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The role of type I interferons in intestinal infection, homeostasis, and inflammation

Hyeseon Cho and **Brian L. Kelsall**

Mucosal Immunobiology Section, Laboratory of Molecular Immunology, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA

Summary

Type I interferons are a widely expressed family of effector cytokines that promote innate antiviral and antibacterial immunity. Paradoxically, they can also suppress immune responses by driving production of anti-inflammatory cytokines, and dysregulation of these cytokines can contribute to host-mediated immunopathology and disease progression. Recent studies describe their anti-inflammatory role in intestinal inflammation and the locus containing IFNAR, a heterodimeric receptor for the type I interferons has been identified as a susceptibility region for human inflammatory bowel disease in a genome-wide association study. This review focuses on the role of type I IFNs in the gut in health and disease and their emerging role as immune modulator. Clear understanding of type I IFN-mediated immune responses may provide revenue for fine-tuning existing IFN treatment for infection and intestinal inflammation.

Keywords

type I interferons; enteric microbial infection; intestinal inflammation

Introduction

Interferons (IFNs) are potent immune-modulatory cytokines that are readily induced in response to a variety of viral and bacterial infections and shape anti-microbial innate immune responses. They are classified into 3 distinct types based on their structure and utilization of specific receptors; type I (IFN-I), II (IFN-II), and III (IFN-III). IFN-I consists of 13 subtypes of IFNα and a single IFNβ in addition to IFN κ, ω, ε, δ, and τ. All IFN-I members share a common heterodimeric IFNα/β receptor that is composed of IFNAR1 and IFNAR2 (1, 2). IFN-II is represented by a single member, IFNγ, that binds a single IFNγ receptor with two chains, IFNGR1 and IFNGR2 (3). IFN-III is comprised of 3 members, IFN-λ1, IFN-λ2, and IFN-λ3 (also called IL-28A, IL-28B, and IL-29, respectively) that are closely related to IL-10 family cytokines (4). The IFN-III members signal through a unique heterodimer consisting of IFNλP1 (also known as IL-28RA) and IL-10R2 (5, 6). IFN-I and the IFNα/β receptor as well as the IFNγ receptor are widely expressed in contrast to the

Correspondence to: Brian Kelsall, Laboratory of Molecular Immunology, National Institute of Allergy and Infectious Diseases, Bldg. 10, Room 11N104, 10 Center Dr. MSC 1886, Bethesda, MD 20892, Tel.: +1 301 496 8490, Fax: +1 301 480 6768, bkelsall@niaid.nih.gov.

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restricted expression patterns of IFNγ, IFN-III, and the IFNλ receptor. IFNγ is predominantly produced by T and NK cells and IFN-III by leukocytes and epithelial cells (1, 3, 7). IFNλ receptors are primarily expressed by epithelial cells, suggesting a role of IFN-III in the protection of epithelial tissue against viral and bacterial infections (8).

All 3 types of the IFN receptors belong to class II cytokine receptors upon ligation, these receptors trigger Janus kinase (JAK)-signal transducer and activator of transcription (STAT) signaling axis. The IFNα/β receptor activates Tyk2 and Jak1 resulting in STAT1-STAT2 dimer formation and their subsequent translocation to the nucleus (Fig. 1). The dimeric STATs in the nucleus recruit additional transcriptional factor, IFN regulatory factor 9 (IRF9), forming a trimeric complex called IFN-stimulated gene factor 3 (ISGF3). ISGF3 then binds to interferon-stimulated response elements (ISREs), inducing hundreds of IFN-stimulated genes (ISGs). Depending on the cell type, IFNα/β receptor-mediated activation of Tyk2 and Jak1 can promote homodimer formation of other STATs such as STAT1 and STAT3 dimers that bind to IFNγ-activated site enhancer elements and STAT3-biding elements, respectively. It can also result in STAT4 activation, leading to IFNγ production during viral infection (9). In addition, IFN-I can activate mitogen-activated protein kinases (MAPKs) and phosphatidylinositol-3 kinase (PI3K) signaling pathways that contribute to antiviral effects. The IFN-II receptor via Jak1 and Jak2 can phosphorylate STAT1 and STAT3 homodimers, which is shown to generate pro- and anti-inflammatory responses, respectively. IFN-III receptor triggers signaling pathways similar to those of IFN-I receptor (1, 7, 10).

Levels of constitutive IFN-I in all tissues including the intestine are generally very low (11). However, they can have major effects on homeostatic balance in many tissues and cells (reviewed in (12)). In particular, constitutive IFN-I signaling drives the expression of baseline levels of STAT proteins including STAT1, STAT2, and STAT6, but not STAT4. Therefore, in mice (or cells) lacking IFNAR or treated with anti-IFN-I antibodies, STAT4 signaling may be favored due to lower levels of STAT 1 and STAT 2 expression. This can alter the balance of JAK-STAT signaling downstream of a variety of signaling receptors. This imbalance can interfere with phagocytic potential of macrophages (MPs) that is normally augmented by LPS/TLR4 signaling-driven IFN-I production, and enhance the differentiation of Th1 and natural killer (NK) cells and increase their production of IFNγ, which is subsequently inhibited by IFNγ-induced STAT1 activation.

In addition to their well-known robust antiviral activities, IFN-I plays a crucial role in host resistance to some bacterial infection. However, they can also be detrimental to the host and even impair bacterial clearance (13, 14). Moreover, IFN-I can regulate inflammasome activation and the production of other inflammatory cytokines (15–18). There are recent excellent reviews on IFN-I signaling and their more general role in immune modulation and infection (10, 14, 16, 19–21). In this review, we focus on the role of IFN-I in enteric viral and bacterial infections, as well as homeostasis and inflammation of the gut and highlight their emerging role as immune modulators.

Enteric viral infections

In response to viral infection, virtually all cells produce IFN-I that can limit viral replication and spread. However, cellular sources for IFN-I production vary depending on the type of viral infection, which subsequently impacts the outcome of antiviral defense (22). Cells employ multiple mechanisms to sense different invading viruses to ensure immediate anti-viral defense. Viral pathogen-associated molecular patterns (PAMPs) are recognized by host pattern recognition receptors (PPRs) such as Toll-like receptors (TLRs), retinoic acid-inducible gene (RIG)-I-like receptors (RLRs), and nucleotide-binding oligomerization domain-containing (NOD)-like receptors (NLRs) in a virus and cell type-specific manner (22–26). Engagement of these diverse sensors converges on activation of downstream IRF3 and nuclear factor κ light-chain enhancer of activated B cells (NFκB) pathways to induce IFN-I and other inflammatory cytokines (Fig. 2). IFN-I in an autocrine as well as paracrine fashion triggers the second wave of transcription of several hundred ISGs, inducing and activating antiviral factors such as the RNA-activated protein kinase (PKR), the 2′-5′-oligoadenylate synthetase (2′-5′ OAS), and myxovirus resistance (Mx) proteins (Fig. 1). These factors are involved in preventing virus replication, inhibiting viral function, and priming neighboring cells to enter a refractory antiviral state. IFN-I also modulates cell viability (27). IFN-I-mediated apoptosis is an important host defense mechanism against viral infection to limit amplification of viral progeny, although it can facilitate viral egress and augment host pathogenesis. In addition, IFN-I bridges innate and adaptive immune responses by enhancing maturation of dendritic cells (DCs), and promoting expansion and differentiation of virus-specific T cells and antibody-producing B cells.

IFN-I plays an important role during enteric viral infections such as rotavirus, reovirus, and norovirus. Both rotavirus and reovirus are non-enveloped double-stranded (ds) RNA viruses that replicate and assemble in the cytoplasm of host cells. They belong to the family *Reoviridae* that is characterized by virions containing a genome of 10–12 dsRNA segments and encased in multiple concentric capsids. Rotavirus is the leading cause of severe dehydrating diarrheal illness in infants and young children (28). Although the illness caused by rotavirus infection is self-limiting and the virus is typically cleared within a week, it can be life threatening in immunocompromised individuals and young children in developing countries. Reoviruses generally cause mild or asymptomatic human respiratory or intestinal infection, but more severe viral encephalitis due to novel reovirus strains has recently been described (29). Reovirus infections in mice have provided good models for studying the pathogenesis of intestinal viral infection, in addition to viral myelitis and myocarditis (30, 31). Noroviruses are non-enveloped, single-stranded RNA viruses and belong to the Caliciviridae family (32). Norovirus is also one of the leading pathogens causing acute self-limiting gastroenteritis, although asymptomatic infections frequently occur (32, 33). Severe illness and fatal disease can occur following norovirus infection in immune compromised individuals (34, 35).

Rotavirus

Rotavirus is a highly infectious virus that infects nearly early every child in the world by the age of five. Immunity develops with each infection, so subsequent infections are less severe

and adults are rarely affected. Rotavirus replicates in epithelial cells of the small intestine, is excreted in the stool, and is transmitted via the fecal oral route. Infection is short-lived (<10 days), results in diarrhea, vomiting, and low-grade fever, and is most severe in young children in developing countries (36). The induction of rotavirus-specific intestinal IgA correlates with clearance of infection and protective immunity (reviewed in 37); however, $CD8^+$ T-cell responses appear to have a role in initial clearance. Despite causing local intestinal symptoms, rotavirus infection in humans and animals results in systemic spread, and viremia can be readily detected following initial infection (37, 38) that is cleared by systemic immune mechanisms (39). There are five species of this virus, referred to as A, B, C, D, and E. *Rotavirus A*, the most common species, causes more than 90% of infections in humans, and multiple serotypes have been identified that are responsible for disease in humans that form the basis for vaccine development (36).

The innate immune mechanisms against early infection are not yet clear, although likely involve interaction of the intestinal immune system with endogenous commensal microbiota (40, 41). Rotavirus can induce the production of IFN-I in epithelial cells, myeloid cells, and plasmacytoid DCs, but also has the ability to suppress IFN-I production and signaling during productive infection (reviewed in 42). Rotavirus infects primarily the intestinal epithelial cells (IECs) of small intestine in human and animals, although it also causes systemic infection (38, 43). These IECs likely provide the first line of defense via IFN signaling (44–46). RIG-I and melanoma differentiation-associated protein 5 (MDA5) are the cytoplasmic PRRs that recognize rotavirus dsRNA and together with interferon-β promoter stimulator-1 (IPS-1)/mitochondrial antiviral signaling protein (MAVS) and IRF3are important for IFN-I production in epithelial cells and bone-marrow-derived DCs (45, 47, 48, 49). Activation of the antiviral response by rotavirus is also dependent on an adapter protein in epithelial cells.

While cytosolic recognition pathways are involved in rotavirus-induced IFN-I production, endosomal TLR recognition of rotavirus has also been described. Recognition of viral structural proteins (Vp4 and/or Vp7) together with viral dsRNA by an endosomal receptor, most likely TLR7 and/or TLR9 was important for the production of IFNα from human plasmacytoid DCs (pDCs) to which only a minor subset is permissive to rotavirus replication (50). The role of endosomal TLR3 during rotavirus infection however remains unclear. One study reported that TLR3, TRIF, and MyD88 had no role in IFN-I production following rotavirus infection, and had no effect on rotavirus infection in adult mice (45). Another, however, demonstrated that TLR3 expression by small intestinal epithelial cells (IECs) increased with age. Adult but not neonatal $TLR3^{-/-}$ or $TRIF^{-/-}$ mice had enhanced rotavirus replication in association with lower levels of IFN-β and IFN-λ and production IFN-response genes by small intestinal IECs (51), suggesting an age-dependent protection against rotavirus mediated by TLR3-driving IFN pathways in epithelial cells. Moreover, studies indicate that TLR3 recognition of rotavirus dsRNA induces epithelial cell apoptosis that may contribute to host defense against rotavirus infection (52–54). Thus, it appears that different cell types can recognize rotavirus using unique PRRs for IFN-I production both *in vitro* and *in vivo*; however, further studies need to be performed to define these pathways more carefully in the more relevant suckling mouse model of infection.

The importance of IFN-I and IFN-III in host defense against rotavirus, however, is also not yet clear. IFN-I pre-treatment can limit viral replication and ameliorate diarrhea during rotavirus infection in weanling pigs and newborn calves (55, 56). In mice, while both IFNβ and IFNλ2/3 are produced in epithelial cells from sucking mice following homologous virulent rotavirus infection, adult and sucking mice lacking IFNAR generally showed no alteration in diarrhea and relatively normal viral clearance, suggesting a minor role of IFN-I in controlling rotavirus infection (46, 57). Instead, suckling mice deficient in functional IFNλ receptor exhibited markedly increased virus replication and pathological changes in epithelial cells compared to IFNAR-deficient mice, which had minimal, but present, increases in viral load and pathological changes compared to WT mice. Moreover, systemic IFNλ administration to sucking mice could suppress viral replication in intestinal epithelium at both a high and low inoculum of rotavirus, while systemic IFN-I had modest effects only at low virus doses (46). Finally, it was shown that the effects of IFN-I and IFN-III are compartmentalized with the major effect of IFN-I on cells in the small intestinal LP, and IFN-III on epithelial cells (46) as measured by expression of Mx1, an IFN-induced protein. These studies demonstrate that IFN-III has a more substantial role than IFN-I in protecting epithelial cells from rotavirus infection in young mice challenged with a virulent homologous virus, although both have protective effects. Furthermore, they suggest possibly 2 levels of IFN mediated control, one at the level of the epithelial cell mediated by IFN-III and another at the level of the LP mediated by IFN-I to protect against local or systemic dissemination.

In fact, a role for IFN-I in systemic dissemination has been suggested by studies of heterologous rotavirus strains. Heterologous simian or bovine rotaviruses replicate poorly and are less virulent in mice compared to murine strains that show efficient enteric replication (58). Suckling mice lacking the IFNAR exhibited a moderate increase in intestinal and extra-intestinal viral loads and systemic but not local disease after oral inoculation of a heterologous rhesus rotavirus (RRV) strain compared to WT mice. Furthermore, systemic dissemination and infection with RRV also appears to be controlled by a synergistic effect of IFN-I and IFN-II as infection of IFNAR/IFNGR double knockout (KO) or STAT1 KO mice (defective in type I, II, and III signaling) with RRV led to dramatic increase in systemic viral replication and severe disease such as lethal hepatitis and pancreatitis. In contrast, when infected with a murine strain EC, wildtype (WT) and the double KO mice showed similar disease manifestation (59). Similar results were found for murine strain EW and simian strain SA11 (59). The reasons for this variation in sensitivity of homologous and homologous strains to IFN-I and IFN-II are not clear, but homologous and heterologous rotavirus strains appear to differ in sensitivity to IFNs, which likely correlates with their ability to subvert innate immunity (60).

In addition to the direct role of IFNs in innate protection against rotavirus infection, IFN-I derived from mucosal plasmacytoid dendritic cells (pDCs) following oral rotavirus infection enhances B cell humoral immunity that promotes viral clearance and protection against reinfection (61). pDCs are innate immune cells in humans and mice that are actually DC precursors first identified in human peripheral blood to produce massive amounts of IFN-I upon exposure to viral products (62, 63). IFN-I, in turn can induce pDCs to differentiate into mature antigen-presenting DCs associated with increased expression of cytokines (such as

IFN-I, TNF-α and IL-6) and costimulatory molecules (64, 65), which can present and cross-present antigens to $CD4^+$ and $CD8^+$ T cells. Furthermore, pDCs can activate B cells and induce antibody class switching and plasma cell differentiation through effects of type I IFN both directly on B cells, and indirectly on T cells and DCs (66–69). During rotavirus infection, mice lacking functional pDCs at the time of infection exhibit defective virus-specific intestinal IgA antibody responses and increased viral shedding, suggesting the significance of pDC-dependent antibody production via IFN-I in viral clearance (61). Taken together, the significance of IFN-I contribution during rotavirus infection seems to vary depending on viral strain, host susceptibility, and synergy with other types of IFNs, and can directly affect viral replication, as well as induction of specific antibody responses that affects viral shedding and clearance.

Reovirus

Similar to rotavirus, reovirus induces IFN-I responses via RIG-I and MDA5 recognition and subsequent activation of IRF3 and NFκB (70–73). LGP2, the third member of the RLR family, further contributes to RIG-I and MDA5-mediated recognition of reovirus through its ATPase domain (74). Interaction of the adapter protein IPS-1 with either RIG-I or MDA5 is also essential for IRF3 activation and ISG expression in response to reovirus and a wide range of other RNA viruses (73). Zhang *et al*. (75) have demonstrated that a cytosolic complex containing RNA helicases DDX1-DDX21-DHX36 can sense viral dsRNA following reovirus or influenza A virus infection and activate IFN-I responses in myeloid DCs via TIR-domain-containing adapter-inducing interferon-β (TRIF). In addition, RNA helicase DHX33 was recently reported to be critical for sensing reovirus in myeloid DCs (76). Very little has been reported regarding the role of TLRs in reovirus recognition except one study demonstrating that TLR3 deficiency neither alters viral pathogenesis nor impairs adaptive antiviral responses after type 3 Dearing reovirus infection in the CNS (77).

Mammalian reoviruses belong to three major serotypes: type 1 Lang (T1L), type 2 Jones (T2J), and type 3 Dearing (T3D) that differ in pathogenic properties such as systemic spread and end organ tropism. The T1L strain has been used to study intestinal mucosal immune responses. T1L, following oral administration, generates infectious subvirion particles that enter Peyer's patches (PPs) via M cells in the small intestine and subsequently infects the follicle-associated epithelium (FAE) overlying PPs (78, 79). The virus can spread to systemic sites including spleen and mesenteric lymph nodes (MLNs) later in infection (80). T1L is usually cleared within 2 weeks after the oral infection in adult mice by mucosal IgA response and both local and systemic Th1 and cytotoxic T cell responses (81–83). It appears that $CD11c^+$ phagocytes in the PP subepithelial dome (SED) can capture and process T1L antigen from infected apoptotic epithelial cells for presentation to T cells (30). Both structural and non-structural viral proteins indicative of productive viral replication were found in the epithelial cells, whereas $CD11c^+$ phagocytes contained only the structural protein, implying antigen uptake by these cells in the absence of infection. Furthermore, these cells contained the markers of apoptotic epithelial cells such as fragmented DNA, activated caspase-3, and the epithelial cell protein cytokeratin and were able to activate T1L-primed CD4 T cells *in vitro* (30). Johansson *et al*. (84) have demonstrated that IFN-I signaling is required for limiting systemic T1L dissemination and subsequent viral clearance

following oral infection. Targeted deletion of IFN-I receptor in mice resulted in fatal systemic infection with extensive cell loss in lymphoid tissues and necrosis of the intestinal mucosa. PP $CD11c^+$ cells, likely including pDCs, were the major source of IFN-I. The authors also showed that TLRs acting via MyD88 were not required for detection or clearance of T1L (84). Together, these studies have established a primary role for PP $CD11c^+$ phagocytes in IFN-I-dependent innate immunity against T1L reovirus and have enhanced understanding of mucosal immunity to viral infections.

