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Type I interferons: diversity of sources, production pathways and effects on immune responses

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Abstract

Type I interferons (IFN-I) were first described over 50 years ago as factors produced by cells that interfere with virus replication and promote an antiviral state. Innate and adaptive immune responses to viruses are also greatly influenced by IFN-I. In this article we discuss the diversity of cellular sources of IFN-I and the pathways leading to IFN-I production during viral infections. Finally, we discuss the effects of IFN-I on cells of the immune system with emphasis on dendritic cells.

Keywords

interferon; virus; dendritic cell; monocyte; macrophage; Toll-like receptor; RIG-I-like receptor

Multiplicity of cellular sources of IFN-I

Type I interferons (IFN-I, i.e. IFN- α and IFN- β) were first described over 50 years ago as cytokines that confer resistance to viral infections [1-3]. Although most cells can produce IFN-I, there is emerging evidence that cellular sources can vary during different viral infections. In the following section we discuss the diversity of IFN-I sources and their importance in antiviral immunity.

pDCs are a source of IFN-I that is limited to specific infections

pDCs are bone marrow-derived cells that secrete large amounts of IFN-I and thus are considered a primary source of IFN-I for antiviral responses. pDCs detect RNA and DNA viruses with two endosomal sensors, Toll-like receptors (TLR) 7 and TLR9, which induce secretion of IFN-I as well as proinflammatory cytokines (i.e. IL-12, IL-6 and TNF- α) through the myeloid differentiation primary response gene 88 (MyD88) signaling pathway [4-6]. Viruses reach endosomal compartments in pDCs through endocytosis or autophagy [7,8]. Because many viruses can induce pDC activation and IFN-I secretion through TLR7/9 (reviewed in [9,10]), it has been thought that pDC may be a crucial player in antiviral responses.

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However, recent evidence suggests that the capacity of pDCs to produce IFN-I and control virus infections in vivo is more restricted than anticipated. In mucosal infections, such as influenza virus infection, cells lining the airways, like epithelial cells and alveolar macrophages, provide the primary source of IFN-I, whereas pDC secrete IFN-I when the virus bypasses the local barrier and becomes systemic [11]. pDCs do provide a primary source of IFN-I in systemic infections like murine cytomegalovirus (MCMV) and vesicular stomatitis virus (VSV), but their impact appears to be limited in time and capacity [12•]. Why are pDCs restricted in their ability to control systemic infections? Our recent data suggests that splenic pDCs upregulate pro-apoptotic molecules and undergo apoptosis in a IFN-I-dependent manner during certain systemic virus infections in vivo [13•]. Sustained pDC survival during an infection might result in more efficient antiviral responses but also lead to immunopathology.

Recent studies have suggested that pDCs may contribute to antiviral responses against selective viral infections of the skin. pDC infiltrate human skin lesions during virus infections caused by Molluscum contagiosum virus (MCV) [14] and Varicella zoster virus (VZV) [15] and pDC accumulation has been associated with lesion regression [14]. What mediates pDC recruitment to infected areas and how they contribute to antiviral responses in the skin is under investigation [16]. Localization of pDCs in virus-induced skin lesions coincides with the presence of dendritic cells (DC) that show the signature of IFN-induced activation (IFN-DC), suggesting that pDCs may promote the differentiation of monocytes into activated DCs, which contribute to antiviral immunity in the skin.

Finally, pDC survival and antiviral functions may be severely compromised if they become infected with viruses. pDCs are normally refractory to viral replication because they constitutively express machinery such as interferon regulatory factor (IRF) 7 which enables them to rapidly secrete IFN-I and exist in an antiviral state [17,18]. Certain viruses such lymphocytic choriomeningitis virus (LCMV) clone 13, which establishes a chronic infection in mice, are relatively insensitive to IFN-I and can replicate in pDCs as well as classical DCs (cDC) [19-22]. There is also evidence that chronically stimulated pDCs become hypofunctional, which may contribute to the persistence of virus infections [23,24]. Thus, the impact of pDC on antiviral defense may also vary depending on the tropism of the virus for pDCs and the duration of pDC activation.

