activating not only the TLR3-TRIF pathway but also the MDA5-IPS-1 pathway (81, 137). Specifically, it was demonstrated that TLR3 activation is essential for the induction of primary $CD8^+$ T-cell responses by enhancing antigen cross-presentation, whereas MDA5 is essential for memory $CD8^+$ T-cell responses by inducing systemic release of IFN-I that promotes the survival of primed $CD8^+$ T cells. This result is consistent with original studies showing that IFN-I provides an important survival signal to $CD8^+$ T cells during viral infections (139–141). Bone marrow chimera experiments indicated that stromal expression of MDA5 is sufficient to promote systemic IFN-I release and survival of activated $CD8^+$ T cells (137), whereas MDA5 expression in hematopoietic cells is dispensable (Fig. 2A). Altogether, these studies indicate that the adjuvant capacity of poly(I:C) in $CD8^+$ T-cell responses is mediated by both TLR3 and MDA5, although these dsRNA sensors act in different accessory cells and mediate distinct functions.

Poly(I:C) can also promote NK cell-mediated antitumor activity. Human NK cells express TLR3 and can directly respond to poly(I:C) stimulation *in vitro* (142–145). Conversely, mouse NK cells do not express TLR3 and poly(I:C)-mediated NK cell activation requires the participation of additional cell types. It was first reported that poly(I:C)-mediated NK cell activation requires myeloid DCs in a TRIF-dependent manner (146). A subsequent report demonstrated that poly(I:C) triggers both the TRIF and IPS-1 pathways in $CD8\alpha^+$ DCs, which in turn activate NK cells (147), suggesting that both TLR3 and MDA5 are important for poly(I:C)-mediated NK cell responses. A recent study showed that *in vivo* MDA5 plays a dominant role in NK cell activation by promoting systemic IFN-I. In contrast, TLR3 has a secondary impact that becomes evident only in the absence of MDA5 (133). Moreover, NK cell activation via IFN-I depends on MDA5-expressing radio-resistant

stromal cells, while TLR3$^+$ hematopoietic cells promote NK cell activation through IL-12 secretion. Therefore, poly(I:C) stimulates mouse NK cells indirectly through the induction of both IFN-I and IL-12 by distinct dsRNA sensors expressed in various cell types (Fig. 2B).

These studies indicate that the poly(I:C)-mediated adjuvant effect involves both TLR3 and MDA5, although their functions are distinct. TLR3 is important for activating antigen-presenting cells, DCs, and possibly macrophages, promoting cross-presentation of antigen to CD8$^+$ T cells and systemic release of IL-12. MDA5 is essential for release of systemic IFN-I by stromal cells, which is essential for enhancing CD4$^+$ T-cell responses, CD8$^+$ T-cell survival, and NK activation (Fig. 2). Even though bone marrow chimera experiments suggest that MDA5-expressing radio-resistant cells (i.e. stromal cells) are primarily responsible for the production of IFN-I, one cannot exclude that some radio-resistant cells within the immune system such as Langerhans cells and subsets of dermal DCs and macrophages (148, 149) may contribute to poly(I:C)-mediated IFN-I responses. Given this, the cells responsible for poly(I:C)-mediated IFN-I production have not been unequivocally identified.

TLR7/9-equipped pDCs: what is their impact on IFN-I response *in vivo*?

pDCs are a specialized DC subset that produces large quantities of IFN-I in response to bacterial and viral stimulation *in vitro* (150–155). Unlike cDCs, pDCs do not express TLR2, TLR4, or TLR3 but detect both RNA and DNA viruses through TLR7 and TLR9, respectively. Engagement of TLR7 and TLR9 with viral products leads to the production of both IFN-I and inflammatory cytokines such as IL-12, IL-6, and TNF-α as well as pDC maturation. pDCs constitutively express IRF7 and hence are refractory to viral replication. Therefore, although both are present, neither RIG-I nor MDA5 contribute significantly to viral recognition in pDCs (156, 157).