Norovirus

Noroviruses are in general classified into five genogroups and three of the genogroups (GI, GII, and GIV) infect humans (85). The genogroups can be further divided into different genetic clusters or genotypes and variants of the GII.4 genotype have been culpable for the majority of norovirus outbreaks in the last decade or so (86). Human histo-blood group antigens that likely recognize the protruding domain of the norovirus capsid protein have been regarded as receptors for norovirus infection, determining host range and susceptibility (87–89). In addition, it has been reported that the innate viral sensor MDA5 senses murine norovirus-1 (MNV-1), an isolate from research mouse facilities and is required to control the viral infection in mice. In contrast, TLR3-deficeint mice exhibit only a slight increase in MNV-1 viral titers, suggesting a minor role of this TLR (90). However, simvastatin, a common cholesterol-lowering drug induces significantly earlier onset and longer duration of fecal viral shedding often with higher fecal viral titers in young piglets following oral inoculation of human norovirus GII.4 strain. The enhanced infectivity has been suggested to result from simvastatin-mediated impairment in TLR3-mediated induction of IFN-I possibly due to down-regulation of TLR3 (91). Downstream of these viral sensors, IRF-3 and IRF-7 play a critical role in IFN-I-mediated control of murine norovirus replication (92). IRF-5 has also been implicated in restricting norovirus replication. Triple KO mice lacking IRF-3, IRF-5, and IRF-7 succumb to murine norovirus infection at rates greater than double KO mice deficient in IRF-3 and IRF-7, establishing IRF-3, IRF-5, and IRF-7 as the critical factors for mediating the IFN-I and ISG response (93).

Both onset and resolution of norovirus-induced disease symptoms are rapid, suggesting that the innate immune components are critical for restricting viral pathogenesis. Discovery of a murine norovirus, MNV-1 has facilitated the examination of norovirus pathogenesis in mice (94). Using the MNV-1 strain, Wobus *et al*. (95) have demonstrated MP and DC tropism of these viruses and the significance of IFN-I signaling in controlling viral replication *in vitro*. MPs derived from the bone marrow (BM) of IFN-I receptor- and STAT-1-deficient mice show higher viral titers following MNV-1 infection (95). Both IFN-I and IFN-II can inhibit the translation of MNV-1 nonstructural proteins (96). Pretreating or treating gnotobiotic piglets with IFNα results in reduction or curtailment of viral shedding following the oral infection of human norovirus (91). Moreover, IFNAR KO mice orally infected with MNV-1 succumb to the viral infection very rapidly, indicating that the IFN-I signaling is essential for controlling the norovirus infection *in vivo* (93). Furthermore, reinforcing the significance of IFN signaling, STAT1 is required for the resistance to norovirus infection and dissemination in mice (94, 97).

Recent studies have also pointed out a complex relationship between murine norovirus infection, autophagy, and Paneth cell function that affects susceptibility to intestinal inflammation been identified (98). Mice with a hypomorphic form of ATG16L1 ($ATG16L1^{HM}$), or specific deletion of ATG5 or ATG7 in the intestinal epithelium, all essential autophagy proteins, results in abnormal Paneth cell granule formation and function (99, 100). In the presence of a chronic form of norovirus infection, MNV CR6, but not in uninfected mice, $ATG16L1^{HM}$ mice develop several enhanced pathological inflammation resembling Crohn's disease (101). The precise mechanisms by which MNV C6 was able to affect disease development in this model are actively being investigated, however, a role for IFN-I is suggested by a study showing that MNV infection resulted IFN-I production that potentiated Nod1 and Nod2 activity leading to an exaggerated and harmful response to *E. coli* (102).

Viral evasion of IFN responses

Like many pathogenic viruses, rotavirus and reovirus have evolved specific mechanisms to subvert the host's IFN antiviral responses (42, 103). The mechanisms involve evading recognition by cellular PRRs or targeting IRFs and NFκB pathway to blunt IFN induction. Rotavirus non-structural protein-1 (NSP1) can mask rotavirus mRNAs to avoid PRR recognition or target RIG-I to down-regulate its PRR activity (104). NSP1 also degrades the IRF transcription factors (IRF3, IRF5, IRF7, and IRF9) and the ubiquitin ligase complex protein β-TrCP to block the NFκB pathway in a strain-dependent manner (105–108). Rotavirus may also circumvent PRR recognition is by sequestering viral RNAs in cytoplasmic inclusion bodies called viroplasms (109). In addition, rotavirus can interfere with IFN-inducible effector functions by inhibiting the nuclear translocation of STAT1 and STAT2 (110) directly inhibiting STAT1 phosphorylation (111), or cleaving IFN-inducible 2′-5′-oligoadenylate, thus antagonizing antiviral RNase L activation (112).

Reovirus also displays virus strain-specific mechanisms to antagonize the IFN response. T1L strain but not T3D represses IFN function in a viral core protein μ2-dependent fashion. The μ2 protein encoded by T1L M1 gene is responsible for the abnormal IRF9 accumulation in the nucleus inhibiting IFN-β-induced gene expression (113). Reovirus σ3 is a virion outer shell protein which binds dsRNA and compete with dsRNA-dependent PKR, thus blocking PKR-mediated down-regulation of translation (114). Interestingly, reovirus is reported to exploit oncogenic Ras to suppress RIG-I signaling and subsequently impair IFN-I production promoting virus spread (115). This ability of reovirus to selectively replicate in and destroys cancer cells with an activated Ras signaling pathway provides revenue for human colon and ovarian cancer treatment (116).

Norovirus has also evolved an evasion tactic against the IFN response. Virulence factor 1 produced from a novel alternative open reading frame, ORF4 of the murine norovirus subgenomic RNA is reported to possess anti-innate immune activity, antagonizing the IFNβ induction and delaying apoptosis (117).

Intestinal bacterial infections

Although IFN-I is typically considered an antiviral cytokine, it is also induced by most bacterial pathogens. Similar to viral sensing, bacterial PAMPs are recognized by cell surface as well as endosomal TLRs and cytosolic PRRs in a bacterium specific manner (13) (Fig. 2). Pathogenic bacteria use specialized secretion systems to inject bacterial products and bacterial ligands can be released to the cytosol following degradation of the phagosome that become targets of cytosolic RLRs or trigger cytosolic DNA-sensing machineries such as the Pol-III-dependent pathway and ZBP-1 (118–120) (Fig. 2). IFN induction in response to cytosolic DNA in some cases requires a signaling adaptor, stimulator of interferon genes (STING) (121–123). In addition, other bacterial products such as muramyl dipeptide can induce IFN-I via NOD-RIP2-NFκB signaling axis (124, 125). These diverse bacterial PAMP sensing mechanisms all lead to activation of IRFs and NFκB, resulting in IFN-I production.

Listeria and *Salmonella* are two common bacterial enteropathogens that induce IFN-I (126–128). *Listeria monocytogenes*, a gram-positive intracellular bacterium is responsible for severe food-borne gastroenteritis and can cause life-threatening meningitis as well as bacteremia in immunocompromised individuals and septic abortion in pregnant women (129). *Salmonella enterica serovar Typhimurium (S. Typhimurium)* is an intracellular gram-negative pathogen of mice that is a model for *Salmonella* infections in humans which are a leading cause of acute food-borne gastroenteritis worldwide. *Salmonella* infection can also lead to systemic disease in animals and human (130). Both positive and negative effects of IFN-I in resistance to *Listeria* and *Salmonella* infections have been reported.

Listeria

L. monocytogenes invades enterocytes via interaction between bacterial surface protein internalin A and host epithelial cell surface protein E-cadherin (131, 132). These bacteria can cross the epithelial barrier by transcytosis and reside in the underlying mucosa or spread to other organs such as spleen and liver via the blood stream (129, 133, 134). When internalized by phagocytes, they escape the phagosome to cytoplasm utilizing a virulence factor called listeriolysin (LLO) and induce innate immune responses including the production of IFN-I. *Listeria* mutants that lack LLO and are thus trapped in the phagosome fail to induce IFN-I (125, 126). Cytoplasmic RLR, RIG-I and MDA5, and the signaling adaptor STING recognize DNA/RNA released from live *Listeria* to trigger IFN-I production via the TBK1-IRF3 signaling axis (135–137). Another major *Listeria* PAMP, second messenger cyclic diadenosine monophosphate (c-di-AMP) is recognized by the DDX41 helicase and also induces IFN-I via STING, TBK1 and IRF3 (138, 139). Deficiency in TLR2, TLR4, TLR9, MyD88, TRIF, or TRAM has virtually no effect on IFN-I induction by *Listeria* in BM-derived macrophages (BMDMs), (140–142). However, TLR2 and TRIF are critical for *Listeria*-mediated IFN-β induction in peritoneal MPs, suggesting that different MP populations use distinct PRRs to sense *Listeria* infection for IFN-I production (143).

Due to relative resistance of mice to *Listeria* that results from a single amino acid alteration in mouse E-cadherin, intravenous or intraperitoneal inoculation has been used to initiate infection in mouse instead of the natural oral route of infection (129). Numerous studies implicate the adverse effects of IFN-I signaling to the host after systemic delivery of *L.*

monocytogenes and several mechanisms appear to be involved in IFN-I-mediated enhanced susceptibility. Mice deficient in IFN-I receptor were more resistant to L. monocytogenes infection that correlated with less *Listeria*-induced apoptosis of spleen cells and (144–146). Furthermore, intravenous co-administration of a sublethal dose of L. monocytogenes and poly (I:C), resulted in drastically increased bacterial burden and enhanced mortality, which was prevented in IFN-I receptor KO mice (146). *Listeria*-induced IFN-I directly caused apoptosis of lymphocytes in infected tissues, and it was argued that their uptake by myeloid cells induced the production of IL-10, which is known to be immunoregulatory in this infection (147, 148). In addition, *Listeria*-induced IFN-I inhibited IFNγ signaling on phagocytes by blocking expression of IFNGR receptor, which decreased IFNγ-induced resistance to infection (149). IFN-I was also shown to inhibit IL-17A secretion by γδ T cells during Listeria infection which suppressed neutrophil infiltration and increased bacterial burdens (150), consistent with the known ability of IL-17A to induce antimicrobial peptides and increase neutrophil number and microbicidal activity (151). *Listeria* c-di-AMP-mediated inhibition of protective cell-mediated immunity upon secondary challenge was largely dependent on IFN-I signaling via STING and IRF3 reflecting the effects of suppressive effects of innate IFN-I on the induction of adaptive immunity (152).

To study mucosal immune response in mice following the natural oral route of infection, a mouse-adapted mutant *L. monocytogenes* strain with increased affinity to murine E-cadherin has been generated (153). In distinct contrast to systemic infection models, *Ifnar1*-deficient mice infected with the murinized *L. monocytogenes* by the intragastric route exhibited higher bacterial numbers in liver and spleen and increased lethality. However, very little difference in invasion of the gut mucosa, PPs, and mesenteric lymph nodes was noted between wildtype and *Ifnar1*-deficient mice (134). While this study suggests that the route of infection may be a critical determinant in affecting *Listeria* pathogenesis, it is not readily apparent why systemic infection would be affected differently by IFN-I following oral versus systemic infection. Further studies using the adapted bacteria are necessary to clarify this issue.

Additional studies, however, have also demonstrated a potential protective role for IFN-I signaling in *Listeria* infection. *Listeria* can activate NLRP3, NLRC4, and AIM3 inflammasomes in phagocytes, resulting in activation of caspase-1, production of IL-1β and IL-18, and induction of caspase-1-dependent cell death. This process contributes to host defense against *Listeria* by driving increased IFN-γ production, enhanced phagocyte killing, and eliminating cellular reservoirs bacterial replication (reviewed in 15). A role for IFN-I in this protection is suggested by studies showing that IFN-I was required for robust secretion of IL-1β and IL-18 in response to *L. monocytogenes* in BMDM cultures (154). Consistent with these findings, IFN-I can enhance AIM2 protein levels and inflammasome activity, which is essential for *Listeria* induced pyroptosis and full expression of IL-1β and IL-18 (155, 156). Finally, IFN-I contributed together with MyD88-induced signaling to prolongd CCL2 production by macrophages in response to *Listeria*, which was essential for the bone marrow emigration and recruitment of $Ly6C^{hi}$ monocytes to sites of *Listeria* infection (157). Therefore, IFN-I has potentially positive and negative influences on the outcome of *Listeria monocytogenes* infection.

Salmonella

Orally ingested virulent *Salmonella* rapidly enters $CD11c^+$ phagocytic macrophage-like cells in the PP and LP macrophages via dendrites that reach into the intestinal lumen, or alternatively by intraepithelial $CD103^+$ LP DCs (158, 159). *Salmonella* can survive and replicate within macrophages where it induces rapid cell death, a virulence strategy thought to enhance bacterial dissemination. It can also activate $TLR5^+$ $CD11c^+$ cells in LP that produce proinflamamtory cytokines and promote bacterial translocation from the intestinal tract to mesenteric lymph nodes through unclear mechanisms (160).

Similar to *Listeria*, *Salmonella* is recognized by multiple TLRs, including TLR2, TLR4, TLR5, and TLR9, as well as by both NLRP3 and NLRC4 inflammasomes, leading to caspase-1 activation and pyroptosis (161–164). Mice lacking TLR2 and TLR4 and mice deficient in both NLRs show markedly increased susceptibility to *Salmonella* infection, while mice deficient in TLR2, TLR4, and TLR9 are protected (161, 162). The latter is thought to be due to a requirement for MyD88-dependent acidification of *Salmonella* containing vacuole that is required for the assembly of *Salmonella* type III secretion system-2 (T3SS-2) and subsequent export of an essential effector protein called SseB (161). Moreover, mice deficient in caspase-1, IL-1β, or IL-18 all show worse *Salmonella* infection than wildtype mice, reinforcing the beneficial role of inflammasome activation in host defense (165–167).

IFN-I may have several effects on immunity to *Salmonella*. Concomitant induction of IFN-I and IL-18 by *S. typhimurium* leads to IL-12-independent STAT4 activation and production of IFNγ that confers protection against *S. typhimurium* infection, suggesting a protective role of IFN-I (168). In contrast, Broz *et al*. (166) demonstrated that *Salmonella*-induced IFNβ via TLR4/TRIF can activate non-canonical caspase-11, promoting detrimental MP death. Mice lacking both caspase-1 and caspase-11 are less susceptible to *Salmonella* infection than caspase-1-deficient mice. This is likely attributed to delayed bacterial egress as a result of dampened MP death in the double KO mice. In the absence of caspase-1, caspase-11-dependent cell death appears to be exploited by *Salmonella* via IFN-I signaling (166). Similarly, IFN-I signaling-driven MP necroptosis via RIP3 (a critical regulator of necroptosis) has been reported as an immune evasion mechanism by *Salmonella*. IFNAR1 KO mice show improved survival following *S. Typhimurium* infection due to the resistance of IFNAR1-deficient MPs to *Salmonella*-induced necroptosis. MPs deficient in RIP3 are also less susceptible to *S. Typhimurium* infection (169). Therefore, in contrast to *Listeria*, IFN-I driven pyroptosis in Salmonella may have negative consequences for the host by inducing the spread rather than the containment of bacteria.

Immune suppression in chronic infections

There is increasing evidence that IFN-I mediates immune suppression and blocking IFN-I-mediated signaling can mitigate immune dysfunction and disease progression. IFN-I can drive anti-inflammatory IL-10, IL-27, and IL-1R antagonist production in MPs and monocytes and negatively regulate IL-12 production in DCs during certain viral infections (170–173). IFN-I is also involved in TAM receptor tyrosine kinases-mediated inhibition of inflammation via induction of anti-inflammatory suppressors of cytokine signaling 1

(SOCS1) and SOCS3 (174). Furthermore, IFN-I can suppress Th17 cell differentiation via IFNAR-Osteopontin axis in DCs and limit Th17-mediated autoimmune inflammation by inducing IL-27 production (175–177). Lastly, IFN-I is reported to mediate apoptotic cell death of pDC during viral infection, implying a negative feedback mechanism to control the source of IFN-I and other cytokines (178). This loss of pDCs likely contributes to immune suppression.

Deleterious immunosuppressive effects of IFN-I signaling during persistent lymphocytic choriomeningitis virus (LCMV) infection have been recently described (179, 180). Although IFN-I signaling is required for the clearance of acute LCMV infection, it is detrimental during chronic phase. Prolonged activation of IFN-I signaling as a result of persistent LCMV infection leads to increased IL-10 production and programmed cell death ligand-1 (PD-L1) expression by lymphocytes, lymphoid disorganization, and reduced viral clearance. Blockade of IFN-I signaling diminishes the immunosuppression and augments IFN-γ production, a critical factor controlling chronic LCMV infection (181, 182). This facilitates viral clearance that requires $CD4^+$ T cells. Consistently, IFN-I is reported to attenuate IFN-γ production via STAT1 activation (9). Furthermore, antagonistic effects of IFN-I on IFN-γ-mediated immune response have been observed (183, 184) (discussed below). In contrast, IFN-I can enhance IFN-γ production via STAT4 phosphorylation during viral infection, demonstrating a context-dependent immunoregulatory role of IFN-I (9). Richter *et al*. (185) suggests that IL-10 produced by $CD4^+$ T cells and MPs early during LCMV infection is a critical factor in determining whether the LCMV will be cleared or persist, reinforcing the critical role of IL-10 in viral chronicity.