Cellular sources of IFN-I vary with the type of viral infection

Given that IFN-I production by pDCs is finite and transient during certain systemic virus infections in vivo, other cell types may critical for promoting IFN-I-mediated antiviral immunity (Figure 1). Epithelial cells in the gut and lung produce IFN-I in response to mucosal infections caused by rotavirus and influenza, respectively [25,26] while neurons are critical sources of IFN-I during brain infections caused by Theiler's virus, La Crosse virus and West Nile virus [27,28]. In systemic infection with encephalomyocarditis virus (EMCV), non-hematopoietic stromal cells have a prominent role in IFN-I production, limiting viral replication [29].

Macrophages are also important filters that produce IFN-I and contain viral spread. Microglial cells and alveolar macrophages are essential sources of IFN-I during brain or respiratory viral infections, respectively [11,30] while tissue resident macrophages in the liver control viral replication in LCMV-infected mice [31]. Marginal zone (MZM) and metallophilic macrophages in the spleen produce IFN-I and contain viral spread during systemic Herpes simplex 1 (HSV-1) [32] and LCMV [33] infections. The function of MZM as viral filters was recently corroborated in CD11c-DTR transgenic mice. These mice have been used for several years to address the impact of DCs on immune responses; however,

treatment of these mice with diphtheria toxin also eliminates MZM and other macrophage subsets [34]. Using CD11c-DTR transgenic mice, it has been shown that macrophages block the spreading of EMCV [29]. Lymph node subcapsular sinus macrophages, which are similar to MZM, produce IFN-I following footpad infection with VSV and prevent viral spread to the central nervous system [35,36••]. CD169-DTR transgenic mice have been described and will be useful for assessing the impact of CD169⁺ subcapsular sinus macrophages and MZM during viral infections [37]. Myeloid cells providing a source of IFN-I also include inflammatory monocytes and DCs. While inflammatory monocytes are necessary for the restriction of systemic Vaccinia virus (VACV) replication [38••], splenic DCs produce IFN-I in response to systemic infections with adenoviruses [39] and MCMV [40].

IFN-I production during bacterial infections

Bacterial infections can also trigger the secretion of IFN-I. Splenic macrophages [41], tumor necrosis factor (TNF) alpha- and inducible nitric oxide synthase-producing DCs (Tip-DC) [42] and a subset of B cells [43] are major sources of IFN-I during *L. monocytogenes* infection. Splenic DCs secrete IFN-I in response to group B streptococcus [44••] while both macrophages and cDCs produce IFN-I following *S. pyogenes* infection [45]. Epithelial cells can also produce IFN-I in response to bacterial pathogens such as *L. pneumophila*, *P. aeruginosa* and *S. aureus* [46-48]. In contrast to viral infections, IFN-I production during bacterial infections appears to be deleterious, promoting pathogenesis [48-52]. The mechanisms behind this are incompletely understood, however, it has been shown that IFN-I inhibits inflammasome activation [53••] and IL-12 production [54], which aid in the clearance of bacterial infections.

Molecular sensors for IFN-I production

The multiplicity of cellular sources of IFN-I is paralleled by a broad spectrum of molecules that sense viruses in different cell types and trigger IFN-I secretion (Figure 2). Some of these sensors, like the Toll-like receptors (TLR), are expressed by cells such as pDCs, macrophages, DCs as well as some stromal cells. Other sensors are expressed in virtually all tissues, either constitutively or after IFN-I-mediated induction. In this section we discuss the specificity and distribution of these sensors.

Toll-like receptors

In pDCs, IFN-I is produced via the TLR7/9-MyD88-interferon regulatory factor (IRF) 7 pathway. MyD88 associates with Interleukin-1 receptor-associated kinase 1/4 (IRAK1/4), TNF-receptor-associated factor (TRAF) 3, inhibitor of nuclear factor κ -light-chain-enhancer of activated B cells (NF- κ B) kinase α (IKK α) and osteopontin leading to the phosphorylation/nuclear translocation of IRF7 and transcription of IFN-I genes [6,55-58••]. The PI(3)K-mTOR-p70S6K pathway positively regulates IRF7 [59••] while eukaryotic initiation factor 4E-binding proteins repress it at the translation level [60••].