pDCs are thought to be the first line of defense against viral infection because of their immediate capacity to produce IFN-I and other factors that prime innate and adaptive immune responses. Until recently, the contribution of pDCs to antiviral responses *in vivo* was examined using antibodies to deplete this subset (158). Although these studies were highly informative, the antibodies used to eliminate pDCs also bind to and deplete other cell types. Within the past few years, genetically engineered mice have become available that more specifically lack pDCs, either constitutively or by inducible depletion (159, 160). pDC are constitutively absent in mice lacking the basic helix-loop-helix transcription factor E2-2/Tcf4, which is essential for pDC development (159). In BDCA2-DTR transgenic mice, which selectively express the diphtheria toxin receptor on pDCs, administration of diphtheria toxin results in the transient but specific depletion of pDCs (160). By infecting BDCA2-DTR mice with VSV or MCMV, it was demonstrated that pDCs provide an initial but limited source of IFN-I and can control viral burden only when relatively low amounts of virus are inoculated. However, in contrast to typical experimental settings that involve inoculation with high doses of virus, many natural infections occur from contact with low doses of virus. Therefore, under physiological conditions, pDCs may effectively control viral replication. Furthermore, early pDC-derived IFN-I may be important for initiating the establishment of an antiviral state by augmenting expression of numerous antiviral ISGs that render cells resistant to viral infections (1, 161, 162). Additionally, early pDC-derived IFN-I contributes to the induction of other viral sensors in both immune and stromal cells, resulting in further amplification of IFN-I responses (Fig. 3).

IFN-I and pDCs in autoimmune diseases

While IFN-I is critical for limiting viral replication and promoting protective immunity, excessive IFN-I production has also been linked to autoimmunity. Chronic IFN-I production has been implicated in systemic lupus erythematosus (SLE) (5, 6, 47, 163–169). Patients treated with long term IFN-I therapy for tumors, multiple sclerosis (MS), or chronic viral infections acquire SLE-like syndromes (170–173), corroborating a pathogenic role for IFN-I in the development of SLE. pDC infiltration into SLE skin lesions has also been reported (174). While pDCs are usually absent in healthy skin, under pathological circumstances including injury, viral infection, or inflammatory disorders, they can accumulate. What attracts pDCs to the skin is somewhat unclear, but chemoattractants produced by resident skin cells in aggravated areas are likely candidates (175). Prochemerin is an inactive precursor protein constitutively released in the skin by dermal endothelial cells, fibroblasts, and keratinocytes. After perturbation, prochemerin is cleaved into its active form, chemerin, by serine proteases. pDCs express the G protein-coupled receptor ChemR23 and hence migrate into lymphoid tissues and inflamed skin in response to chemerin (175, 176). CXCR3 ligands may also be important for recruiting pDCs to skin lesions (177, 178). Additional factors that could attract pDCs to injured skin are adenosine, FPRL2 ligand (F2L), C3a, and C5a (175).

In skin lesions of SLE patients, self-DNA/RNA immunocomplexes are internalized through Fc receptors and stimulate IFN-I secretion by pDCs through TLR7 and TLR9, resulting in increased serum IFN-I levels and IFN signatures in the transcriptome of peripheral blood mononuclear cells (179–184). Recently, it was reported that in SLE lesions, neutrophils are recruited to inflamed skin where they undergo cell death releasing neutrophil extracellular traps (NETs) upon exposure to SLE-derived anti-ribonucleoprotein antibodies (185, 186). These NETs contain self-DNA complexed with the antimicrobial peptide LL37 and HMGB1. LL37 converts inert self-DNA into aggregated, condensed structures that are delivered to and retained within early $TLR9^+$ endocytic compartments, where they trigger IFN-I production by pDCs (187). Additionally self-DNA also can be delivered in a complex with HMGB1 through the RAGE receptor (188). Steroids, such as glucocorticoids (GCs), are often used to treat inflammatory conditions, because they induce apoptosis of several immune cell types. However, stimulation of pDCs with TLR7/9 ligands confers resistance to GC-induced apoptosis (189, 190). Thus, corticosteroids are not effective in SLE. However, blocking the TLR9 pathway with chloroquine has been shown to prevent IFN-I production by pDCs following exposure to DNA/immunocomplexes (183). Thus, elimination of pDCs or blocking their secretion of IFN-I may be viable alternative strategies for treating SLE.