The stage-specific opposing effects of IFN-I have been described during HIV-1 infection (186, 187). IFN-I has a potential antiviral effect during acute HIV-1 infection, while it contributes to T-cell depletion, dysregulation of cellular immunity, and disease progression in chronic phase. IFN-I appears to function as a central regulator of the immunosuppressive program during chronic viral infection and may serve as a reasonable drug target. It has been reported that the blockade of IFN-I receptor results in dampened caspase-1 activation in DCs and MPs infected with LCMV, suggesting a positive role of IFN-I in inflammasome activation (180). However, it remains unclear whether IFN-I-mediated activation of inflammasome during LCMV infection is beneficial or detrimental to the host, as discussed earlier in *Listeria* and *Salmonella* infection. In contrast, a previous study has described that IFN-I can inhibit inflammasome activation in BMDM, again suggesting context-dependent duality of IFN-I signaling (18). Taken together, it is evident that IFN-I has both protective and detrimental roles likely depending on the stage of infection (acute versus chronic) and/or cellular context such as expression of particular sensors and downstream signaling molecules necessary for responses to a given virus.

IFN-I can have a predominantly immunosuppressive role during mycobacterial infection. IFN-I signaling suppresses IL-1α/β production, a critical cytokine for controlling *Mycobacterium tuberculosis* in mice likely via IL-10 (17). In the absence of MAP3K tumor progression locus 2 (TPL-2) that negatively regulates IFN-I production, IFN-I-mediated IL-10 production exacerbates *M. tuberculosis* infection (188). Moreover, augmented production of IFN-I by co-infecting mice with influenza and *M. tuberculosis* enhances

mycobacterial growth and reduces survival of infected mice (189). Furthermore, IFN-I-induced IL-10 during *M. leprae* infection inhibits IFNγ-mediated antimicrobial activity (190). In addition, Berry *et al*. (191) have described a strong correlation of IFN-I transcript signatures with the tuberculosis disease severity, demonstrating the role of IFN-I signaling in the pathogenesis of tuberculosis. Lastly, expression of suppressive PD-L1 is also reported to increase in whole blood of active tuberculosis patients (192). Whether the IFN-I-mediated immune suppression is a common feature to limit host pathogenesis during chronic infection and how acute antimicrobial IFN-I responses are reprogrammed to drive IL-10 and PD-L1 expression during chronic phase represent an important area for future research.

Immune modulation in the intestine

The intestinal tracts harbor the largest and most diverse commensal microbes that facilitate host metabolism, limit pathogens by competing for environmental niche, and educate immune cells. Numerous studies have suggested a protective role of commensal microbiota in maintaining intestine homeostasis and have associated changes in bacterial communities with susceptibility to infectious or inflammatory diseases in the gastrointestinal tract and metabolic diseases such as diabetes and obesity (193, 194). In particular, the loss of appropriate regulation of immune responses to commensal bacteria results in abnormal intestinal inflammation that is the hallmark of inflammatory bowel disease (IBD).

IBD is a group of inflammatory conditions of the small and large intestine that includes two major conditions, Crohn's disease (CD) and ulcerative colitis (UC). The incidence of CD and UC has been steadily increasing in last few decades, but the causes are not yet clear. This is likely due to fact that the pathogenesis of IBD is complex and multifactorial with an influence of a broad range of genetic, immunological, and environmental factors including the composition of the intestinal microbiota. Despite this complexity, constitutive and induced production of IFN-I is emerging as a central factor in maintaining gut homeostasis and preventing intestinal inflammation.

Murine studies

Constitutive IFN-I production

The most convincing data indicating a role for IFN-1 in regulation of intestinal homeostasis and inflammation have come from studies in mice. IFN-I is constitutively produced in the intestine, as they are in many tissues (11, 195–198). In conventionally housed mice, small intestine and colon LP $CD11c^+$ mononuclear cells (that includes both MPs and DCs) constitutively produce IFN-β. (11, 198). In the colon, $CD11c^+$ cells also express mRNA for IFNα5 and IFNα9, but interestingly little to no mRNA for IFNα4, an early IFN-I often produced together with IFNβ. In addition, these cells express mRNA for IFN-I/ISGS3-induced genes including 2′-5′ OAS, OAS-like family members, IRF5, IRF7, CXCL10, RNase L, and PKR as well as IL-15α for which expression is dependent on IFNAR signaling (199, 200, Kelsall, unpublished observations), further indicating constitutive IFN-I production and signaling in the colon LP.

Whether constitutive IFN-I production in the intestine is driven by commensal microbial signals is not completely clear; however, several studies imply that this is the case. Specific pathogen-free (SPF) and germ-free (GF) mice exposed to normal SPF flora at birth exhibit enhanced expression of genes involved in IFN-I signaling in the colon indicating the ability of endogenous bacteria to drive IFN-I signaling (201). In addition, TLR3 has been proposed as a sensor in the small intestine that recognizes commensal dsRNA, contributing to anti-inflammatory and protective immune responses via IFN-β production. In contrast to pathogenic bacteria, a variety of lactic acid-producing commensal bacteria (LAB) from the terminal ileum have high levels of dsRNA. LAB as well as ileal contents that contain high levels of dsRNA, induce IFNβ production by BM-derived DCs *in vitro* that is dependent on endosomal recognition by TLR3 and TLR9. Furthermore, ileal LP cells from TLR3-deficient mice lack IFNβ mRNA, implying a role for TLR3 in the constitutive production of IFNβ (202). Finally, constitutive transcription of IFN-β in the colon mononuclear phagocytes was dependent on TRIF, an adapter molecule downstream of TLR3, TLR4, and dsRNA-sensing intracellular helicases (75), but not on MyD88 (11). In mononuclear phagocytes from the colon, constitutive IFN-I is also at least partially dependent on TLR4 signaling (Kelsall, unpublished observations) suggesting that bacterial recognition by this PRR may also be important in the colon.

IFN-I in models of acute colitis

The role of IFN-I, TLR9 activation, and administered immunostimulatory bacterial CpG-containing DNA sequences (immunostimulatory sequences, ISS-ODN) was initially explored in acute models of colitis. In these experiments, administration of dextran sodium sulfate (DSS) or haptens [di- or trinitrobenzene sulfonic acid (DNBS, TNBS)] to mice results in acute inflammation in both WT and lymphopenic $RAG^{-/-}$ and SCID mice. Several studies showed that administration of ISS-ODN or commensal bacterial DNA protected mice from DSS and hapten–induced colitis, as well as inhibited proinflammatory cytokine production from inflamed ulcerative colitis tissue *ex vivo* (203–205). The protective effect of CpG ODNs appeared to be independent of IL-10, as they additionally suppressed spontaneous colitis in $IL\text{-}10^{-/-}$ mice. IFN-I was implicated in the suppression as TLR9-induced anti-inflammatory effects of ISS-ODN, as well as probiotic were nullified by IFN-I neutralizing antibody, while IFNβ injection mimicked the effect of ISS-ODN treatment. Furthermore, mice lacking IFN-I receptor were less susceptible to the protective effects of ISS-ODN in DSS-induced colitis (206). IFN-I produced by TLR9-activated $CD11c^{+}$ cells were in part responsible for the protection against DSS colitis induced by ISS-ODN, which occurred in a T-cell-independent manner. IFN-I was argued to reduce trafficking of neutrophils and monocytes to the inflamed colon and to control the inflammatory products of tissue MPs (207). In addition, mice lacking IFNAR or pretreated with IFNβ-expressing *Lactobacillus* strain, which resulted in IFNAR downregulation (likely due to internalization and degradation of the receptor) were more susceptible to DSS colitis in the absence of exogenous ISS administration (206, 208), supporting a role for constitutive IFN-I in the maintenance of intestinal immune homeostasis following intestinal epithelial cell injury by DSS.

Additional studies have also supported the ability of IFN-I to have regulatory effects when stimulated *in vivo* in the DSS model of colitis. Treatment with granulocyte macrophage colony-stimulating factor (GM-CSF/CSF2), imiquimod (TLR7 agonist), and poly (I:C) (TLR3 agonist) ameliorated acute DSS-induced colitis (209–211). GM-CSF treatment led to pDC expansion and IFN-I production, resulting in reduced pro-inflammatory TNF-α and IL-1β expression, and better disease outcome in DSS-induced colitis. Oral imiquimod treatment stimulated IFN-I (IFNα2) production in the colon, resulted in improved DSS-colitis severity, and drove the production of antimicrobial peptides by $CD11c^+$ cells and epithelial cell lines. Poly (I:C) treatment ameliorated DSS colitis when given systemically, which was dependent on TLR3, but acted independently of IL-10. While not showing a direct role for IFN-I, the latter two studies are consistent with a role for IFN-I in the protective effects, since these ligands are potent inducers of IFN-I production *in vivo*. Finally, lactic acid bacteria when administered orally protected mice from experimental DSS-induced colitis in a manner that is dependent on TLR3 and IFNβ (202). Together, these results indicated the ability of IFN-I to suppress acute colitis, when driven by exogenous signals and that this suppression could occur through T-cell-independent effects.

IFN-I in models of chronic colitis

The role of IFN-I induced by exogenous signals has also been explored in T-cell adoptive transfer models of chronic colitis that more accurately reflect the chronic inflammation of human CD. CpG-ISS-ODN treatment was shown to limit the colitogenic potential of $CD4^+$ $CD62L^+$ T cells via effects on $CD11c^+$ DCs. $CD4^+$ $CD62L^+$ T cells that were co-cultured with either splenocytes or BM-derived $CD11c^+$ DCs and treated with CpG-ISS-ODN *in vitro* and then transferred into SCID mice induced less severe colitis compared to $CD4^+$ $CD62L^+$ T cells co-cultured in the absence of ISS-ODN, while CpG-ISS-ODN-treated $CD4^+$ $CD62L^+$ T cells cultured alone had similar colitogenic potential (212). Furthermore, $CD4^+CD62L^+$ cells from WT but not $IFNAR^{-/-}$ mice treated systemically with CpG-ISS-ODN or with recombinant IFNβ were less colitogenic. Furthermore, the decreased colitogenic potential of co-cultured $CD4^+$ $CD62L^+$ T cells correlated with enhanced production of IL-10 by T cells DC co-cultures. These data were consistent with CpG-ISS-ODN having an indirect effect on T cell differentiation through IFN-I effects on $CD11c^+$ cells. However, whether this effect resulted in functionally suppressive T cells rather than simply less colitogenic T cells was not demonstrated (212).

Similarly, $CD4^+CD62L^+$ T cells from CpG-ISS-ODN treated WT but not $IL\text{-}10^{-/-}$ GF mice expressed higher levels of FoxP3, PD1 and CD25, and induced less colitis than cells from untreated GF mice, which was partially inhibited by anti-IFN-I (but also anti-TGFβ) treatment of the GF mice during CpG-ISS-ODN treatment (213). These data are also consistent with a study demonstrating that pDCs (that produce IFN-I) were able to drive IL-10-producing T cells *in vitro* in mice (214), and when stimulated with CpG-ISS-ODN induced $CD4^+Foxp3^+$ regulatory T cells in humans (215). Together, these studies indicate that exogenous CpG-ISS-ODN either *in vitro* or *in vivo* can affect T cells to become less colitogenic and more regulatory, most likely through an indirect mechanism that is dependent on IFN-I effects on $CD11c^+$ cells.

More direct effects of induced IFN-I on $CD4^+$ T cells were implicated in additional studies in the adoptive transfer model (216, 217). Systemic poly (I:C) administration suppressed colitis following transfer of WT but not $IFNAR^{-/-}$ $CD4^+CD45RB^{hi}$ T cells to $RAG^{-/-}$ mice, which was argued to be due to IFN-I induced CD69 expression on $CD4^+$ T cells. CD69-defective CD4 T cells produced more pro-inflammatory cytokines and had a reduced potential to differentiate into $FoxP3^+$ Tregs both *in vitro* and *in vivo*, and transfer of $CD4^+$ $CD45RB^{hi}$ T cells from $CD69^{-/-}$ mice to $RAG^{-/-}$ mice caused more severe colitis than transfer of WT cells. This study indicated the potential of IFN-I to directly influence $CD4^+$ T-cell differentiation by an indirect effect on $FoxP3^+$ Treg differentiation via effects on CD69 expression. Remarkably, to the best of our knowledge, no data showing the direct effect of IFN-I on the *de novo* differentiation of $CD4^+$ $FoxP3^+$ T cells in now well-established *in vitro* or *in vivo* systems have been published.

The role of endogenous IFN-I in the transfer colitis model has also been addressed. Lee *et al*. (217) demonstrated that co-transfer of IFN-I receptor-deficient $CD4^+CD45RB^{hi}CD25^+$ T cells (90–95% $Foxp3^+$) failed to prevent colitis induced by WT $CD4^+CD45RB^{hi}$ T-cell transfer to WT $RAG^{-/-}$ mice. Furthermore, the percentage of $CD4^+CD45RB^{hi}CD25^+$ co-transferred T cells that retained their Foxp3 expression was less when from $IFNAR1^{-/-}$ than WT mice, suggesting, that IFNAR signaling on regulatory T cells was important for their suppressive activity, possibly via the stabilization of their phenotype. Moreover, administration of IFNα to $IFNAR1^{-/-}$ $RAG^{-/-}$ mice transferred with $CD4^+CD45RB^{hi}$ together with $CD4^+FoxP3^+$ T cells at a high ratio (10:1) ameliorated the colitis by increasing the intestinal $Foxp3^+$ Treg number and enhancing their suppressive function. IL-10 also provided an additional non-redundant protective activity, since mice lacking both IL-10 and the IFN-I receptor develop severe spontaneous colitis compared to single KO mice deficient in either IL-10 or the IFN-I receptor (217).

Studies from our laboratory provided somewhat different results. We found that co-transfer of WT and $IFNAR^{-/-}$ $CD4^+CD45RB^{lo}CD25^+$ T cells with WT $CD4^+$ $CD45RB^{hi}$ T cells had an equivalent and effective ability to suppress colitis development (11). Furthermore, disease induced by $CD4^+CD45RB^{hi}$ from either WT or $IFNAR^{-/-}$ mice was similar, consistent with others (216), suggesting little effect of endogenous IFN-I signaling directly on T-cell populations in this model. The reason for the discrepancy of our results with the prior study currently unclear, but could potentially be due to differences in commensal intestinal microbiota including commensal viruses, present in the immunodeficient mouse colonies that were studied. Differences in commensal microbiota could influence either the production of IFN-1 and/or their effects on T cells, DCs, and MPs.

Differences in commensal microbiota may also explain some discrepancies in studies of the role of TLR9 and CpG-ISS-ODN in regulating immune homeostasis in the intestine. Thus, in contrast to the studies by Hofmann *et al.* (discussed above), bacterial DNA isolated from the colon and cecum of C57BL/6 mice limited the capacity of LP DCs to drive the differentiation of $CD4^+Foxp3^+$ *in vitro*, and when given orally to favor effector over regulatory T-cell differentiation in mice treated with antibiotics. In addition, $TLR9^{-/-}$ mice had higher numbers of $CD4^+Foxp3^+$ regulatory T cells, and lower numbers of IFNγ and IL-17 producing effector T cells in intestinal effector sites, and developed impaired

responses to intestinal infection and vaccination (218). In followup studies, DNA from different commensal bacteria was found to have profoundly different immunomodulatory effects. DNA from *Lactobacillus* species contained significantly more regulatory DNA sequences compared to *E. coli*, and was more efficient in driving $CD4^+Foxp3^+$ regulatory T cell differentiation *in vitro* in co-cultures of naïve T cells and LP DCs, and less efficient in inducing effector T cell responses in antibiotic-treated mice, when compared to *E. coli* DNA. Suppressive DNA sequences represented in *Lactobacillus* species inhibited activation of LP DCs by TLR9-dependent immunostimulatory ODNs, and when administered orally protected mice from DSS colitis and preserved $Foxp3^+$ regulatory T cell numbers during *T. gondii* infection (219). Furthermore, administration of probiotic (VSL-3) bacteria or isolated DNA was able to suppress DSS colitis by a mechanism that was dependent on MyD88, TLR9, and IFNβ (204, 220), indicating that CpG-ISS-ODN from different bacterial strains may be more or less capable of inducing immune protection through TLR9-signaling.

In contrast to direct effects on T cells, we found that endogenous IFNAR signaling of innate immune cells was critical for controlling T-cell-mediated colitis development (11). $CD4^+CD45RB^{hi}$ T cells from WT mice transferred into $RAG^{-/-}$ $IFNAR^{-/-}$ mice developed worse colitis than $RAG^{-/-}$ mice. IFNAR was required on a BM-derived cell to suppress colitis development, and LP MPs lacking IFNAR show dampened production of anti-inflammatory cytokines such as IL-10, IL-1R antagonist, and IL-27, consistent with prior studies (see above discussion). Furthermore, enhanced colitis development in the $RAG^{-/-}IFNAR^{-/-}$ was associated with higher expansion of effector cells and less of $CD4^+FoxP3^+$ T cells in the MNLs as well as an increase in $CD11c^+CD103^-CD11b^+$ cells into the MLNs soon after T cell transfer (7–10 day) and well before colitis development. These cellular changes, as well as the enhanced colitis development in $RAG^{-/-}IFNR1^{-/-}$ mice were prevented by systemic administration of a soluble human IL-1R-antagonist (anakinra) that had activity in mice. Furthermore, WT $CD4^+CD25^+Foxp3$ (GFP^+) Tregs co-transferred with $CD4^+CD45RB^{hi}$ T cells into DKO hosts failed to expand or maintain their Foxp3 expression and instead gained the ability to produce both IFNγ and IL-17 in the colon. These data demonstrated an essential role for IFN-I in regulating the production of inflammatory and anti-inflammatory cytokines by gut MPs, and in the indirect maintenance of intestinal T-cell homeostasis by both limiting effector T-cell expansion and promoting Treg stability. These data are consistent with the aforementioned studies of mice treated with ISS-ODN, GM-CSF, or imiquimod, which resulted in suppressed proinflammatory cytokine production by myelomonocytic cells (207, 209, 210), as well as the indirect effects of CpG-ISS-ODN on $CD11c^+$ cells discussed above.

Additional roles of IFN-I in the immune regulation in the intestine

In addition to the immunoregulatory roles of IFN-I in models of colitis, a contribution of IFN-I in regulating epithelial cell function, in driving T-cell independent B-cell class switching for IgA production, and in setting the threshold for the innate immune activation and have recently been described.