Production of inflammatory cytokines in pDCs requires association of MyD88 with IRAK1/4, which triggers the TRAF6-transforming growth factor β -activated kinase (TAK1) pathway, leading to activation of NF- κ B and mitogen-activated protein kinase (MAPK). MyD88 also recruits IRF5, which induces inflammatory cytokine/chemokine production in concert with NF- κ B [61]. pDC production of IFN-I or inflammatory cytokine following TLR7/9 engagement depends on the type of endosomal compartment where TLRs meet their ligands [62,63].

IFN-I secretion occurs when TLR7/9 are translocated from the endoplasmic reticulum (ER) to a specialized lysosome-related organelle. This process requires UNC93B [64,65], adaptor protein 3 (AP-3) as well as Slc15a4, BLOC-1, and BLOC-2 [66•,67•]. TLR9 activation also requires proteolytic cleavage and cofactors in the endosome [68-73] such that DNA can efficiently bind to TLR9. TLR8 also signals through the MyD88 pathway and senses viral ssRNA in human monocytes [74]. The murine homolog was thought to be nonfunctional, however, it was recently shown that VACV DNA activates pDCs via TLR8 [75].

TLR3 has a prominent role in virus recognition and IFN-I production in cDCs, macrophages and stromal cells [55,76,77]. TLR3 detects viral dsRNA and the synthetic analog polyinosinic:polycytidylic acid [poly(I:C)], which gain access to the endosomal compartment by phagocytosis or endocytosis [78-80]. TLR3 signals through the Toll/IL-1 receptor (TIR) domain-containing adaptor-inducing IFN- β (TRIF) pathway, which results in the phosphorylation and nuclear translocation of IRF3 and the transcription and secretion of IFN- β [81,82]. TLR3-TRIF signaling also activates NF- κ B and the transcription of inflammatory cytokine genes. Association of TRAF3 with TRIF or MyD88 results in different modes of TRAF3 ubiquitination (degradation or activating) that regulate inflammatory cytokine and IFN-I production [83•]. TLR3 has been implicated in the recognition of many RNA viruses (reviewed in [9,10]). However, in human, TLR3 has proven essential for the recognition of a DNA virus, herpes simplex virus 1 (HSV-1), in the brain most likely though the generation of RNA intermediates that occur during viral replication [84-89•].

TLR2 may also contribute to virus recognition and IFN-I production in DCs and inflammatory monocytes. TLR2 is located on the cell surface and senses viral hemagglutinin as well as other unknown viral components [38•,90-98]. Monocytes produce IFN-I in a TLR2-dependent manner during VACV infection and are essential for viral clearance [38•]. However, in an earlier study, it was shown that TLR2 was important for cytokine responses to VACV but not IFN-I production [97]. Thus, the roles of TLR2 and/or monocytes in promoting antiviral immunity await further clarification.

RIG-I-like receptors

The retinoic acid inducible gene-I-like (RIG-I-like) receptors (RLRs): RIG-I, melanoma differentiation-associated gene 5 (MDA5) and laboratory of genetics and physiology-2 (LGP2) detect RNA intermediates that accumulate in the cytosol during viral replication [55,77,99-102]. In contrast to the selective expression of TLRs in certain cell types, RLR expression is induced in most cells by IFN-I. Ligand binding to RLRs induces conformational changes allowing interaction with the adapter molecule IFN- β -promoter stimulator 1 (IPS-1, also known as MAVS, VISA or Cardif) [103-106]. IPS-1 is localized on the mitochondria and recruits TRAF3, which activates TANK-binding kinase 1 (TBK1) and IKK ϵ , leading to the phosphorylation and nuclear translocation of IRF3 and IRF7 and production of both IFN- β and IFN- α [107-109]. Additionally, IPS-1 associates with FAS-associated death domain protein (FADD) and receptor-interacting protein-1 (RIP-1), which activate caspase-8 and caspase-10, resulting in NF- κ B activation and production of inflammatory cytokines [103,110,111]. IPS-1 is also located on peroxisomes and facilitates rapid antiviral responses through IRF1 [112•].