IFN-I-producing pDCs are present in psoriatic skin lesions. The recruitment of pDCs to psoriatic skin is thought to be mediated by chemerin (175, 191). In a xenograft model for psoriasis, blockade of pDC-derived IFN-I hindered the development of psoriasis, but disease progressed after reconstitution with IFNα, indicating that pDCs and IFN-I are necessary for the pathogenesis of psoriasis *in vivo* (192). Furthermore, treatment of psoriatic lesions with Aldara cream, which contains the TLR7/8 agonist imiquimod, exacerbates disease by recruiting pDCs to lesions and inducing IFN-I production (193). Within psoriatic skin lesions, pDCs internalize self-DNA complexed with LL37 and secrete IFN-I.

Although pDC accumulation in SLE and psoriatic skin lesions appears to be problematic, their recruitment to the skin can have positive consequences in other situations. Aldara cream is often used to treat skin lesions induced by human papilloma virus (HPV), molluscum contagiosum virus (MCV), and certain skin cancers. How Aldara cream induces regression of skin lesions is not well understood, although hallmarks of treatment include pDC accumulation and IFN-I production (194, 195), Two groups (196, 197) demonstrated

recently that pDCs are recruited to the skin, produce IFN-I, and promote wound healing following injury by tape stripping or chemical insult. However, such injury and subsequent pDC responses in a lupus-prone background results in the development of SLE-like lesions. Thus, whether pDC infiltration and IFN-I production in the skin is harmful or protective depends largely on the context.

IFN-I and pDCs have been implicated in autoimmune neuroinflammation and multiple sclerosis (MS); however, their roles remain controversial. Avonex, or IFNβ-1a, is used to prevent symptoms and slow the development of disease in patients with relapsing-remitting MS, suggesting that IFN-I plays a beneficial role in MS. A number of groups have explored the role of pDCs and IFN-I in a mouse model for MS, experimental autoimmune encephalomyelitis (EAE), and provide evidence that IFN-I and pDCs are protective in this model. IFN-I constrains T-helper 17 (Th17)-mediated autoimmune inflammation (198), while IFNAR deficiency in myeloid cells leads to severe disease with an enhanced effector phase and increased lethality (199). Depletion of pDCs with mPDCA-1 anitbody during the acute or relapsing phase of EAE also augments disease severity (200). In addition, mice lacking MHC class II expression on pDCs develop exacerbated EAE due to enhanced priming of encephalitogenic $CD4^+$ T-cell responses in secondary lymphoid tissues (201). In WT mice, pDCs apparently curb the autoimmune T-cell response by promoting the expansion of myelin-specific T-regulatory cells through MHC class II-dependent interactions with $CD4^+$ T cells. Alternatively, it has been reported that depletion of pDCs at the time of immunization ameliorates the clinical symptoms of EAE by reducing the numbers of myelin-specific Th17 T cells (202). Thus, the contribution of pDCs to EAE induction and progression is unclear at this time; further work in mice specifically lacking pDCs should help clarify this issue.

A role for IFN-I, pDCs, and dsRNA sensors in autoimmune diabetes

Type I diabetes (T1D) is an autoimmune disease characterized by destruction of the pancreatic β-cells. Dysregulation of the adaptive immune response has been implicated in T1D by early findings of autoantibodies against a variety of islet antigens in human patients, and animal models, particularly the non-obese diabetic (NOD) mouse, have been crucial for defining the loss of T-cell tolerance in T1D (203). More recently, innate immune defects involving activation of viral sensors and subsequent IFN-I responses have also been implicated in the pathogenesis of T1D; emphasis has been placed on RLRs as well as TLR7 and 9 in pDCs (172, 204). However, experimental results from a number of systems have proved confusing and somewhat contradictory; depending on the model system and specific pathogen used, viruses and IFN-I have been shown to be both protective and pathogenic during T1D.