Several studies demonstrated that IFN-I can protect epithelial cells from apoptosis to promote intestinal barrier function. Thus, ability of CpG-ISS-ODN administration to protect

mice from colitis was suggested in part to be due to the ability of IFN-I to protection epithelial cell apoptosis. Basolateral administration of IFNα to polarized monolayers of intestinal epithelial cells was shown to protect the cells against apoptosis and disruption of the epithelial tight junctions (206), although an additional major effect of CpG-ISS-ODN is through direct apical signaling that inhibits NFκB activation (221). Furthermore, exposure of immature intestinal epithelium to *E. coli* and directly to IFNα induced an IFNα-mediated protection from apoptosis induced by staurosporin, that was mediated by guanylate binding protein-1 (222).

An additional direct effect of IFN-I on epithelial cell function was recently described. Mice with an intestinal epithelial cell-specific deletion of IFNAR1 displayed an expansion of Paneth cell numbers and epithelial cell hyperproliferation as well as an increased tumor burden in mice given DSS and the chemical carcinogen azoxymethane (AOM) (223). Interestingly, the development of hyperproliferation and increased tumorogenesis in the epithelial cell-specific IFNAR-deficient mice was not dependent on differences in the severity of the DSS-induced inflammation, but was dependent on the specific microbiota in these mice, indicating a role for IFN-I in epithelial and/or paneth cells to influence the composition of the commensal microbiota (223). Therefore, IFN-I signaling in intestinal epithelial cells has effects on apoptosis and barrier function, particularly mediated by IFNα, and on the regulation of commensal microbiota by as yet to be identified mechanisms.

A role for IFN-I in the regulation of IgA B cell responses has also been described. Tezuka *et al*. (225) report a critical role of stromal cell-derived IFN-I signaling in conditioning pDCs in the gut-associated lymphoid tissues (PPs and MLNs). Under steady-state conditions, IFN-I derived from stromal cells promotes the expression of APRIL and BAFF in pDCs, which is in turn required for T-cell-independent IgA production by B cells. Prior studies had established that IFN-I was potent inducers of APRIL and BAFF production by human DCs (224). IFN-I-pDC-B-cell axis may provide another mechanism to control gut homeostasis (225).

Intestinal microbiota have been shown to influence systemic immune responses to a wide variety of pathogens and susceptibility to autoimmune and allergic diseases by affecting the systemic induction of $Foxp3^+$, Th17, and $CD8^+$ T-cell responses and by yet unexplained mechanisms. Furthermore, intestinal microbiota were shown to contribute to T-cell priming after influenza infection by affecting DC maturation in the lung (226). An involvement of IFN-I in microbiota-regulated systemic immunity has been indicated by recent studies (227, 228). In particular, intestinal microbiota were shown to condition mononuclear phagocytes throughout the body to rapidly produce IFN-I after virus infection by driving tonic signaling through IFN-I receptor. Transcriptional profiling of peritoneal MPs isolated from naive mice treated with antibiotics revealed reduced expression of IFN-I pathway and induced genes, including MDA5 and RIG-I compare to untreated mice. These MPs responded poorly to IFN-I and IFN-II as shown by the lack of induced intracellular phospho-STAT1 by flow cytometry, and could not control viral replication, which was rescued by restoration of the IFN responsiveness through systemic treatment with poly (I;C) (227). In addition, GF mice failed to produce IFN-I and certain inflammatory response genes in response to systemic poly (I:C), LPS, or murine cytomegalovirus infection, which correlated with poor

responsiveness to LPS and Poly (I:C) of $CD11c^+$ cells from the spleen. This led to severely compromised NK cell priming and antiviral immunity. Binding (but not activation) of NFκB and IRF3 to their respective cytokine promoters is impaired in the GF mononuclear phagocytes. Therefore, microbiota can induce chromatin level changes, poising mononuclear phagocyte system to initiate immune responses including the production of IFN-I (228), which, in turn can prime cells for enhanced IFN-I production and its antiviral effects and regulatory effects.

Human studies

Data addressing the role of IFN-I in the human intestine are more limited, but include genetic studies of IBD patients, treatment trials with IFN-I for CD and UC, and analysis of tissues from patients with celiac disease.

At least 163 genetic loci that contribute to IBD susceptibility have been identified by genome-wide association studies (GWAS), immunochip single nucleotide polymorphism microarray, and deep re-sequencing of GWAS loci (229–234). In a recent meta-analysis of GWAS data IFNAR and MDA-5 (IFIH1) were identified as primary candidate genes in susceptible loci for IBD (232). Furthermore, a gain-of-function coding polymorphism (PTPN22 Arg620Trp) of the protein tyrosine phosphatase nonreceptor type 22 (PTPN22) that is required for efficient TLR-mediated IFN-I production in myeloid cells and also acts to suppresses T-cell function is associated with risk for UC, but paradoxically negatively associated with risk for CD (235, 236).

IFN-I treatment trials for IBD have yielded mixed results. Several studies have shown promising effects in inducing remission and preventing relapse in patients with UC (237–240). In particular, a long-term uncontrolled trial of IFNβ treatment of steroid-refractory patients with UC, showed a dose-dependent positive effect in preventing remissions (237). An additional open-labeled randomized study comparing systemic IFNα2A and prednisolone enemas in the treatment of left-sided UC resulted in significant suppression of disease activity in the IFNα2A-treated group (238). Finally, in an uncontrolled, open-labeled interventional drug trial, interferon-β-1a induced a clinical response and remission in a large subset of patients with UC that was associated with significant inhibition of LP mononuclear cells production of IL-13 a cytokine implicated in UC pathogenesis (240). Furthermore, LP mononuclear cells from non-responders produced higher levels of IL-6 and IL-17 when cultured *in vitro* (240). Consistent with these studies, IFN-I has been shown to suppress IL-13 production by human peripheral blood mononuclear cells upon stimulation *in vitro* (241).

Despite these promising results from small uncontrolled studies of patients with UC, negative results were seen in small uncontrolled and placebo-controlled studies of IFNα and IFNβ-1a treatment for the induction and maintenance of remission in patients with CD (242, 243). Furthermore, placebo-controlled clinical trials with UC patients have also shown less promising results. In one placebo-controlled, randomized dose escalation trial of 18 patients with moderately active UC, treatment with IFNβ-1a resulted in a trend toward increased clinical responses and a significant effect on remission in a few small number of patients

(239). Furthermore, a larger multi-center, double-blind placebo-controlled, randomized, dose escalation trial of 194 patients found no effects of IFNβ-1a treatment overall on endoscopically-confirmed remission in adult patients with moderately active UC. There was, however, a subgroup of patients with more severe disease and higher compliance rates that had higher responses, and remission rates were higher on therapy in the placebo group. Another caveat to this study was the fact that there were unusually high placebo response rates compared to other UC trials, while the subgroup with better responses had normal placebo response rates (244). An additional randomized, double-blind, placebo-controlled trial of 91 patients for the treatment of steroid-refractory UC showed no effect of IFNβ–1α treatment on endoscopically–confirmed responses (245), although these patients were continued on standard therapy in addition to IFNβ–1α treatment.

Overall, the treatment of IBD with IFN-I has been disappointing to date, likely reflecting the complexities of immunological effects induced by IFN-I. Some patients with UC, however, have quite dramatic responses to treatment (240), and some groups of patients have shown better responses than others to IFN-I treatment (239, 240, 244), suggesting that further studies to define subgroups of patients with UC who may benefit from IFN-I are warranted; as are further studies of patients with CD and their response to IFN-I treatment, as few studies have addressed the dose, timing and response of patients with different disease patterns and severity to IFN-I treatment in this disease.

Finally, IFN-I may have a role in driving Th1 responses in celiac disease. Celiac disease is a small intestinal inflammatory disorder characterized by a strong Th1 response to gliadin, a protein found within wheat gluten that is induced in individuals with the HLA-DQ2 or HLA-DQ8 MHC alleles. IFNα has been implicated in celiac disease pathogenesis by studies from Monteleone *et al.* who reported an increase in the number of pDCs that produce IFNα, as well as the induction of IFNα mRNA and protein in active celiac disease tissue (246). Di Sabatino et al reported evidence for the role of IFNα production by DCs in the Th1 response in celiac disease (247). In functional assays, the addition of anti-IFNα antibodies inhibited an increase in IFNγ production induced by gliadin peptides in biopsies from treated celiac disease patients (246), and addition of IFNα to fetal tissue explants treated with anti-CD3 resulted in increased IFNγ production, villous atrophy and crypt hyperplasia, hallmarks of celiac disease suggesting that IFNα contributes to disease by enhancing IFNγ production from pathogenic T cells (247).

Conclusions

While IFN-I have long been known for their protective role in viral infections, they can either protect or exacerbate bacterial infections and contribute to immune homeostasis in the intestine through both immune activating and suppressive signals (Fig. 3). IFN-I appears to largely protect intestinal infections with several model intestinal virus infections, including those caused by rotavirus, reovirus, and noroviruses. However, viral pathogens have evolved complex cell-type-specific mechanisms to escape these potent anti-viral pathways by blocking IFN-1 production, as well as its autocrine and paracrine signaling that can affect viral tropism and pathogenicity. This is perhaps most clear with studies of rotavirus, in which IFN-I may play a less important direct antiviral role in infections with homologous

viruses than with heterologous infections, and may allow for IFN-I signaling in hematopoietic cells but less so in epithelial cells where homologous strains actively replicate.

IFN-I also have broader effects on adaptive immunity during intestinal virus infection, such as activating pDC production of IFN-I to help induce B-cell activation and differentiation in GALT. While shown in other systems, the ability of IFN-I in driving $CD4^+$ and $CD8^+$ T-cell responses to intestinal viruses through direct or indirect effects on DCs or pDCs is not yet clear, but it is likely to be the case and requires further study. It is also evident in mouse models that IFN-III has a more important role in restricting rotavirus replication in intestinal epithelial cells than IFN-I. IFN-III production is induced by many cell types after viral infection by IRF3 and IRF7 and NFκB signaling, it can be also induced by either IRF or NFκB signals (reviewed in 248, 249). Furthermore, its functional receptor is restricted to epithelial cells, hepatocytes, pDCs, and B cells, and possibly by DCs and monocytes, but not by T cells or NK cells. Signaling through IFN-I and IFN-III receptors is similar. Therefore, its role in infections in the intestine and its response to intestinal microbes, as well as its ability to regulate intestinal homeostasis and immune regulation may be different from that of IFN-I, and warrants further study, as does the cross regulation of IFN-I and IFN-III and the combined effects of INF-I, IFN-II, and IFN-III.

In the intestine, constitutive IFN-I is produced in response to microbial products, at least in part, by mononuclear phagocytes, possibly including pDCs in the intestinal LP, and by stromal cells in the GALT (PPs and MLNs). Signals for stromal cell-mediated production of IFN-I in the GALT are not known, and neither are the precise sources and signals responsible for the full complement of constitutive IFN-I in the majority of intestinal tissues, including the role of TLR9 signaling by commensal bacterial DNA. Constitutive IFN-I contributes to intestinal barrier function, drives IgA against commensal bacteria, and regulates intestinal macrophage function. Through these mechanisms, constitutive IFN-1 signaling may be essential for maintaining intestinal immune homeostasis by enhancing innate responses to bacteria, increasing intestinal barrier functions, and producing factors that prevent intestinal dysbiosis.

The studies showing that commensal intestinal microbes condition systemic and likely local myeloid cells to both produce IFN-I and poise such cells to produce high IFN-I, as well as other proinflammatory cytokines through epigenetic modifications that allow for effective innate and adaptive immunity to lung and systemic viral infections are important to consider, in particular in light of the many studies performed with $IFNAR1^{-/-}$ mice. Baseline conditioning of immune responses by IFN-I, including epigenetic modification and effects on relative STAT protein levels will need to be taken into account in studies of the intestinal immunity and homeostasis, as they could broadly affect defense against intestinal viral pathogens as well as against pathogenic and commensal intestinal bacteria. It will be important to determine the intestinal microbes and the mechanisms responsible for this conditioning, as well as the extent to which this conditioning affect inflammatory and suppressive cytokines, in what cell types, and in which intestinal cell compartments, as our studies indicate a selective inhibition of suppressive cytokines IL-10, IL-1RA, and IL-27 in mononuclear cells from colon of mice from our colony. Furthermore, a broad effect on

antibiotic-induced dysbioses that can result in broad immunosuppression via these mechanisms would have significant ramifications for risks to viral and bacterial infections in patients treated with broad-spectrum antibiotics.

A focus of recent studies has been to explore how IFN-I production acts in regulating innate immune responses in mouse models of colitis, which represent abnormal conditions in which the intestinal barrier is severely breeched, there is a absence of $CD4^+Foxp3^+$ regulatory T cells, or B cells, and there is the presence of lymphopenic expansion. In this regard, IFN-I appears to have an overall regulatory role in acute colitis models induced by DSS or haptens, and in T-cell transfer models through suppressive effects on innate proinflamatory cytokine production by $CD11c^+$ LP phaogocytes, which can be enhanced by systemically administered CpG-ISS-ODN, or poly (I:C) that act at least largely via IFN-I-dependent mechanisms. Furthermore, our studies in T-cell transfer mouse models of colitis suggest that IFN-I conditioning of intestinal MPs for the production of anti-inflammatory cytokines including IL-10, IL-27, and IL-1RA which is consistent with other studies of non-mucosal cells, may have broad downstream effects including blocking the induction of pathogenic T cells and maintaining the pool of functional $CD4^+Foxp3^+$ T cells in the LP. Whether IFN-I also inhibits NLRP3 or other inflammasome activation to block IL1β production by intestinal phagocytes, as has been shown by others, remains to be determined, however the ability to block accelerated T-cell expansion and enhanced colitis in $IFNAR1^{-/-} \times RAG^{-/-}$ mice, given WT $CD4^+CD45RB^{hi}$ T cells with exogenous IL-1RA is consistent with an net imbalance of IL-1β and IL-1RA production in the absence of IFN-I signaling. An overall working model for how IFN-I effects on myelomonocytic cell production of IL-10, IL-1RA, and IL-27 could affect intestinal homeostasis is presented in Fig. 4.

An effect of IFN-I directly on T cells to allow for the induction or maintenance of $CD4^+Foxp3^+$ T cells is suggested by some but not all studies, possibly through an effect on CD69 expression; however, studies directly showing the ability of IFN-I to inhibit *de novo* induction of $CD4^+Foxp3^+$ T cells have not yet been published. Furthermore, since IFN-I can induce the production of IL-10 from human peripheral T cells and help drive the high IL-10 production from human T cells when added in conjunction with IL-10 *in vitro*, it will be of great interest to determine the ability of IFN-I to directly drive IL-10 production from $CD4^+Foxp3^+$ T cells in the intestine. In preliminary unpublished studies from our laboratory, $CD4^+Foxp3^+$ T cells from the small intestine of $IFNAR1^{-/-}$ mice fail to express IL-10, while IL-10 production from $CD4^+Foxp3^+$ T cells from the colon is minimally affected. A role for IFN-I in the accumulation of IL-10-producing $CD4^+Foxp3^+$ T cells was also shown in T cells from the tumor microenvironment, so it is likely that this may provide an additional important function for IFN-I in the intestine. The fact that adoptively transferred $CD4^+Foxp3^+$ T cells from $IFNAR1^{-/-}$ mice can still suppress colitis on adoptive transfer, at least in experiments in our laboratory, is consistent with published studies showing that such transferred cells traffic primarily via CCR4 to the MLN to suppress the induction of colitogenic T cells in a largely IL-10-independent fashion.

Another important question to address with future studies is the ability of different commensal bacteria to drive IFN-I production. The studies to date indicate that certain

commensal bacteria, such as LAB, are more able to both induce IFN-I production by intestinal myleomonocytic cells, as well as provide intestinal DCs with an enhanced ability to induce the differentiation of $CD4^+Foxp3^+$ T cells, in contrast to others, such as *E. coli* that may have more pathogenic potential. Whether the effect of these bacterial species act through differential signaling through TLR3 and TLR9, and the link between IFN-I production and pathogenic or protective effects in homeostatic or inflammatory conditions is not yet clear. While the fact that TLR9-deficient mice have a higher percentage of $CD4^+Foxp3^+$ regulatory T cells in the intestine suggests that the overall effect of bacterial DNA in homeostatic conditions is in conditioning cells for effector T-cell responses, the composition of commensal microbes, including viruses, as well as the predisposing mechanisms for colitis development may influence the overall role for microbial driven IFN-I in regulating intestinal homeostasis and inflammation.

The role of IFN-I in regulating host defense to intestinal bacterial pathogens is complex, and depends on the nature of the infecting bacteria. While protective in *S. typhimurium* infection, it inhibits responses to *L. monocytogenes* through a variety of mechanisms. Whether these mechanisms apply to other intestinal bacterial infections is not as clear; however, it may be important to understand the interactions of viral infections that can drive IFN-I, including HIV, with susceptibility to pathogenic bacterial infections in the intestine, including mycobacterial infections such as *Mycobaterium avium* species that are known to infect humans through an intestinal route.

Trials of IFN-I treatment of inflammatory bowel disease in humans have been largely disappointing to date likely reflecting the complexities of immunological effects induced by IFN-I. Furthermore, several patients being treated with IFN-I for other disorders, such as chronic hepatitis, multiple sclerosis, or myeloid leukemia have developed either exacerbations of UC or development of UC or celiac disease, indicating potential harmful side effects of IFN-I treatment (250, 249). Some patients with UC, however, have quite dramatic responses to treatment (240), and some groups of patients have shown better responses than others to IFN-I treatment (239, 240, 244), suggesting that further studies to define subgroups of patients with UC who may benefit from IFN-I are warranted, as are further studies of patients with CD and their response to IFN-I treatment, as few studies have addressed the dose, timing, and response of patients with different disease patterns and severity to IFN-I treatment in this disease.