RLRs recognize RNA structures that are highly specific to viral RNA and distinct from endogenous 5'-capped mRNA [113-126•]. RIG-I preferentially binds to 5'-triphosphorylated ssRNA as well as short dsRNA while MDA5 recognizes long dsRNA like poly(I:C) and does not require 5'-triphosphorylation. The distinct ligand preferences of MDA5 and RIG-I permit recognition of disparate viruses (reviewed in [9,10]). Recent

studies have shown that RIG-I also recognizes DNA viruses by detecting RNA intermediates generated through the RNA polymerase III-mediated transcription of dsDNA [127•,128•].

Laboratory of genetics and physiology-2 (LGP2) is an RLR that detects dsRNA [129-131]. LGP2 does not contain any signaling domains and was initially thought to negatively regulate MDA5 and RIG-I [131]. Accordingly, LGP2-deficient mice have more robust IFN-I responses following poly(I:C) stimulation and VSV infection compared to WT mice [130]. However, recent data has demonstrated that LGP2 may positively influence antiviral responses, as RLR-mediated IFN-I responses were impaired in mice lacking LGP2 or the LGP2 ATP-binding site [129].

The RLR signaling pathway is tightly controlled. RIG-I activation is regulated by Lys63-linked polyubiquitination and E3 ubiquitin ligases such as RNF125, TRIM25 and Riplet [132-134]. Caspase-12 positively regulates E3 ubiquitin ligase TRIM25-mediated ubiquitination of RIG-I [135] while caspase-8 cleavage of RIP-1 negatively regulates RIG-I activation [136]. Small ubiquitin-like modifier-1 (SUMO-1) may also impact RIG-I- and MDA5-mediated IFN-I responses [137,138]. NLRX1 localizes to the mitochondrial outer membrane and interacts with IPS-1 to inhibit IFN-I responses [139,140]. Mir-146a, a microRNA, was found to negatively regulate RIG-I-mediated IFN-I production in macrophages [141]. Moreover, viruses have evolved mechanisms to counter RIG-I and MDA5 signaling. Ebola virus VP35 protein binds to dsRNA and blocks RLR-mediated IFN-I production [142,143] while paramyxovirus V proteins bind to MDA5, but not RIG-I, and inhibit dsRNA-induced activation of IFN-I genes [144,145].

Other cytoplasmic virus sensors

The presence of viral DNA in the cytosol also leads to IFN-I production through cytoplasmic sensors [146]. DNA sensors, like RLRs, seem to be broadly distributed and mediate IFN-I production in most cell types. 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 [147,148]. DAI-deficient mice respond normally to DNA-based vaccines [149,150], suggesting redundancy in detection of cytosolic viral DNA. IFI16 (p204 in mice), a member of the PYHIN protein family, detects non-AT-rich dsDNA like VACV DNA in vitro [151•]; however, due to the lack of in vivo evidence for its impact on antiviral responses, the physiological importance of IFI16 is unknown.

Stimulator of interferon genes (STING) is an ER-associated protein required for the cytosolic DNA-sensing pathway [152-154•]. Given the close proximity between mitochondria and ER, it has been proposed that STING assists RIG-I recognition of viral RNA from ER-attached ribosomes and association with IPS-1 [146]. High mobility group box (HMGB) proteins also have a role in sensing nucleic acids. Both intracellular DNA and poly(I:C)-mediated IFN-I responses are defective in cells lacking HMGB1, while only intracellular DNA-mediated IFN-I production is impaired in HMGB2-deficient cells [155]. In pDCs, DNA-containing immune complexes elicit TLR9-mediated IFN-I production in an HMGB1-RAGE-dependent manner [156]. LRRFIP1, a cytosolic nucleic acid sensor, modulates IFN-I production via the β -catenin pathway in macrophages exposed to VSV or *L. monocytogenes* [157•].