A large number of studies support the general concept that detection of viral infection and perhaps excessive subsequent IFN-I responses can lead to onset of T1D. RNA virus infections have been associated with the pathogenesis of T1D. Viruses with tropism for the pancreas can induce T1D by directly destroying β-cells or by causing immune cell-mediated β-cell death (204). Enterovirus family members such as CVB have been linked to human T1D, and EMCV-D has been used to study T1D in animal models. In the BioBreeding rat model, infection with Kilham's rat virus induces T-cell-mediated diabetes (205). In mice, CVB and EMCV-D can replicate in the pancreas causing extensive tissue damage and diabetes (122, 129). T1D onset in mice infected with CVB has been attributed to bystander damage of β-cells leading to inflammation, tissue damage, and the release of sequestered islet antigen, resulting in the restimulation of resting autoreactive T cells (206). In contrast, diabetes induced by EMCV-D seems to be a consequence of direct β-cell destruction due to the cytopathic effect of viral infection and macrophage-mediated phagocytosis of apoptotic

cells rather than T-cell-mediated insulitis (207). Clearly, initiation and progression of disease vary considerably in these studies, and hypotheses for the link between viral infection with the development of T1D reflect this diversity. Perhaps the most widely known hypotheses are molecular mimicry, bystander activation, and viral persistence (127)

In addition to direct viral infection, dsRNA agonists such as poly(I:C) can stimulate T1D development in animal models (208–210). This observation suggests that dsRNA detection by MDA5 and perhaps TLR3 during viral infection may affect T1D progression in an IFN-I-dependent fashion. IFN-I production has been associated with the progression of T1D, (203, 204, 211). One report demonstrated that transgenic mice expressing IFN-I in β-cells develop diabetes and islet inflammation (212). A more recent study revealed that antibody blockade of IFNAR1 in NOD mice delayed the onset of T1D (213). Further work by this group has demonstrated that early antibody-mediated depletion of pDCs in NOD mice results in decreased incidence of T1D (214). Although these studies were done in mice, expansion of IFN-I-producing pDCs has also been observed in human patients with T1D around the time of diagnosis (215). These studies support a role for viral sensors and pDCs in promoting a pathogenic IFN-I response during T1D.

In contrast, another set of studies, more in line with the hygiene hypothesis, indicate that viral detection and IFN-I responses may be beneficial in the setting of autoimmunity because they induce T-cell tolerance. Consistent with this theory, NOD mice have delayed or complete protection from the onset of diabetes following infection with a variety of viral pathogens (216–218). A number of mechanisms have been proposed for the prevention or amelioration of autoimmunity consequent to viral infection, including enhanced T-regulatory cell activity and the upregulation of inhibitory molecules and cytokines (218–221).

IFN-I and viral sensors have also been mechanistically linked to the prevention of T1D caused by viral infection. Treatment of NOD mice with IFN-I or dsRNA can be protective and reduce the incidence of T1D depending on the time of administration (222–224). Interestingly, human genetic analyses have demonstrated that polymorphisms in the MDA5 gene are linked with resistance to T1D. Importantly, the ‘protective’ polymorphisms either reduce expression or functional dsRNA-mediated IFN-I responses of MDA5 (225–229). These salient studies have provided a potential mechanism by which viruses, through recognition by viral sensors and the production of IFN-I can contribute to the pathogenesis of T1D. As we have learned from previous studies, the combination of viruses, viral sensors, and IFN-I can have both pro-inflammatory and tolerogenic effects, and further work is needed to dissect how their interactions lead to autoimmunity.

This conundrum was recently addressed in a mouse model of viral induced diabetes (124). In this study, TLR3 was critical for protecting pancreatic islets from viral infection; TLR3 knockout animals developed severe hyperglycemia after infection with EMCV-D. Similarly, mice lacking one allele of MDA5 developed transient hyperglycemia. The unresolved hyperglycemia observed in TLR3-deficient mice was a direct result of hematopoietic cells failing to mount an early IFN-β response that protects β-cells from virus-induced damage. These data demonstrate that IFN-I responses mediated by MDA5 and TLR3 serve to limit the pathology of virus-induced diabetes when caused by direct infection of the islets (Fig. 4). The role of these sensors in the pathogenesis of autoimmune diabetes remains to be seen.

Cumulatively, these studies suggest that the beneficial or detrimental effect of sensors and IFN-I depends on the pathogenesis of diabetes and therefore viral sensors may play multiple roles in the spectrum of human T1D.