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References

1. Pestka S, Krause CD, Walter MR. Interferons, interferon-like cytokines, and their receptors. Immunological reviews. 2004; 202:8–32. [PubMed: 15546383]
2. Hertzog PJ, Williams BR. Fine tuning type I interferon responses. Cytokine & growth factor reviews. 2013; 24:217–225. [PubMed: 23711406]

3. Young HA, Bream JH. IFN-gamma: recent advances in understanding regulation of expression, biological functions, and clinical applications. Current topics in microbiology and immunology. 2007; 316:97–117. [PubMed: 17969445]
4. Gad HH, Dellgren C, Hamming OJ, Vends S, Paludan SR, Hartmann R. Interferon-lambda is functionally an interferon but structurally related to the interleukin-10 family. The Journal of biological chemistry. 2009; 284:20869–20875. [PubMed: 19457860]
5. Kotenko SV, et al. IFN-lambdas mediate antiviral protection through a distinct class II cytokine receptor complex. Nature immunology. 2003; 4:69–77. [PubMed: 12483210]
6. Sheppard P, et al. IL-28, IL-29 and their class II cytokine receptor IL-28R. Nature immunology. 2003; 4:63–68. [PubMed: 12469119]
7. Kotenko SV. IFN-lambdas. Current opinion in immunology. 2011; 23:583–590. [PubMed: 21840693]
8. Sommereyns C, Paul S, Staeheli P, Michiels T. IFN-lambda (IFN-lambda) is expressed in a tissue-dependent fashion and primarily acts on epithelial cells in vivo. PLoS pathogens. 2008; 4:e1000017. [PubMed: 18369468]
9. Nguyen KB, et al. Critical role for STAT4 activation by type 1 interferons in the interferon-gamma response to viral infection. Science. 2002; 297:2063–2066. [PubMed: 12242445]
10. Gonzalez-Navajas JM, Lee J, David M, Raz E. Immunomodulatory functions of type I interferons. Nature reviews Immunology. 2012; 12:125–135.
11. Kole A, et al. Type I IFNs regulate effector and regulatory T cell accumulation and anti-inflammatory cytokine production during T cell-mediated colitis. Journal of immunology. 2013; 191:2771–2779.
12. Gough DJ, Messina NL, Clarke CJ, Johnstone RW, Levy DE. Constitutive type I interferon modulates homeostatic balance through tonic signaling. Immunity. 2012; 36:166–174. [PubMed: 22365663]
13. Monroe KM, McWhirter SM, Vance RE. Induction of type I interferons by bacteria. Cellular microbiology. 2010; 12:881–890. [PubMed: 20482555]
14. Trinchieri G. Type I interferon: friend or foe? The Journal of experimental medicine. 2010; 207:2053–2063. [PubMed: 20837696]
15. Eitel J, Suttorp N, Opitz B. Innate immune recognition and inflammasome activation in listeria monocytogenes infection. Frontiers in microbiology. 2010; 1:149. [PubMed: 21607087]
16. Malireddi RK, Kanneganti TD. Role of type I interferons in inflammasome activation, cell death, and disease during microbial infection. Frontiers in cellular and infection microbiology. 2013; 3:77. [PubMed: 24273750]
17. Mayer-Barber KD, et al. Innate and adaptive interferons suppress IL-1alpha and IL-1beta production by distinct pulmonary myeloid subsets during Mycobacterium tuberculosis infection. Immunity. 2011; 35:1023–1034. [PubMed: 22195750]
18. Guarda G, et al. Type I interferon inhibits interleukin-1 production and inflammasome activation. Immunity. 2011; 34:213–223. [PubMed: 21349431]
19. MacMicking JD. Interferon-inducible effector mechanisms in cell-autonomous immunity. Nature reviews Immunology. 2012; 12:367–382.
20. Wilson EB, Brooks DG. Decoding the complexity of type I interferon to treat persistent viral infections. Trends in microbiology. 2013; 21:634–640. [PubMed: 24216022]
21. Ivashkiv LB, Donlin LT. Regulation of type I interferon responses. Nature reviews Immunology. 2014; 14:36–49.
22. Swiecki M, Colonna M. Type I interferons: diversity of sources, production pathways and effects on immune responses. Current opinion in virology. 2011; 1:463–475. [PubMed: 22440910]
23. Takeuchi O, Akira S. Pattern recognition receptors and inflammation. Cell. 2010; 140:805–820. [PubMed: 20303872]
24. Wilkins C, Gale M Jr. Recognition of viruses by cytoplasmic sensors. Current opinion in immunology. 2010; 22:41–47. [PubMed: 20061127]
25. Jensen S, Thomsen AR. Sensing of RNA viruses: a review of innate immune receptors involved in recognizing RNA virus invasion. Journal of virology. 2012; 86:2900–2910. [PubMed: 22258243]

26. Lupfer C, Kanneganti TD. The expanding role of NLRs in antiviral immunity. Immunological reviews. 2013; 255:13–24. [PubMed: 23947344]
27. Mattei F, Schiavoni G, Tough DF. Regulation of immune cell homeostasis by type I interferons. Cytokine & growth factor reviews. 2010; 21:227–236. [PubMed: 20627800]
28. Tate JE, et al. 2008 estimate of worldwide rotavirus-associated mortality in children younger than 5 years before the introduction of universal rotavirus vaccination programmes: a systematic review and meta-analysis. The Lancet infectious diseases. 2012; 12:136–141. [PubMed: 22030330]
29. Ouattara LA, et al. Novel human reovirus isolated from children with acute necrotizing encephalopathy. Emerging infectious diseases. 2011; 17:1436–1444. [PubMed: 21801621]
30. Fleeton MN, Contractor N, Leon F, Wetzel JD, Dermody TS, Kelsall BL. Peyer's patch dendritic cells process viral antigen from apoptotic epithelial cells in the intestine of reovirus-infected mice. The Journal of experimental medicine. 2004; 200:235–245. [PubMed: 15263030]
31. Forrest JC, Dermody TS. Reovirus receptors and pathogenesis. Journal of virology. 2003; 77:9109–9115. [PubMed: 12915527]
32. Glass RI, Parashar UD, Estes MK. Norovirus gastroenteritis. The New England journal of medicine. 2009; 361:1776–1785. [PubMed: 19864676]
33. Zhang S, et al. Symptomatic and asymptomatic infections of rotavirus, norovirus, and adenovirus among hospitalized children in Xi'an, China. Journal of medical virology. 2011; 83:1476–1484. [PubMed: 21618552]
34. Schwartz S, et al. Norovirus gastroenteritis causes severe and lethal complications after chemotherapy and hematopoietic stem cell transplantation. Blood. 2011; 117:5850–5856. [PubMed: 21487110]
35. Roos-Weil D, et al. Impact of norovirus/sapovirus-related diarrhea in renal transplant recipients hospitalized for diarrhea. Transplantation. 2011; 92:61–69. [PubMed: 21555974]
36. Santos N, Hoshino Y. Global distribution of rotavirus serotypes/genotypes and its implication for the development and implementation of an effective rotavirus vaccine. Reviews in medical virology. 2005; 15:29–56. [PubMed: 15484186]
37. Blutt SE, Conner ME. The Gastrointestinal Frontier: IgA and Viruses. Frontiers in immunology. 2013; 4:402. [PubMed: 24348474]
38. Blutt SE, et al. Rotavirus antigenemia in children is associated with viremia. PLoS medicine. 2007; 4:e121. [PubMed: 17439294]
39. Lopatin U, Blutt SE, Conner ME, Kelsall BL. Lymphotoxin alpha-deficient mice clear persistent rotavirus infection after local generation of mucosal IgA. Journal of virology. 2013; 87:524–530. [PubMed: 23097456]
40. Kuss SK, et al. Intestinal microbiota promote enteric virus replication and systemic pathogenesis. Science. 2011; 334:249–252. [PubMed: 21998395]
41. Pfeiffer JK, Sonnenburg JL. The intestinal microbiota and viral susceptibility. Frontiers in microbiology. 2011; 2:92. [PubMed: 21833331]
42. Arnold MM, Sen A, Greenberg HB, Patton JT. The battle between rotavirus and its host for control of the interferon signaling pathway. PLoS pathogens. 2013; 9:e1003064. [PubMed: 23359266]
43. Davidson GP, Barnes GL. Structural and functional abnormalities of the small intestine in infants and young children with rotavirus enteritis. Acta paediatrica Scandinavica. 1979; 68:181–186. [PubMed: 217231]
44. Frias AH, et al. Intestinal epithelia activate anti-viral signaling via intracellular sensing of rotavirus structural components. Mucosal immunology. 2010; 3:622–632. [PubMed: 20664578]
45. Broquet AH, Hirata Y, McAllister CS, Kagnoff MF. RIG-I/MDA5/MAVS are required to signal a protective IFN response in rotavirus-infected intestinal epithelium. Journal of immunology. 2011; 186:1618–1626.
46. Pott J, et al. IFN-lambda determines the intestinal epithelial antiviral host defense. Proceedings of the National Academy of Sciences of the United States of America. 2011; 108:7944–7949. [PubMed: 21518880]
47. Sen A, Pruijssers AJ, Dermody TS, Garcia-Sastre A, Greenberg HB. The early interferon response to rotavirus is regulated by PKR and depends on MAVS/IPS-1, RIG-I, MDA-5, and IRF3. Journal of virology. 2011; 85:3717–3732. [PubMed: 21307186]

48. Douagi I, et al. Role of interferon regulatory factor 3 in type I interferon responses in rotavirus-infected dendritic cells and fibroblasts. Journal of virology. 2007; 81:2758–2768. [PubMed: 17215281]
49. Uzri D, Greenberg HB. Characterization of rotavirus RNAs that activate innate immune signaling through the RIG-I-like receptors. PloS one. 2013; 8:e69825. [PubMed: 23894547]
50. Deal EM, Jaimes MC, Crawford SE, Estes MK, Greenberg HB. Rotavirus structural proteins and dsRNA are required for the human primary plasmacytoid dendritic cell IFNalpha response. PLoS pathogens. 2010; 6:e1000931. [PubMed: 20532161]
51. Pott J, et al. Age-dependent TLR3 expression of the intestinal epithelium contributes to rotavirus susceptibility. PLoS pathogens. 2012; 8:e1002670. [PubMed: 22570612]
52. Sato A, et al. Rotavirus double-stranded RNA induces apoptosis and diminishes wound repair in rat intestinal epithelial cells. Journal of gastroenterology and hepatology. 2006; 21:521–530. [PubMed: 16638093]
53. Zhou R, Wei H, Sun R, Tian Z. Recognition of double-stranded RNA by TLR3 induces severe small intestinal injury in mice. Journal of immunology. 2007; 178:4548–4556.
54. McAllister CS, et al. TLR3, TRIF, and caspase 8 determine double-stranded RNA-induced epithelial cell death and survival in vivo. Journal of immunology. 2013; 190:418–427.
55. Lecce JG, Cummins JM, Richards AB. Treatment of rotavirus infection in neonate and weanling pigs using natural human interferon alpha. Molecular biotherapy. 1990; 2:211–216. [PubMed: 1963065]
56. Schwers A, Vanden Broecke C, Maenhoudt M, Beduin JM, Werenne J, Pastoret PP. Experimental rotavirus diarrhoea in colostrum-deprived newborn calves: assay of treatment by administration of bacterially produced human interferon (Hu-IFN alpha 2). Annales de recherches veterinaires Annals of veterinary research. 1985; 16:213–218. [PubMed: 4062197]
57. Angel J, Franco MA, Greenberg HB, Bass D. Lack of a role for type I and type II interferons in the resolution of rotavirus-induced diarrhea and infection in mice. Journal of interferon & cytokine research : the official journal of the International Society for Interferon and Cytokine Research. 1999; 19:655–659.
58. Broome RL, Vo PT, Ward RL, Clark HF, Greenberg HB. Murine rotavirus genes encoding outer capsid proteins VP4 and VP7 are not major determinants of host range restriction and virulence. Journal of virology. 1993; 67:2448–2455. [PubMed: 8386262]
59. Feng N, et al. Role of interferon in homologous and heterologous rotavirus infection in the intestines and extraintestinal organs of suckling mice. Journal of virology. 2008; 82:7578–7590. [PubMed: 18495762]
60. Sen A, et al. Innate immune response to homologous rotavirus infection in the small intestinal villous epithelium at single-cell resolution. Proceedings of the National Academy of Sciences of the United States of America. 2012; 109:20667–20672. [PubMed: 23188796]
61. Deal EM, Lahl K, Narvaez CF, Butcher EC, Greenberg HB. Plasmacytoid dendritic cells promote rotavirus-induced human and murine B cell responses. The Journal of clinical investigation. 2013; 123:2464–2474. [PubMed: 23635775]
62. Siegal FP, et al. The nature of the principal type 1 interferon-producing cells in human blood. Science. 1999; 284:1835–1837. [PubMed: 10364556]
63. Asselin-Paturel C, et al. Mouse type I IFN-producing cells are immature APCs with plasmacytoid morphology. Nature immunology. 2001; 2:1144–1150. [PubMed: 11713464]
64. Cella M, Facchetti F, Lanzavecchia A, Colonna M. Plasmacytoid dendritic cells activated by influenza virus and CD40L drive a potent TH1 polarization. Nature immunology. 2000; 1:305–310. [PubMed: 11017101]
65. Cella M, et al. Plasmacytoid monocytes migrate to inflamed lymph nodes and produce large amounts of type I interferon. Nature medicine. 1999; 5:919–923.
66. Cerutti A, Qiao X, He B. Plasmacytoid dendritic cells and the regulation of immunoglobulin heavy chain class switching. Immunology and cell biology. 2005; 83:554–562. [PubMed: 16174107]
67. Jego G, Palucka AK, Blanck JP, Chalouni C, Pascual V, Banchereau J. Plasmacytoid dendritic cells induce plasma cell differentiation through type I interferon and interleukin 6. Immunity. 2003; 19:225–234. [PubMed: 12932356]

68. Le Bon A, Schiavoni G, D'Agostino G, Gresser I, Belardelli F, Tough DF. Type i interferons potently enhance humoral immunity and can promote isotype switching by stimulating dendritic cells in vivo. Immunity. 2001; 14:461–470. [PubMed: 11336691]
69. Varani S, et al. Human cytomegalovirus differentially controls B cell and T cell responses through effects on plasmacytoid dendritic cells. Journal of immunology. 2007; 179:7767–7776.
70. Holm GH, et al. Retinoic acid-inducible gene-I and interferon-beta promoter stimulator-1 augment proapoptotic responses following mammalian reovirus infection via interferon regulatory factor-3. The Journal of biological chemistry. 2007; 282:21953–21961. [PubMed: 17540767]
71. Saito T, et al. Regulation of innate antiviral defenses through a shared repressor domain in RIG-I and LGP2. Proceedings of the National Academy of Sciences of the United States of America. 2007; 104:582–587. [PubMed: 17190814]
72. Kato H, et al. Length-dependent recognition of double-stranded ribonucleic acids by retinoic acid-inducible gene-I and melanoma differentiation-associated gene 5. The Journal of experimental medicine. 2008; 205:1601–1610. [PubMed: 18591409]
73. Loo YM, et al. Distinct RIG-I and MDA5 signaling by RNA viruses in innate immunity. Journal of virology. 2008; 82:335–345. [PubMed: 17942531]
74. Satoh T, et al. LGP2 is a positive regulator of RIG-I- and MDA5-mediated antiviral responses. Proceedings of the National Academy of Sciences of the United States of America. 2010; 107:1512–1517. [PubMed: 20080593]
75. Zhang Z, et al. DDX1, DDX21, and DHX36 helicases form a complex with the adaptor molecule TRIF to sense dsRNA in dendritic cells. Immunity. 2011; 34:866–878. [PubMed: 21703541]
76. Liu Y, et al. The interaction between the helicase DHX33 and IPS-1 as a novel pathway to sense double-stranded RNA and RNA viruses in myeloid dendritic cells. Cellular & molecular immunology. 2014; 11:49–57. [PubMed: 24037184]
77. Edelmann KH, Richardson-Burns S, Alexopoulou L, Tyler KL, Flavell RA, Oldstone MB. Does Toll-like receptor 3 play a biological role in virus infections? Virology. 2004; 322:231–238. [PubMed: 15110521]
78. Wolf JL, et al. Intestinal M cells: a pathway for entry of reovirus into the host. Science. 1981; 212:471–472. [PubMed: 6259737]
79. Bodkin DK, Nibert ML, Fields BN. Proteolytic digestion of reovirus in the intestinal lumens of neonatal mice. Journal of virology. 1989; 63:4676–4681. [PubMed: 2677401]
80. Kauffman RS, Wolf JL, Finberg R, Trier JS, Fields BN. The sigma 1 protein determines the extent of spread of reovirus from the gastrointestinal tract of mice. Virology. 1983; 124:403–410. [PubMed: 6823749]
81. Fan JY, Boyce CS, Cuff CF. T-Helper 1 and T-helper 2 cytokine responses in gut-associated lymphoid tissue following enteric reovirus infection. Cellular immunology. 1998; 188:55–63. [PubMed: 9743558]
82. Major AS, Cuff CF. Enhanced mucosal and systemic immune responses to intestinal reovirus infection in beta2-microglobulin-deficient mice. Journal of virology. 1997; 71:5782–5789. [PubMed: 9223466]
83. London SD, Rubin DH, Cebra JJ. Gut mucosal immunization with reovirus serotype 1/L stimulates virus-specific cytotoxic T cell precursors as well as IgA memory cells in Peyer's patches. The Journal of experimental medicine. 1987; 165:830–847. [PubMed: 2950199]
84. Johansson C, Wetzel JD, He J, Mikacenic C, Dermody TS, Kelsall BL. Type I interferons produced by hematopoietic cells protect mice against lethal infection by mammalian reovirus. The Journal of experimental medicine. 2007; 204:1349–1358. [PubMed: 17502662]
85. Zheng DP, Ando T, Fankhauser RL, Beard RS, Glass RI, Monroe SS. Norovirus classification and proposed strain nomenclature. Virology. 2006; 346:312–323. [PubMed: 16343580]
86. Bull RA, Eden JS, Rawlinson WD, White PA. Rapid evolution of pandemic noroviruses of the GII. 4 lineage. PLoS pathogens. 2010; 6:e1000831. [PubMed: 20360972]
87. Hutson AM, Atmar RL, Graham DY, Estes MK. Norwalk virus infection and disease is associated with ABO histo-blood group type. The Journal of infectious diseases. 2002; 185:1335–1337. [PubMed: 12001052]