Recently, DExD/H box-containing helicases, DHX1, DDX21 and DDX36, were found to form a viral sensor with TRIF that recognizes cytosolic dsRNA in cDCs [158•]. DDX36 and DDX9 selectively bind to synthetic oligonucleotides that mimic microbial DNA (CpGA and CpGB), promoting either IFN-I or inflammatory cytokine secretion in human pDCs, respectively [159•]. DDX41 is another sensor that depends on STING to sense intracellular

DNA in cDCs [160••]. Finally, two inflammasomes, AIM2 and NLRP3, detect cytosolic viral nucleic acids [161-170] triggering the activation of caspase-1 and maturation of IL-1 β rather than IFN-I production (reviewed in [171-173]). In conclusion, over the past few years many novel molecules have been described in addition to TLRs and RLRs that participate in viral recognition, IFN-I responses and immunity. Future studies will reveal whether these sensors have prominent roles in innate and adaptive immune responses in vivo and if they can be exploited for therapeutic purposes.

The effects of IFN-I: cell resistance and immune responses

IFN-I limit viral spreading by inducing apoptosis of virus-infected cells and inducing an antiviral state in uninfected cells through the induction of interferon stimulated genes (ISG). ISGs have been reviewed elsewhere in this issue of *Current Opinion in Virology* and will not be discussed in this article. More recently, it has been appreciated that IFN-I has immunoregulatory roles, stimulating both innate and adaptive immunity [174]. In this section we review the impact of IFN-I on immune responses.

The impact of IFN-I on immune responses

While it has been known for many years that IFN-I promote resistance to viral infections, the impact of IFN-I on immune cell functions is becoming increasingly appreciated (Figure 3). IFN-I together with IL-12 augment NK cell and CD8⁺ T cell cytolytic activity and IFN- γ production in vitro and in vivo [175], promote T helper 1 (T_H1) polarization of CD4⁺ T cells, as well as long-term T cell survival and memory [176-179]. IFN-I together with IL-6 induce the differentiation of B cells into immunoglobulin secreting plasma cells [180,181]. Thus, mice unable to respond to IFN-I, such as IFNAR^{-/-} mice, often have profound defects in their antiviral immune responses. CD8⁺ T cell and NK cell responses that are essential for the resolution of LCMV and MCMV infections, respectively, are impaired in IFNAR^{-/-} mice [178,182]. Moreover, the production of neutralizing antibodies that are critical for the clearance of VSV is also weakened in IFNAR^{-/-} mice [183,184].

IFN-I have multiple and complex effects on DCs (Figure 4). By preventing viral infection of DCs, IFN-I allow DCs to acquire viral antigens and the appropriate maturation signals from the infection site. Moreover, IFN-I enhance the antigen presenting machinery of DCs [185-187] and their migratory capacity [188], facilitating priming of naïve T cells [189]. IFN-I also promote the differentiation of monocytes to DCs [190]. Several studies have revealed that DC turnover is strongly influenced by IFN-I in vivo. IFN-I regulate cDC and pDC numbers in vivo by inducing the downregulation of anti-apoptotic molecules, upregulation of pro-apoptotic molecules and caspase activation [13•,191-193•]. Furthermore, IFN-I induce the proliferation and differentiation of dormant hematopoietic stem cells (HSC) [194], which may replace activated or dying DCs in the periphery during virus infections. A tightly regulated turnover of cDCs and pDCs during an IFN-I response may prevent excessive immune responses, immunopathology and perhaps autoimmunity.

On the other hand, chronic IFN-I production may impair immune responses and promote disease progression. Prolonged exposure of HSC to IFN-I impairs their functions [194], such that the turnover of cells might be delayed or severely compromised. During Human immunodeficiency virus 1 (HIV-1) infection, chronic IFN-I production has been associated with the upregulation of markers of exhaustion on CD8⁺ T cells and progressive CD4⁺ T cell depletion through apoptotic mechanisms [195,196]. Thus, while IFN-I enhance innate and adaptive immune defense against viruses, the duration of their secretion need to be tightly controlled.