Concluding remarks and future perspectives

Clearly multiple cell types and sensors are required for protective responses to viral infection. Although most cell types are capable producing IFN-I, pDCs provide an immediate burst of IFN-I in response to viruses. However, the pDC IFN-I response is limited in both magnitude and time, and other cells play a critical role in containing most viruses (160). Both splenic and hepatic macrophages are important for IFN-I production and control of viral replication in LCMV-infected mice (230, 231). Molecularly, LCMV-mediated IFN-I production requires both TLR and RLR pathways (19, 232, 233). Restriction of VACV infection by IFN-I requires TLR2 and inflammatory monocytes (20). Furthermore, MDA5-expressing stromal cells and TLR3-expressing DCs are critical sources of IFN-I during poly(I:C)-mediated immunity and EMCV infection (72, 124, 136). Although the pDC contribution to IFN-I production is limited, it is likely that the initial burst of pDC-derived IFN-I drives the expression of RLRs, amplifying IFN-I responses. Altogether, these findings indicate that *in vivo* IFN-I is derived from diverse molecular and cellular sources that probably depend on the nature of the pathogens and their tropisms.

The diversity of viral sensors is essential to mount effective IFN-I responses against invading pathogens. Distinct sensors differ in their specificity for viral products, permitting recognition of a plethora of viruses. Viral sensors also differ in their tissue distribution enabling a given organ to effectively respond to a specific virus. For EMCV-D, MDA5 expression is essential in the heart, while both TLR3 and MDA5 are required for controlling EMCV-mediated β-cell damage in the pancreas. Furthermore, within the same organ, different sensors might be required at different time points during infection. Because MDA5 is an ISG, its expression is negligible before infection, whereas TLR3 is constitutively expressed. Therefore, MDA5-mediated responses to EMCV may require early IFN-I production induced by TLR3 signaling (66, 124). In conclusion, pathogen specificity, tissue distribution, and the timing of viral sensor expression are all essential parameters that shape IFN-I responses during viral infections. Depending on the nature of the virus and the particular tissue or cell types infected, viral sensors can have either complementary or redundant roles and may synergize or antagonize each other.

While IFN-I is critical for limiting viral replication and eliciting protective immunity, excessive IFN-I production can promote autoimmune responses. However, IFN-I can also ameliorate autoimmunity. Thus, the beneficial or detrimental effect of sensors and IFN-I depends largely on disease pathogenesis. Given this, viral sensors may play multiple roles in the spectrum of autoimmune disease. Undoubtedly, understanding the interplay among these viral sensors will ultimately help us design better vaccines and therapies for infectious and autoimmune diseases.

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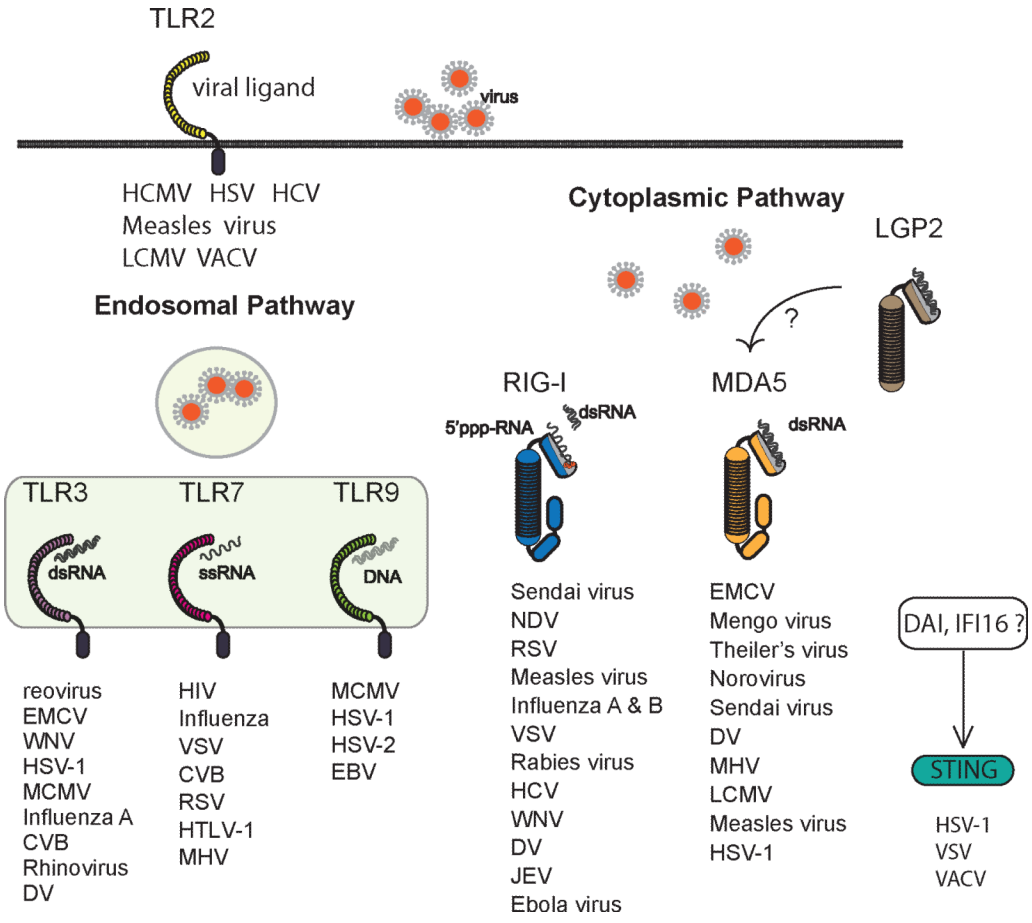