88. Tan M, Jiang X. Norovirus gastroenteritis, carbohydrate receptors, and animal models. PLoS pathogens. 2010; 6:e1000983. [PubMed: 20865168]

89. Strong DW, Thackray LB, Smith TJ, Virgin HW. Protruding domain of capsid protein is necessary and sufficient to determine murine norovirus replication and pathogenesis in vivo. Journal of virology. 2012; 86:2950–2958. [PubMed: 22258242]

90. McCartney SA, Thackray LB, Gitlin L, Gilfillan S, Virgin HW, Colonna M. MDA-5 recognition of a murine norovirus. PLoS pathogens. 2008; 4:e1000108. [PubMed: 18636103]

91. Jung K, et al. The effects of simvastatin or interferon-alpha on infectivity of human norovirus using a gnotobiotic pig model for the study of antivirals. PloS one. 2012; 7:e41619. [PubMed: 22911825]

92. Thackray LB, et al. Critical role for interferon regulatory factor 3 (IRF-3) and IRF-7 in type I interferon-mediated control of murine norovirus replication. Journal of virology. 2012; 86:13515–13523. [PubMed: 23035219]

93. Lazear HM, et al. IRF-3, IRF-5, and IRF-7 coordinately regulate the type I IFN response in myeloid dendritic cells downstream of MAVS signaling. PLoS pathogens. 2013; 9:e1003118. [PubMed: 23300459]

94. Karst SM, Wobus CE, Lay M, Davidson J, Virgin HWt. STAT1-dependent innate immunity to a Norwalk-like virus. Science. 2003; 299:1575–1578. [PubMed: 12624267]

95. Wobus CE, et al. Replication of Norovirus in cell culture reveals a tropism for dendritic cells and macrophages. PLoS biology. 2004; 2:e432. [PubMed: 15562321]

96. Changotra H, et al. Type I and type II interferons inhibit the translation of murine norovirus proteins. Journal of virology. 2009; 83:5683–5692. [PubMed: 19297466]

97. Mumphrey SM, et al. Murine norovirus 1 infection is associated with histopathological changes in immunocompetent hosts, but clinical disease is prevented by STAT1-dependent interferon responses. Journal of virology. 2007; 81:3251–3263. [PubMed: 17229692]

98. Hubbard VM, Cadwell K. Viruses, autophagy genes, and Crohn's disease. Viruses. 2011; 3:1281–1311. [PubMed: 21994779]

99. Cadwell K, et al. A key role for autophagy and the autophagy gene Atg16l1 in mouse and human intestinal Paneth cells. Nature. 2008; 456:259–263. [PubMed: 18849966]

100. Cadwell K, Patel KK, Komatsu M, Virgin HWt, Stappenbeck TS. A common role for Atg16L1, Atg5 and Atg7 in small intestinal Paneth cells and Crohn disease. Autophagy. 2009; 5:250–252. [PubMed: 19139628]

101. Cadwell K, et al. Virus-plus-susceptibility gene interaction determines Crohn's disease gene Atg16L1 phenotypes in intestine. Cell. 2010; 141:1135–1145. [PubMed: 20602997]

102. Kim YG, et al. Viral infection augments Nod1/2 signaling to potentiate lethality associated with secondary bacterial infections. Cell host & microbe. 2011; 9:496–507. [PubMed: 21669398]

103. Sherry B. Rotavirus and reovirus modulation of the interferon response. Journal of interferon & cytokine research : the official journal of the International Society for Interferon and Cytokine Research. 2009; 29:559–567.

104. Hua J, Chen X, Patton JT. Deletion mapping of the rotavirus metalloprotein NS53 (NSP1): the conserved cysteine-rich region is essential for virus-specific RNA binding. Journal of virology. 1994; 68:3990–4000. [PubMed: 8189533]

105. Barro M, Patton JT. Rotavirus NSP1 inhibits expression of type I interferon by antagonizing the function of interferon regulatory factors IRF3, IRF5, and IRF7. Journal of virology. 2007; 81:4473–4481. [PubMed: 17301153]

106. Arnold MM, Patton JT. Diversity of interferon antagonist activities mediated by NSP1 proteins of different rotavirus strains. Journal of virology. 2011; 85:1970–1979. [PubMed: 21177809]

107. Arnold MM, Barro M, Patton JT. Rotavirus NSP1 mediates degradation of interferon regulatory factors through targeting of the dimerization domain. Journal of virology. 2013; 87:9813–9821. [PubMed: 23824805]

108. Graff JW, Ettayebi K, Hardy ME. Rotavirus NSP1 inhibits NFkappaB activation by inducing proteasome-dependent degradation of beta-TrCP: a novel mechanism of IFN antagonism. PLoS pathogens. 2009; 5:e1000280. [PubMed: 19180189]

109. Silvestri LS, Taraporewala ZF, Patton JT. Rotavirus replication: plus-sense templates for double-stranded RNA synthesis are made in viroplasms. Journal of virology. 2004; 78:7763–7774. [PubMed: 15220450]
110. Holloway G, Truong TT, Coulson BS. Rotavirus antagonizes cellular antiviral responses by inhibiting the nuclear accumulation of STAT1, STAT2, and NF-kappaB. Journal of virology. 2009; 83:4942–4951. [PubMed: 19244315]
111. Sen A, Rott L, Phan N, Mukherjee G, Greenberg HB. Rotavirus NSP1 protein inhibits interferon-mediated STAT1 activation. Journal of virology. 2014; 88:41–53. [PubMed: 24131713]
112. Zhang R, et al. Homologous 2′,5′-phosphodiesterases from disparate RNA viruses antagonize antiviral innate immunity. Proceedings of the National Academy of Sciences of the United States of America. 2013; 110:13114–13119. [PubMed: 23878220]
113. Zurney J, Kobayashi T, Holm GH, Dermody TS, Sherry B. Reovirus mu2 protein inhibits interferon signaling through a novel mechanism involving nuclear accumulation of interferon regulatory factor 9. Journal of virology. 2009; 83:2178–2187. [PubMed: 19109390]
114. Yue Z, Shatkin AJ. Double-stranded RNA-dependent protein kinase (PKR) is regulated by reovirus structural proteins. Virology. 1997; 234:364–371. [PubMed: 9268168]
115. Shmulevitz M, Pan LZ, Garant K, Pan D, Lee PW. Oncogenic Ras promotes reovirus spread by suppressing IFN-beta production through negative regulation of RIG-I signaling. Cancer research. 2010; 70:4912–4921. [PubMed: 20501842]
116. Hirasawa K, Nishikawa SG, Norman KL, Alain T, Kossakowska A, Lee PW. Oncolytic reovirus against ovarian and colon cancer. Cancer research. 2002; 62:1696–1701. [PubMed: 11912142]
117. McFadden N, et al. Norovirus regulation of the innate immune response and apoptosis occurs via the product of the alternative open reading frame 4. PLoS pathogens. 2011; 7:e1002413. [PubMed: 22174679]
118. Ablasser A, Bauernfeind F, Hartmann G, Latz E, Fitzgerald KA, Hornung V. RIG-I-dependent sensing of poly (dA:dT) through the induction of an RNA polymerase III-transcribed RNA intermediate. Nature immunology. 2009; 10:1065–1072. [PubMed: 19609254]
119. Takaoka A, et al. DAI (DLM-1/ZBP1) is a cytosolic DNA sensor and an activator of innate immune response. Nature. 2007; 448:501–505. [PubMed: 17618271]
120. Wang Z, et al. Regulation of innate immune responses by DAI (DLM-1/ZBP1) and other DNA-sensing molecules. Proceedings of the National Academy of Sciences of the United States of America. 2008; 105:5477–5482. [PubMed: 18375758]
121. Ishikawa H, Barber GN. STING is an endoplasmic reticulum adaptor that facilitates innate immune signalling. Nature. 2008; 455:674–678. [PubMed: 18724357]
122. Zhong B, et al. The adaptor protein MITA links virus-sensing receptors to IRF3 transcription factor activation. Immunity. 2008; 29:538–550. [PubMed: 18818105]
123. Sun W, et al. ERIS, an endoplasmic reticulum IFN stimulator, activates innate immune signaling through dimerization. Proceedings of the National Academy of Sciences of the United States of America. 2009; 106:8653–8658. [PubMed: 19433799]
124. Park JH, et al. RICK/RIP2 mediates innate immune responses induced through Nod1 and Nod2 but not TLRs. Journal of immunology. 2007; 178:2380–2386.
125. Leber JH, Crimmins GT, Raghavan S, Meyer-Morse NP, Cox JS, Portnoy DA. Distinct TLR- and NLR-mediated transcriptional responses to an intracellular pathogen. PLoS pathogens. 2008; 4:e6. [PubMed: 18193943]
126. O'Riordan M, Yi CH, Gonzales R, Lee KD, Portnoy DA. Innate recognition of bacteria by a macrophage cytosolic surveillance pathway. Proceedings of the National Academy of Sciences of the United States of America. 2002; 99:13861–13866. [PubMed: 12359878]
127. Reimer T, Schweizer M, Jungi TW. Type I IFN induction in response to Listeria monocytogenes in human macrophages: evidence for a differential activation of IFN regulatory factor 3 (IRF3). Journal of immunology. 2007; 179:1166–1177.
128. Sing A, et al. Bacterial induction of beta interferon in mice is a function of the lipopolysaccharide component. Infection and immunity. 2000; 68:1600–1607. [PubMed: 10678979]
129. Pamer EG. Immune responses to Listeria monocytogenes. Nature reviews Immunology. 2004; 4:812–823.

130. Guiney DG. The role of host cell death in Salmonella infections. Current topics in microbiology and immunology. 2005; 289:131–150. [PubMed: 15791954]
131. Gaillard JL, Berche P, Frehel C, Gouin E, Cossart P. Entry of L. monocytogenes into cells is mediated by internalin, a repeat protein reminiscent of surface antigens from gram-positive cocci. Cell. 1991; 65:1127–1141. [PubMed: 1905979]
132. Pentecost M, Otto G, Theriot JA, Amieva MR. Listeria monocytogenes invades the epithelial junctions at sites of cell extrusion. PLoS pathogens. 2006; 2:e3. [PubMed: 16446782]
133. Nikitas G, Deschamps C, Disson O, Niault T, Cossart P, Lecuit M. Transcytosis of Listeria monocytogenes across the intestinal barrier upon specific targeting of goblet cell accessible E-cadherin. The Journal of experimental medicine. 2011; 208:2263–2277. [PubMed: 21967767]
134. Kernbauer E, Maier V, Rauch I, Muller M, Decker T. Route of Infection Determines the Impact of Type I Interferons on Innate Immunity to. PloS one. 2013; 8:e65007. [PubMed: 23840314]
135. Ishikawa H, Ma Z, Barber GN. STING regulates intracellular DNA-mediated, type I interferon-dependent innate immunity. Nature. 2009; 461:788–792. [PubMed: 19776740]
136. Abdullah Z, et al. RIG-I detects infection with live Listeria by sensing secreted bacterial nucleic acids. The EMBO journal. 2012; 31:4153–4164. [PubMed: 23064150]
137. Hagmann CA, et al. RIG-I detects triphosphorylated RNA of Listeria monocytogenes during infection in non-immune cells. PloS one. 2013; 8:e62872. [PubMed: 23653683]
138. Woodward JJ, Iavarone AT, Portnoy DA. c-di-AMP secreted by intracellular Listeria monocytogenes activates a host type I interferon response. Science. 2010; 328:1703–1705. [PubMed: 20508090]
139. Parvatiyar K, et al. The helicase DDX41 recognizes the bacterial secondary messengers cyclic di-GMP and cyclic di-AMP to activate a type I interferon immune response. Nature immunology. 2012; 13:1155–1161. [PubMed: 23142775]
140. Stockinger S, et al. IFN regulatory factor 3-dependent induction of type I IFNs by intracellular bacteria is mediated by a TLR- and Nod2-independent mechanism. Journal of immunology. 2004; 173:7416–7425.
141. O'Connell RM, Vaidya SA, Perry AK, Saha SK, Dempsey PW, Cheng G. Immune activation of type I IFNs by Listeria monocytogenes occurs independently of TLR4, TLR2, and receptor interacting protein 2 but involves TNFR-associated NF kappa B kinase-binding kinase 1. Journal of immunology. 2005; 174:1602–1607.
142. Stockinger S, Decker T. Novel functions of type I interferons revealed by infection studies with Listeria monocytogenes. Immunobiology. 2008; 213:889–897. [PubMed: 18926303]
143. Aubry C, et al. Both TLR2 and TRIF contribute to interferon-beta production during Listeria infection. PloS one. 2012; 7:e33299. [PubMed: 22432012]
144. Auerbuch V, Brockstedt DG, Meyer-Morse N, O'Riordan M, Portnoy DA. Mice lacking the type I interferon receptor are resistant to Listeria monocytogenes. The Journal of experimental medicine. 2004; 200:527–533. [PubMed: 15302899]
145. Carrero JA, Calderon B, Unanue ER. Type I interferon sensitizes lymphocytes to apoptosis and reduces resistance to Listeria infection. The Journal of experimental medicine. 2004; 200:535–540. [PubMed: 15302900]
146. O'Connell RM, et al. Type I interferon production enhances susceptibility to Listeria monocytogenes infection. The Journal of experimental medicine. 2004; 200:437–445. [PubMed: 15302901]
147. Carrero JA, Calderon B, Unanue ER. Lymphocytes are detrimental during the early innate immune response against Listeria monocytogenes. The Journal of experimental medicine. 2006; 203:933–940. [PubMed: 16549598]
148. Dai WJ, Kohler G, Brombacher F. Both innate and acquired immunity to Listeria monocytogenes infection are increased in IL-10-deficient mice. Journal of immunology. 1997; 158:2259–2267.
149. Rayamajhi M, Humann J, Penheiter K, Andreasen K, Lenz LL. Induction of IFN-alphabeta enables Listeria monocytogenes to suppress macrophage activation by IFN-gamma. The Journal of experimental medicine. 2010; 207:327–337. [PubMed: 20123961]
150. Henry T, et al. Type I IFN signaling constrains IL-17A/F secretion by gammadelta T cells during bacterial infections. Journal of immunology. 2010; 184:3755–3767.

151. Iwakura Y, Nakae S, Saijo S, Ishigame H. The roles of IL-17A in inflammatory immune responses and host defense against pathogens. Immunological reviews. 2008; 226:57–79. [PubMed: 19161416]

152. Archer KA, Durack J, Portnoy DA. STING-dependent type I IFN production inhibits cell-mediated immunity to Listeria monocytogenes. PLoS pathogens. 2014; 10:e1003861. [PubMed: 24391507]

153. Wollert T, et al. Extending the host range of Listeria monocytogenes by rational protein design. Cell. 2007; 129:891–902. [PubMed: 17540170]

154. Henry T, Brotcke A, Weiss DS, Thompson LJ, Monack DM. Type I interferon signaling is required for activation of the inflammasome during Francisella infection. The Journal of experimental medicine. 2007; 204:987–994. [PubMed: 17452523]

155. Sauer JD, Witte CE, Zemansky J, Hanson B, Lauer P, Portnoy DA. Listeria monocytogenes triggers AIM2-mediated pyroptosis upon infrequent bacteriolysis in the macrophage cytosol. Cell host & microbe. 2010; 7:412–419. [PubMed: 20417169]

156. Jones JW, et al. Absent in melanoma 2 is required for innate immune recognition of Francisella tularensis. Proceedings of the National Academy of Sciences of the United States of America. 2010; 107:9771–9776. [PubMed: 20457908]

157. Jia T, Leiner I, Dorothee G, Brandl K, Pamer EG. MyD88 and Type I interferon receptor-mediated chemokine induction and monocyte recruitment during Listeria monocytogenes infection. Journal of immunology. 2009; 183:1271–1278.

158. Lindgren SW, Stojiljkovic I, Heffron F. Macrophage killing is an essential virulence mechanism of Salmonella typhimurium. Proceedings of the National Academy of Sciences of the United States of America. 1996; 93:4197–4201. [PubMed: 8633040]

159. Farache J, et al. Luminal bacteria recruit CD103+ dendritic cells into the intestinal epithelium to sample bacterial antigens for presentation. Immunity. 2013; 38:581–595. [PubMed: 23395676]

160. Uematsu S, et al. Detection of pathogenic intestinal bacteria by Toll-like receptor 5 on intestinal CD11c+ lamina propria cells. Nature immunology. 2006; 7:868–874. [PubMed: 16829963]

161. Arpaia N, et al. TLR signaling is required for Salmonella typhimurium virulence. Cell. 2011; 144:675–688. [PubMed: 21376231]

162. Broz P, Newton K, Lamkanfi M, Mariathasan S, Dixit VM, Monack DM. Redundant roles for inflammasome receptors NLRP3 and NLRC4 in host defense against Salmonella. The Journal of experimental medicine. 2010; 207:1745–1755. [PubMed: 20603313]

163. Franchi L, et al. Cytosolic flagellin requires Ipaf for activation of caspase-1 and interleukin 1beta in salmonella-infected macrophages. Nature immunology. 2006; 7:576–582. [PubMed: 16648852]

164. Miao EA, et al. Cytoplasmic flagellin activates caspase-1 and secretion of interleukin 1beta via Ipaf. Nature immunology. 2006; 7:569–575. [PubMed: 16648853]

165. Raupach B, Peuschel SK, Monack DM, Zychlinsky A. Caspase-1-mediated activation of interleukin-1beta (IL-1beta) and IL-18 contributes to innate immune defenses against Salmonella enterica serovar Typhimurium infection. Infection and immunity. 2006; 74:4922–4926. [PubMed: 16861683]

166. Broz P, et al. Caspase-11 increases susceptibility to Salmonella infection in the absence of caspase-1. Nature. 2012; 490:288–291. [PubMed: 22895188]

167. Lara-Tejero M, et al. Role of the caspase-1 inflammasome in Salmonella typhimurium pathogenesis. The Journal of experimental medicine. 2006; 203:1407–1412. [PubMed: 16717117]

168. Freudenberg MA, Merlin T, Kalis C, Chvatchko Y, Stubig H, Galanos C. Cutting edge: a murine, IL-12-independent pathway of IFN-gamma induction by gram-negative bacteria based on STAT4 activation by Type I IFN and IL-18 signaling. Journal of immunology. 2002; 169:1665–1668.