Concluding Remarks

For several years, pDCs were presumed to be critical for antiviral responses because of their propensity to rapidly produce IFN-I in vitro after exposure to viruses. However, recent evidence suggests that pDCs have a limited capacity to control viral burden and are a very early and transient source of IFN-I during certain systemic virus infections in vivo [12•]. Given the restricted ability of pDCs to control such viral infections, a variety of cell types, and viral sensors seem necessary for effective IFN-I-mediated antiviral responses. Clearly, distinct sensors differ in their specificity for viruses, viral components and mechanism of action. Furthermore, the expression of sensors may differ in cellular and tissue distribution, such that sensors required for responses to a given virus in one anatomical location may vary in another. The kinetics of sensor expression might also vary with cell type, virus and site of infection. Emerging studies should yield a better understanding of how cellular sources of IFN-I and viral sensors complement, synergize or antagonize each other during antiviral immune responses. New viral sensors inducing IFN-I production are constantly being identified. Future work will shed light on how these newly described sensors influence viral replication in vivo and roles they may play in innate and adaptive immune responses.

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Highlights

- A variety of cell types produce IFN-I during virus infections.
- Cells use multiple molecular pathways leading to IFN-I secretion.
- IFN-I impact the immune system, particularly DC.

Figure 1. Cellular sources of IFN-I during virus infections

The cells involved in the production of IFN-I depend on the route of infection and tissue tropism of the virus. During skin and mucosal infections, epithelial cells, fibroblasts, tissue resident macrophages and DCs secrete IFN-I and restrict viral replication. In infected organs, IFN-I is produced by parenchymal cells, fibroblasts, tissue resident macrophages and DCs. In draining lymph nodes, subcapsular sinus macrophages have a major role in the secretion of IFN-I and restriction of viral spread. During systemic virus infections, marginal zone macrophages, pDCs, monocytes and non-hematopoietic stromal cells contribute to IFN-I production and viral containment.

Figure 2. Molecular sensors involved in virus recognition and IFN-I production

Toll-like receptors (TLR), RIG-I-like receptors (RIG-I, MDA5, LGP2) and newly identified cytoplasmic nucleic acid sensors detect microbial products and initiate IFN-I secretion. TLR2 is expressed by cDCs, monocytes and macrophages and senses viral ligands such as hemagglutinin. TLR7/8 detects ssRNA and are expressed by pDCs, cDCs, monocytes, macrophages and B cells. TLR9 is expressed by pDCs, cDCs (in mouse, not human), macrophages and B cells and recognizes dsDNA. TLR3 detects dsRNA and is expressed mainly in cDCs, macrophages, B cells and stromal cells. RLRs are induced by IFN-I and sense distinct forms of RNA. LGP2 lacks signaling domains and may regulate MDA5 and RIG-I. Unlike TLRs, RLRs have a more broad cellular and tissue distribution. Cytoplasmic nucleic acid sensors such as DDX1, DDX21, DDX36, DDX9, DDX36 and DDX41 have been recently identified and appear to be more restricted in their expression patterns (i.e. cDC or pDC).

Figure 3. Effects of IFN-I on cells during virus infections

IFN-I promote the death of virus-infected cells through the induction of pro-apoptotic molecules involved in the extrinsic (TRAIL/DR4/DR5 or Fas/FasL) and intrinsic (i.e. p53, Bim, Bid, Bax, Noxa, Puma) apoptosis pathways. In addition, IFN-I act on uninfected cells by inducing hundreds of interferon-stimulated genes (ISGs) that restrict viral replication and confer an antiviral state. The maturation, expansion and effector functions of NK cells, T and B cells, DCs and macrophages are also profoundly influenced by IFN-I. mDC, mature DC.

Figure 4. Effects of IFN-I on dendritic cell subsets

IFN-I promote the migration, maturation and antigen (Ag) presenting capabilities of DCs. IFN-I also induces the differentiation of monocytes into a specialized subset of DC called interferon-induced DC (IFN-DC). Recent evidence suggests that IFN-I regulates DC turnover. Both splenic cDCs and pDCs upregulate caspases and molecules involved in the intrinsic apoptosis pathway following exposure to IFN-I. Furthermore, dormant hematopoietic stem cells (HSC) are activated by IFN-I to proliferate and differentiate which may replace activated or dying DCs during antiviral responses. The regulated turnover of cDCs and pDCs during IFN-I-mediated responses may be a mechanism to prevent excessive immune stimulation and immunopathology. iDC, immature DC; mDC, mature DC.