Fig. 1. Diversity and specificity of viral sensors

Multiple viral sensors detect invading viruses. Genetic loss-of-function experiments have revealed the specificity of viral sensors in numerous viral infections. TLR2 is expressed on the cell surface and detects Human cytomegalovirus (HCMV), HSV-1, Hepatitis C virus (HCV), Measles virus, LCMV, and VACV virus (12–20). TLR3, TLR7, and TLR9 are located in endosomes. TLR3 recognizes RNA and DNA viruses such as reovirus (25), EMCV (123), West Nile virus (WNV) (234, 235), HSV-1 (35), MCMV (236), Influenza A (40), CVB (128), rhinovirus (237, 238), and Dengue virus (DV) (239). TLR7 recognizes ssRNA viruses such as human immunodeficiency virus (HIV) (240), Influenza virus (41, 42), VSV (43), CVB (241) and respiratory syncytial virus (RSV) (242), human T-cell leukemia virus (HTLV-1) (257) and mouse hepatitis virus (MHV) (258). TLR9 recognizes DNA viruses such as MCMV (243), HSV-1 (244), HSV-2 (245) and Epstein-Barr virus (EBV) (246). RIG-I and MDA5 sense replicating viruses in the cytosol. RIG-I recognizes a series of ssRNA viruses including paramyxoviruses such as Sendai virus (71, 247), Newcastle disease virus (NDV) (71, 247), RSV (248) and Measles virus (249, 250); Orthomyxovirus (Influenza A and B viruses (71)); Rhabdovirus (VSV (71, 247), Rabies virus (251)); Flavivirus (HCV (74), WNV (252), DV (239), Japanese encephalitis virus (JEV) (71)); and Filovirus (Ebola virus (95)). MDA5 detects picornaviruses such as EMCV, Mengo virus, and Theiler virus (71, 72), as well as calicivurses, such as norovirus (253). MDA5 has also been shown to recognize Sendai virus (75), DV (239), mouse hepatitis virus (MHV) (254), LCMV (233), Measles virus (249) and HSV-1 (255). DNA sensors such as DAI and IFI16 recognize cytosolic DNA viruses in a STING-dependent manner (99, 100,

103-106). STING is also involved in the recognition of RNA viruses such as VSV (105, 106).