169. Robinson N, McComb S, Mulligan R, Dudani R, Krishnan L, Sad S. Type I interferon induces necroptosis in macrophages during infection with Salmonella enterica serovar Typhimurium. Nature immunology. 2012; 13:954–962. [PubMed: 22922364]

170. Chang EY, Guo B, Doyle SE, Cheng G. Cutting edge: involvement of the type I IFN production and signaling pathway in lipopolysaccharide-induced IL-10 production. Journal of immunology. 2007; 178:6705–6709.

171. Fitzgerald DC, et al. Independent and interdependent immunoregulatory effects of IL-27, IFN-beta, and IL-10 in the suppression of human Th17 cells and murine experimental autoimmune encephalomyelitis. Journal of immunology. 2013; 190:3225–3234.

172. Molnarfi N, Hyka-Nouspikel N, Gruaz L, Dayer JM, Burger D. The production of IL-1 receptor antagonist in IFN-beta-stimulated human monocytes depends on the activation of phosphatidylinositol 3-kinase but not of STAT1. Journal of immunology. 2005; 174:2974–2980.

173. Dalod M, et al. Interferon alpha/beta and interleukin 12 responses to viral infections: pathways regulating dendritic cell cytokine expression in vivo. The Journal of experimental medicine. 2002; 195:517–528. [PubMed: 11854364]

174. Rothlin CV, Ghosh S, Zuniga EI, Oldstone MB, Lemke G. TAM receptors are pleiotropic inhibitors of the innate immune response. Cell. 2007; 131:1124–1136. [PubMed: 18083102]

175. Shinohara ML, Kim JH, Garcia VA, Cantor H. Engagement of the type I interferon receptor on dendritic cells inhibits T helper 17 cell development: role of intracellular osteopontin. Immunity. 2008; 29:68–78. [PubMed: 18619869]

176. Ramgolam VS, Sha Y, Jin J, Zhang X, Markovic-Plese S. IFN-beta inhibits human Th17 cell differentiation. Journal of immunology. 2009; 183:5418–5427.

177. Guo B, Chang EY, Cheng G. The type I IFN induction pathway constrains Th17-mediated autoimmune inflammation in mice. The Journal of clinical investigation. 2008; 118:1680–1690. [PubMed: 18382764]

178. Swiecki M, Wang Y, Vermi W, Gilfillan S, Schreiber RD, Colonna M. Type I interferon negatively controls plasmacytoid dendritic cell numbers in vivo. The Journal of experimental medicine. 2011; 208:2367–2374. [PubMed: 22084408]

179. Teijaro JR, et al. Persistent LCMV infection is controlled by blockade of type I interferon signaling. Science. 2013; 340:207–211. [PubMed: 23580529]

180. Wilson EB, et al. Blockade of chronic type I interferon signaling to control persistent LCMV infection. Science. 2013; 340:202–207. [PubMed: 23580528]

181. Muller U, et al. Functional role of type I and type II interferons in antiviral defense. Science. 1994; 264:1918–1921. [PubMed: 8009221]

182. Tishon A, Lewicki H, Rall G, Von Herrath M, Oldstone MB. An essential role for type 1 interferon-gamma in terminating persistent viral infection. Virology. 1995; 212:244–250. [PubMed: 7676639]

183. Ling PD, Warren MK, Vogel SN. Antagonistic effect of interferon-beta on the interferon-gamma-induced expression of Ia antigen in murine macrophages. Journal of immunology. 1985; 135:1857–1863.

184. Yoshida R, Murray HW, Nathan CF. Agonist and antagonist effects of interferon alpha and beta on activation of human macrophages. Two classes of interferon gamma receptors and blockade of the high-affinity sites by interferon alpha or beta. The Journal of experimental medicine. 1988; 167:1171–1185. [PubMed: 2965208]

185. Richter K, et al. Macrophage and T cell produced IL-10 promotes viral chronicity. PLoS pathogens. 2013; 9:e1003735. [PubMed: 24244162]

186. Fraietta JA, et al. Type I interferon upregulates Bak and contributes to T cell loss during human immunodeficiency virus (HIV) infection. PLoS pathogens. 2013; 9:e1003658. [PubMed: 24130482]

187. Kulpa DA, Lawani M, Cooper A, Peretz Y, Ahlers J, Sekaly RP. PD-1 coinhibitory signals: the link between pathogenesis and protection. Seminars in immunology. 2013; 25:219–227. [PubMed: 23548749]

188. McNab FW, et al. TPL-2-ERK1/2 signaling promotes host resistance against intracellular bacterial infection by negative regulation of type I IFN production. Journal of immunology. 2013; 191:1732–1743.

189. Redford PS, et al. Influenza A virus impairs control of Mycobacterium tuberculosis coinfection through a type I interferon receptor-dependent pathway. The Journal of infectious diseases. 2014; 209:270–274. [PubMed: 23935205]

190. Teles RM, et al. Type I interferon suppresses type II interferon-triggered human anti-mycobacterial responses. Science. 2013; 339:1448–1453. [PubMed: 23449998]

191. Berry MP, et al. An interferon-inducible neutrophil-driven blood transcriptional signature in human tuberculosis. Nature. 2010; 466:973–977. [PubMed: 20725040]

192. McNab FW, et al. Programmed death ligand 1 is over-expressed by neutrophils in the blood of patients with active tuberculosis. European journal of immunology. 2011; 41:1941–1947. [PubMed: 21509782]

193. Littman DR, Pamer EG. Role of the commensal microbiota in normal and pathogenic host immune responses. Cell host & microbe. 2011; 10:311–323. [PubMed: 22018232]

194. Honda K, Littman DR. The microbiome in infectious disease and inflammation. Annual review of immunology. 2012; 30:759–795.

195. Gresser I, Belardelli F. Endogenous type I interferons as a defense against tumors. Cytokine & growth factor reviews. 2002; 13:111–118. [PubMed: 11900987]

196. Lienenklaus S, et al. Novel reporter mouse reveals constitutive and inflammatory expression of IFN-beta in vivo. Journal of immunology. 2009; 183:3229–3236.

197. Munakata K, et al. Importance of the interferon-alpha system in murine large intestine indicated by microarray analysis of commensal bacteria-induced immunological changes. BMC genomics. 2008; 9:192. [PubMed: 18439305]

198. Chirdo FG, Millington OR, Beacock-Sharp H, Mowat AM. Immunomodulatory dendritic cells in intestinal lamina propria. European journal of immunology. 2005; 35:1831–1840. [PubMed: 16010704]

199. Lucas M, Schachterle W, Oberle K, Aichele P, Diefenbach A. Dendritic cells prime natural killer cells by trans-presenting interleukin 15. Immunity. 2007; 26:503–517. [PubMed: 17398124]

200. Mattei F, Schiavoni G, Belardelli F, Tough DF. IL-15 is expressed by dendritic cells in response to type I IFN, double-stranded RNA, or lipopolysaccharide and promotes dendritic cell activation. Journal of immunology. 2001; 167:1179–1187.

201. Yamamoto M, et al. A microarray analysis of gnotobiotic mice indicating that microbial exposure during the neonatal period plays an essential role in immune system development. BMC genomics. 2012; 13:335. [PubMed: 22823934]

202. Kawashima T, et al. Double-stranded RNA of intestinal commensal but not pathogenic bacteria triggers production of protective interferon-beta. Immunity. 2013; 38:1187–1197. [PubMed: 23791646]

203. Rachmilewitz D, et al. Immunostimulatory DNA ameliorates experimental and spontaneous murine colitis. Gastroenterology. 2002; 122:1428–1441. [PubMed: 11984528]

204. Rachmilewitz D, et al. Toll-like receptor 9 signaling mediates the anti-inflammatory effects of probiotics in murine experimental colitis. Gastroenterology. 2004; 126:520–528. [PubMed: 14762789]

205. Rachmilewitz D, Karmeli F, Shteingart S, Lee J, Takabayashi K, Raz E. Immunostimulatory oligonucleotides inhibit colonic proinflammatory cytokine production in ulcerative colitis. Inflammatory bowel diseases. 2006; 12:339–345. [PubMed: 16670522]

206. Katakura K, Lee J, Rachmilewitz D, Li G, Eckmann L, Raz E. Toll-like receptor 9-induced type I IFN protects mice from experimental colitis. The Journal of clinical investigation. 2005; 115:695–702. [PubMed: 15765149]

207. Abe K, et al. Conventional dendritic cells regulate the outcome of colonic inflammation independently of T cells. Proceedings of the National Academy of Sciences of the United States of America. 2007; 104:17022–17027. [PubMed: 17942668]

208. McFarland AP, et al. Localized delivery of interferon-beta by Lactobacillus exacerbates experimental colitis. PloS one. 2011; 6:e16967. [PubMed: 21365015]

209. Sainathan SK, et al. Granulocyte macrophage colony-stimulating factor ameliorates DSS-induced experimental colitis. Inflammatory bowel diseases. 2008; 14:88–99. [PubMed: 17932977]

210. Sainathan SK, et al. Toll-like receptor-7 ligand Imiquimod induces type I interferon and antimicrobial peptides to ameliorate dextran sodium sulfate-induced acute colitis. Inflammatory bowel diseases. 2012; 18:955–967. [PubMed: 21953855]
211. Vijay-Kumar M, et al. Activation of toll-like receptor 3 protects against DSS-induced acute colitis. Inflammatory bowel diseases. 2007; 13:856–864. [PubMed: 17393379]
212. Hofmann C, et al. T cell-dependent protective effects of CpG motifs of bacterial DNA in experimental colitis are mediated by CD11c+ dendritic cells. Gut. 2010; 59:1347–1354. [PubMed: 20732920]
213. Bleich A, et al. CpG motifs of bacterial DNA exert protective effects in mouse models of IBD by antigen-independent tolerance induction. Gastroenterology. 2009; 136:278–287. [PubMed: 18952084]
214. Bilsborough J, George TC, Norment A, Viney JL. Mucosal CD8alpha+ DC, with a plasmacytoid phenotype, induce differentiation and support function of T cells with regulatory properties. Immunology. 2003; 108:481–492. [PubMed: 12667210]
215. Moseman EA, et al. Human plasmacytoid dendritic cells activated by CpG oligodeoxynucleotides induce the generation of CD4+CD25+ regulatory T cells. Journal of immunology. 2004; 173:4433–4442.
216. Radulovic K, et al. CD69 regulates type I IFN-induced tolerogenic signals to mucosal CD4 T cells that attenuate their colitogenic potential. Journal of immunology. 2012; 188:2001–2013.
217. Lee SE, et al. Type I interferons maintain Foxp3 expression and T-regulatory cell functions under inflammatory conditions in mice. Gastroenterology. 2012; 143:145–154. [PubMed: 22475534]
218. Hall JA, et al. Commensal DNA limits regulatory T cell conversion and is a natural adjuvant of intestinal immune responses. Immunity. 2008; 29:637–649. [PubMed: 18835196]
219. Bouladoux N, et al. Regulatory role of suppressive motifs from commensal DNA. Mucosal immunology. 2012; 5:623–634. [PubMed: 22617839]
220. Lee J, Rachmilewitz D, Raz E. Homeostatic effects of TLR9 signaling in experimental colitis. Annals of the New York Academy of Sciences. 2006; 1072:351–355. [PubMed: 17057215]
221. Lee J, et al. Maintenance of colonic homeostasis by distinctive apical TLR9 signalling in intestinal epithelial cells. Nature cell biology. 2006; 8:1327–1336. [PubMed: 17128265]
222. Mirpuri J, et al. Commensal Escherichia coli reduces epithelial apoptosis through IFN-alphaA-mediated induction of guanylate binding protein-1 in human and murine models of developing intestine. Journal of immunology. 2010; 184:7186–7195.
223. Tschurtschenthaler M, et al. Type I interferon signalling in the intestinal epithelium affects Paneth cells, microbial ecology and epithelial regeneration. Gut. 2014
224. Litinskiy MB, et al. DCs induce CD40-independent immunoglobulin class switching through BLyS and APRIL. Nature immunology. 2002; 3:822–829. [PubMed: 12154359]
225. Tezuka H, et al. Prominent role for plasmacytoid dendritic cells in mucosal T cell-independent IgA induction. Immunity. 2011; 34:247–257. [PubMed: 21333555]
226. Ichinohe T, et al. Microbiota regulates immune defense against respiratory tract influenza A virus infection. Proceedings of the National Academy of Sciences of the United States of America. 2011; 108:5354–5359. [PubMed: 21402903]
227. Abt MC, et al. Commensal bacteria calibrate the activation threshold of innate antiviral immunity. Immunity. 2012; 37:158–170. [PubMed: 22705104]
228. Ganal SC, et al. Priming of natural killer cells by nonmucosal mononuclear phagocytes requires instructive signals from commensal microbiota. Immunity. 2012; 37:171–186. [PubMed: 22749822]
229. Franke A, et al. Genome-wide meta-analysis increases to 71 the number of confirmed Crohn's disease susceptibility loci. Nature genetics. 2010; 42:1118–1125. [PubMed: 21102463]
230. Anderson CA, et al. Meta-analysis identifies 29 additional ulcerative colitis risk loci, increasing the number of confirmed associations to 47. Nature genetics. 2011; 43:246–252. [PubMed: 21297633]
231. Rivas MA, et al. Deep resequencing of GWAS loci identifies independent rare variants associated with inflammatory bowel disease. Nature genetics. 2011; 43:1066–1073. [PubMed: 21983784]

232. Jostins L, et al. Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease. Nature. 2012; 491:119–124. [PubMed: 23128233]

233. Beaudoin M, et al. Deep resequencing of GWAS loci identifies rare variants in CARD9, IL23R and RNF186 that are associated with ulcerative colitis. PLoS genetics. 2013; 9:e1003723. [PubMed: 24068945]

234. Brant SR. Promises, delivery, and challenges of inflammatory bowel disease risk gene discovery. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association. 2013; 11:22–26. [PubMed: 23131344]

235. Wang Y, et al. The autoimmunity-associated gene PTPN22 potentiates toll-like receptor-driven, type 1 interferon-dependent immunity. Immunity. 2013; 39:111–122. [PubMed: 23871208]

236. Cho JH, Brant SR. Recent insights into the genetics of inflammatory bowel disease. Gastroenterology. 2011; 140:1704–1712. [PubMed: 21530736]

237. Musch E, Andus T, Malek M, Chrissafidou A, Schulz M. Successful treatment of steroid refractory active ulcerative colitis with natural interferon-beta–an open long-term trial. Zeitschrift fur Gastroenterologie. 2007; 45:1235–1240. [PubMed: 18080224]

238. Madsen SM, et al. An open-labeled, randomized study comparing systemic interferon-alpha-2A and prednisolone enemas in the treatment of left-sided ulcerative colitis. The American journal of gastroenterology. 2001; 96:1807–1815. [PubMed: 11419834]

239. Nikolaus S, et al. Interferon beta-1a in ulcerative colitis: a placebo controlled, randomised, dose escalating study. Gut. 2003; 52:1286–1290. [PubMed: 12912859]

240. Mannon PJ, et al. Suppression of inflammation in ulcerative colitis by interferon-beta-1a is accompanied by inhibition of IL-13 production. Gut. 2011; 60:449–455. [PubMed: 20971977]

241. Kaser A, Molnar C, Tilg H. Differential regulation of interleukin 4 and interleukin 13 production by interferon alpha. Cytokine. 1998; 10:75–81. [PubMed: 9512896]

242. Gasche C, et al. Prospective evaluation of interferon-alpha in treatment of chronic active Crohn's disease. Digestive diseases and sciences. 1995; 40:800–804. [PubMed: 7720472]

243. Pena Rossi C, Hanauer SB, Tomasevic R, Hunter JO, Shafran I, Graffner H. Interferon beta-1a for the maintenance of remission in patients with Crohn's disease: results of a phase II dose-finding study. BMC gastroenterology. 2009; 9:22. [PubMed: 19302707]

244. Pena-Rossi C, et al. Clinical trial: a multicentre, randomized, double-blind, placebo-controlled, dose-finding, phase II study of subcutaneous interferon-beta-la in moderately active ulcerative colitis. Alimentary pharmacology & therapeutics. 2008; 28:758–767. [PubMed: 19145731]

245. Musch E, et al. Interferon-beta-1a for the treatment of steroid-refractory ulcerative colitis: a randomized, double-blind, placebo-controlled trial. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association. 2005; 3:581–586. [PubMed: 15952100]

246. Monteleone G, Pender SL, Wathen NC, MacDonald TT. Interferon-alpha drives T cell-mediated immunopathology in the intestine. European journal of immunology. 2001; 31:2247–2255. [PubMed: 11477536]

247. Di Sabatino A, et al. Evidence for the role of interferon-alfa production by dendritic cells in the Th1 response in celiac disease. Gastroenterology. 2007; 133:1175–1187. [PubMed: 17919493]

248. Donnelly RP, Kotenko SV. Interferon-lambda: a new addition to an old family. Journal of interferon & cytokine research : the official journal of the International Society for Interferon and Cytokine Research. 2010; 30:555–564.