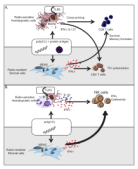

Fig. 2. Hematopoietic and stromal contributions to poly(I:C)-mediated immunity

(A). Poly(I:C) promotes $CD4^+$ and $CD8^+$ T cell immunity through the production of IFN-I and other cytokines. Poly(I:C)-mediated IFN-I responses are dependent on stromal expression of MDA5. However, adjuvant effects of poly(I:C) on $CD4^+$ T cell immunity require MDA5 expression in both hematopoietic and stromal compartments. Poly(I:C) triggers the TLR3 pathway in $CD8\alpha^+$ DCs to promote cross-presentation to $CD8^+$ T cells while signaling through MDA5 pathway in stromal cells promotes $CD8^+$ T cell survival and memory formation. (B). Poly(I:C) promotes NK cell activation through the production of IFN-I and IL-12. NK cell activation via IFN-I depends on MDA5-expressing radio-resistant stromal cells while $TLR3^+$ hematopoietic cells promote NK cell activation through IL-12 secretion. The MDA5 pathway plays a dominant role in NK cell responses to poly(I:C) while the TLR3 pathway has a secondary effect.

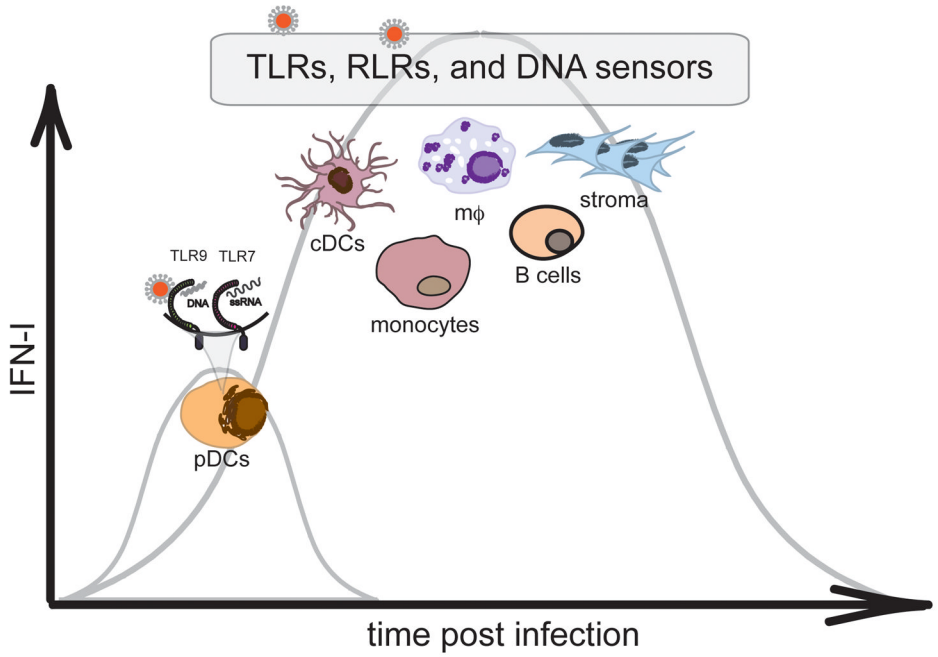

Fig. 3. Cellular sources of IFN-I during viral infections

TLR7- and TLR9-expressing pDCs detect RNA and DNA viruses and provide an initial source of IFN-I. However, pDC-mediated IFN-I production is limited and transient, indicating that the majority IFN-I required for controlling viral replication is derived from additional cellular sources such as cDCs, macrophages, monocytes, B cells, and stromal cells that utilize TLRs, RLRs, and DNA sensors for viral detection. The expression of RLRs and DNA sensors is often low but highly inducible in response of IFN-I, suggesting that initial IFN-I by pDCs may be essential for RLR- and DNA sensor-mediated responses.

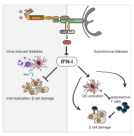

Fig. 4. MDA5 and IFN-I in virus-induced and autoimmune diabetes

Viruses such as EMCV and CVB cause diabetes in mice. Polymorphisms in MDA5, a sensor for β-cell tropic viruses such as CVB and EMCV-D, have been linked to the development of human T1D. In virus-induced diabetes, activation of the MDA5 pathway in DCs and macrophages triggers IFN-I responses, which inhibits viral replication and prevents βcell injury. On the other hand, in autoimmune diabetes, MDA5 signaling might elicit excessive IFN-I production that could induce apoptosis of β-cells and promote presentation of β-cell antigens to autoreactive T cells by islet-resident DCs (256). IFN-I is also capable of activating autoreactive T cells directly in an antigen non-specific fashion.