249. Durbin RK, Kotenko SV, Durbin JE. Interferon induction and function at the mucosal surface. Immunological reviews. 2013; 255:25–39. [PubMed: 23947345]

250. Monteleone G, et al. Role of interferon alpha in promoting T helper cell type 1 responses in the small intestine in coeliac disease. Gut. 2001; 48:425–429. [PubMed: 11171837]

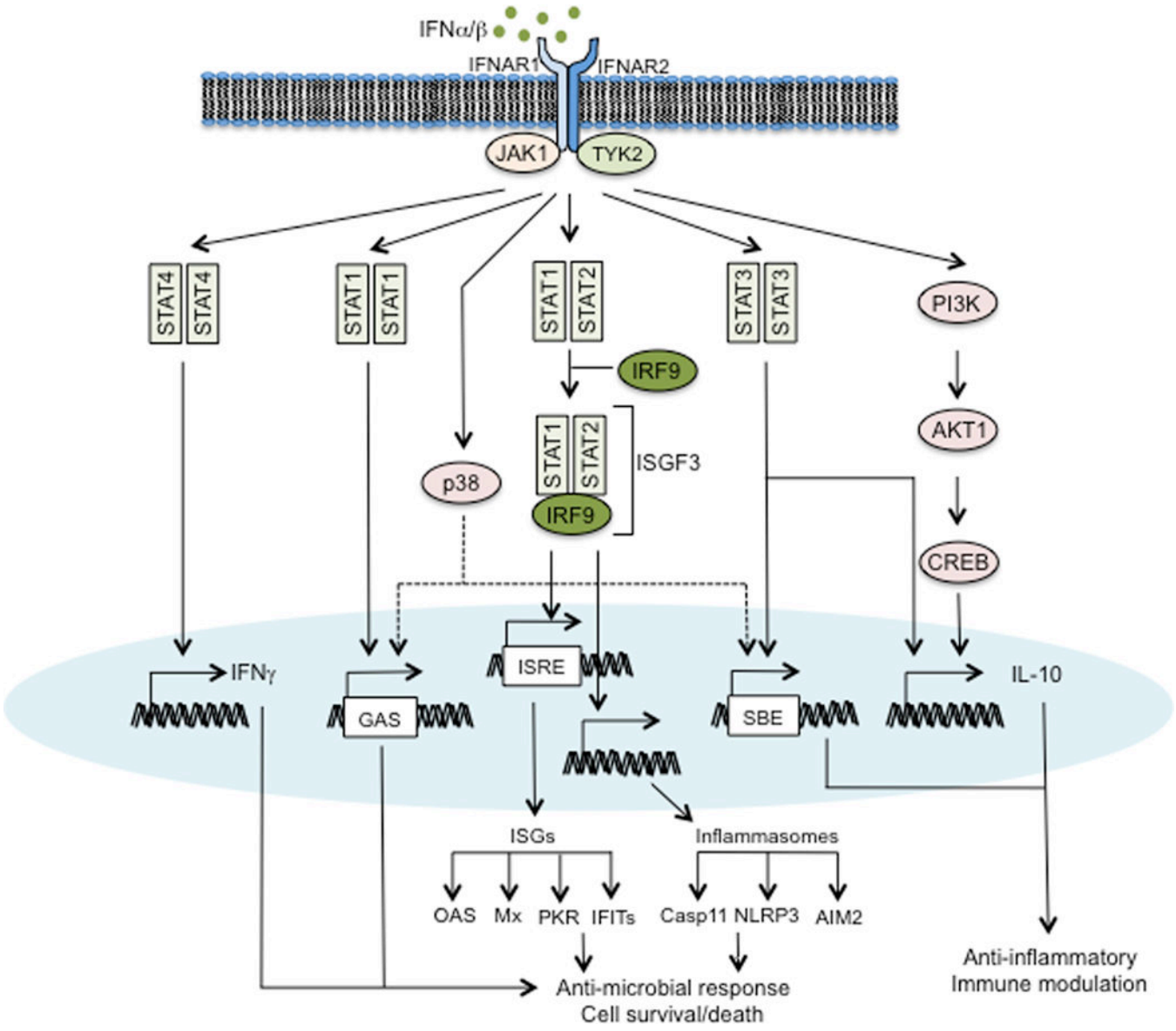

Fig. 1. IFN-I receptor-mediated signaling pathways

IFN-I binds to IFNAR receptor and activates JAK-STAT signaling pathways, resulting in formation of downstream transcriptional complexes such as STAT homodimers and heterodimers and ISGF3. These complexes bind to their corresponding DNA elements including ISRE, SBE, GAS, and the promoters of various immune modulatory genes. IFNAR signaling can also activate PI3K and a MAPK, p38. This leads to expression of ISGs such as PKR, OAS, and Mx and production of pro-inflammatory and anti-inflammatory cytokines, promoting antimicrobial defense and regulating immune responses. In addition, engagement of IFNAR results in priming expression of several inflammasome components such as non-canonical caspase-11, NLRP3, and AIM2. Furthermore, IFNAR signaling can modulate cell death such as apoptosis, pyroptosis, and necroptosis. CREB, cAMP-responsive element; GAS, IFNγ-activated site; SBE, STAT3-binding element.

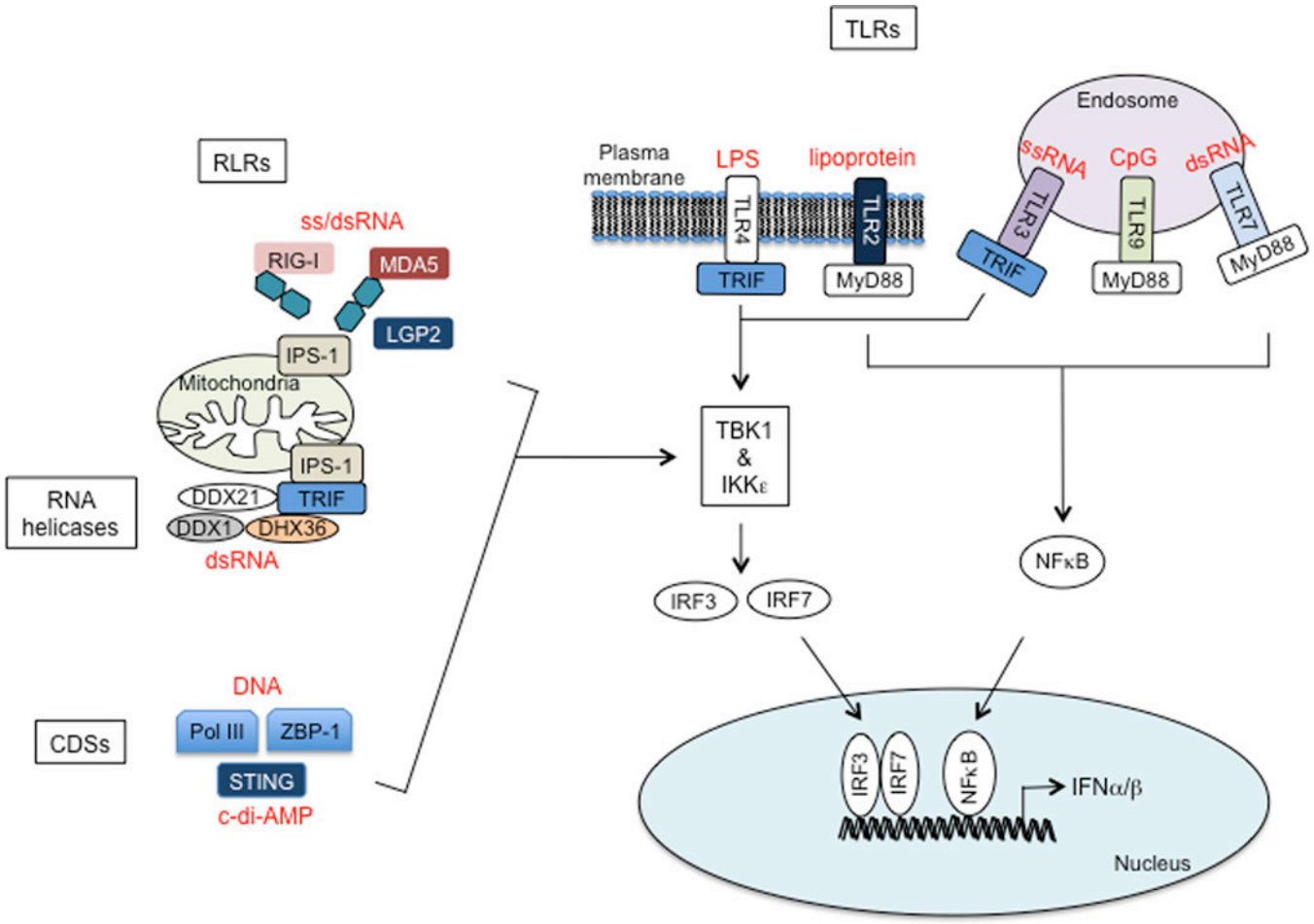

Fig. 2. Sensing of microbial products and induction of IFN-I

TLRs, RLRs, CDSs, and helicase complexes can sense PAMPs and MAMPs such as ss/dsRNA, DNA, LPS, and c-di-AMP. Engagement of these sensors converges on activation of IRF3 and IRF7 via the common downstream kinases, TBK1/IKKε in addition to NFκB activation. This leads to the production of IFN-I and other cytokines. The adapter protein IPS-1 (also called MAVS) is required for transferring signals from the RLRs and helicases to IRFs. CDSs, cytosolic DNA sensors; MAMPs, microbe-associated molecular patterns; MAVS, mitochondrial antiviral signaling protein; Pol III, RNA polymerase III; ZBP-1, Z-DNA-binding protein 1 (also called DAI, DNA-dependent activator of IFN-regulatory factors).

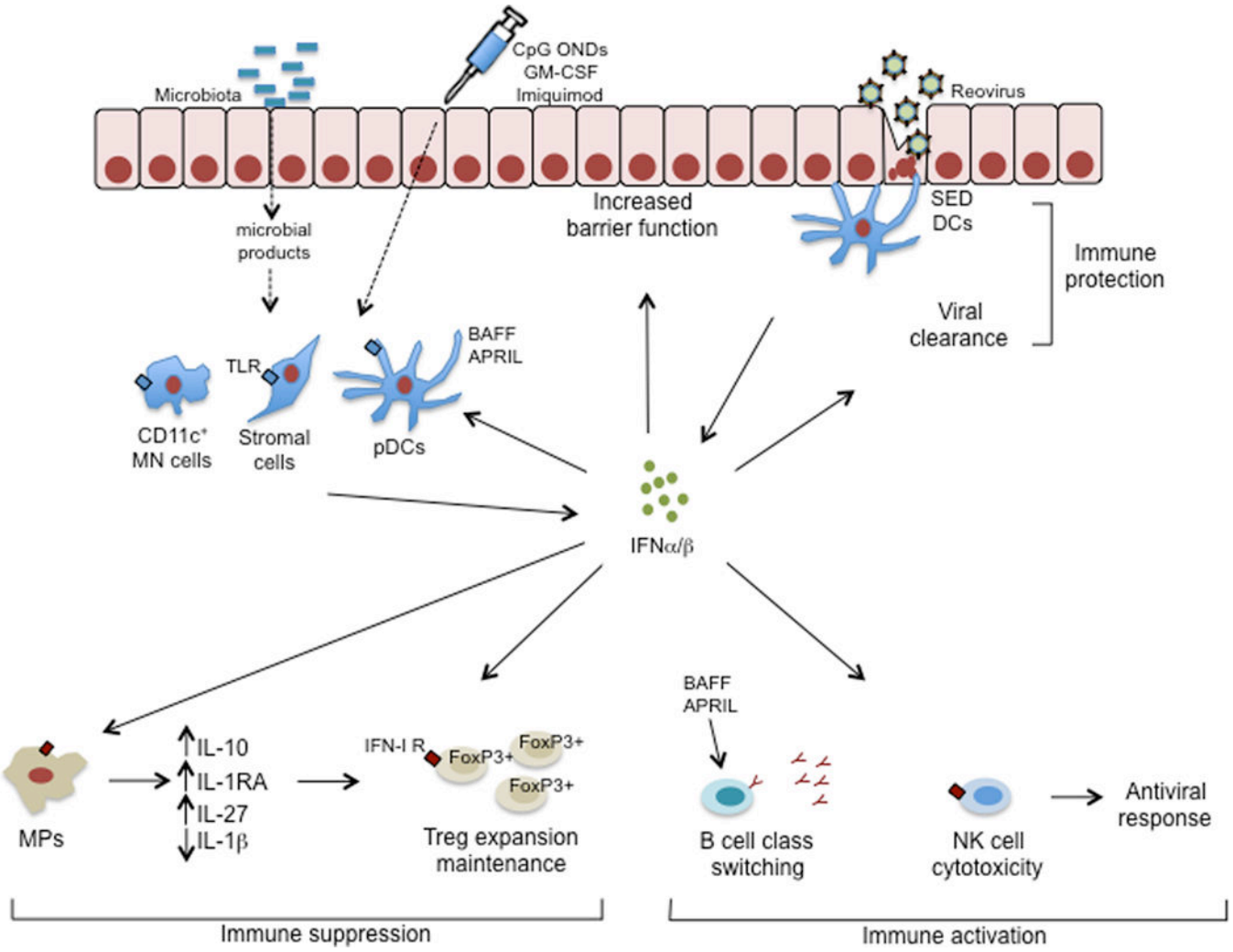

Fig. 3. IFN-I-mediated immune protection, activation, and suppression in the gut

TLR ligands such as CpG and Imiquimod, a cytokine GM-CSF, commensal microbiota, and pathogens are known to stimulate IFN-I production from DCs, pDCs, and stromal cells that reside in the gut and gut-associated lymphoid tissues (GALTs). Following reovirus infection, SED DC-derived IFN-I can protect animals by promoting viral clearance. IFN-I can also promote immunity by increasing T cell-independent IgA production in B cells via pDC-mediated production of APRIL and BAFF in addition to enhancing NK cell priming and antiviral immunity. In contrast, IFN-I is known to contribute to intestinal homeostasis via production of anti-inflammatory cytokines and Treg maintenance and expansion. GM-CSF, granulocyte-macrophage colony-stimulating factor; MN, mononuclear; SED, subepithelial dome.

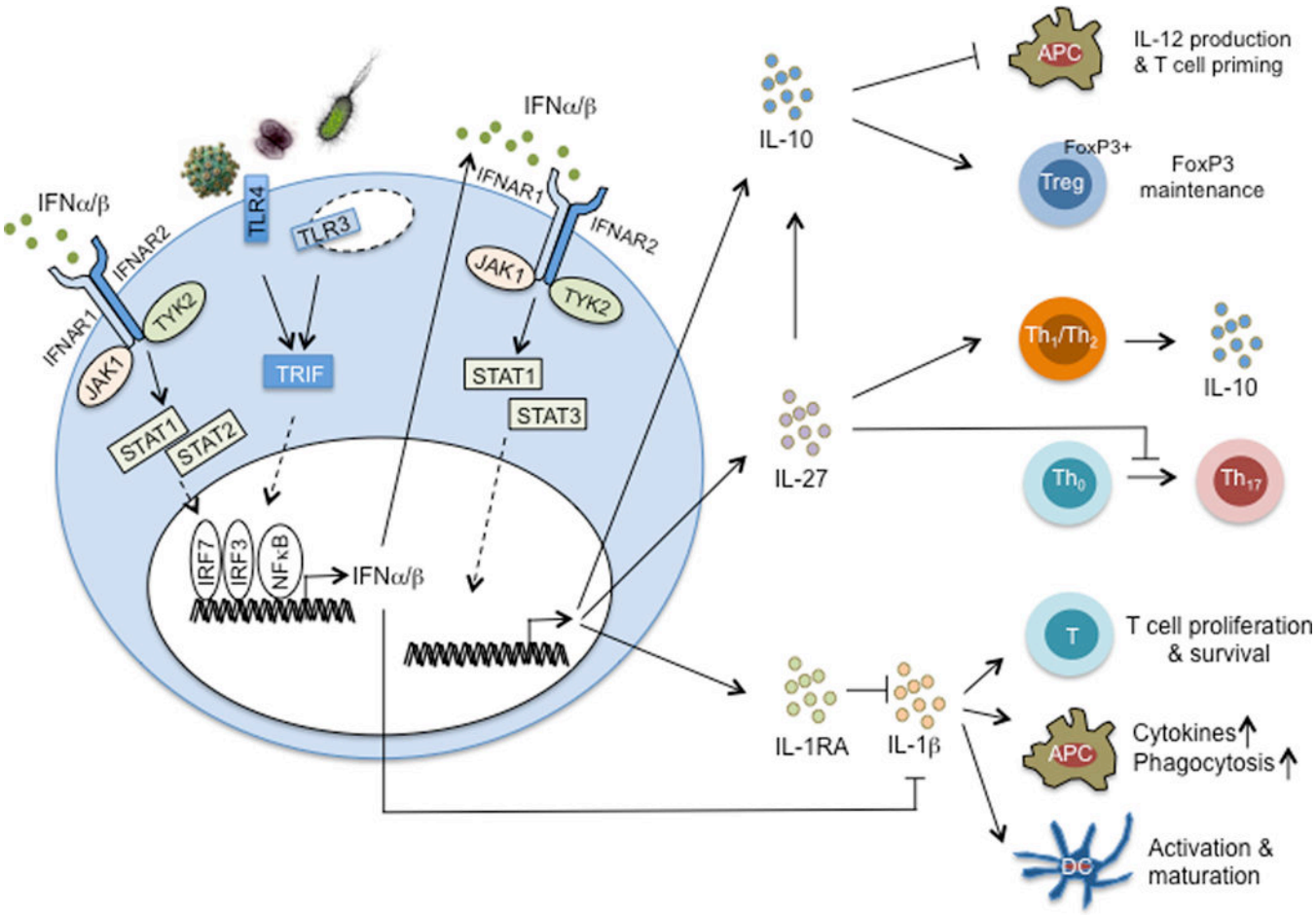

Fig. 4. A simplified working model of how IFN-I may contribute to the maintenance of intestinal immune homeostasis by affecting mononuclear phagocyte function

Products from commensal bacteria and/or viruses act via TRIF-dependent pathways together with autocrine IFNAR signaling to drive IFN-I production. Autocrine IFNAR signaling activates STAT1 and STAT3 to drive the production of anti-inflammatory cytokines, such as IL-10, IL-27, and IL-1RA. These cytokines each have downstream effects supported in the literature. IL-10 can inhibit APC/DC function by blocking T-cell priming and regulating the production of cytokines, such as IL-12, and can act to maintain Foxp3^{+} regulatory T cells in the *lamina propria*. IL-27 can help drive IL-10 production from mononuclear cells and T cells through STAT3 activation, and can inhibit Th17 differentiation. IL-1α and IL-1β can activate DCs, induce phagocytosis of and proinflamamtory cytokine production by monocyte/macrophages and recruited PMNs during inflammation, and can promote T-cell proliferation and survival. IFN-I can both suppress inflammasome activation and drive the production of IL-1RA leading to relative low IL-1 signaling, that may be important for maintaining intestinal macrophage function through effects on ILCs.