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No Love Lost Between Viruses and Interferons

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Abstract

The interferon system protects mammals against virus infections. There are several types of interferons, which are characterized by their ability to inhibit virus replication and resultant pathogenesis by triggering both innate and cell-mediated immune responses. Virus infection is sensed by a variety of cellular pattern-recognition receptors and triggers the synthesis of interferons, which are secreted by the infected cells. In uninfected cells, cell surface receptors recognize the secreted interferons and activate intracellular signaling pathways that induce the expression of interferon-stimulated genes; the proteins encoded by these genes inhibit different stages of virus replication. To avoid extinction, almost all viruses have evolved mechanisms to defend themselves against the interferon system. Consequently, a dynamic equilibrium of survival is established between the virus and its host, an equilibrium that can be shifted to the host's favor by the use of exogenous interferon as a therapeutic antiviral agent.

Keywords

virus infection; innate immunity; interferon-stimulated gene; pathogenesis; antiviral action; viral evasion; dsRNA; pattern-recognition receptor; interferon-λ

INTRODUCTION

Interferons (IFNs) are cytokines that act upon cells to impart resistance to virus replication. This property of the large family of IFN proteins was discovered by Isaacs and Lindenmann in 1957 (1). In general, virus infection triggers transient synthesis and secretion of IFNs to promote protection of as-yet-uninfected cells. IFNs induce the transcription of hundreds of IFN-stimulated genes (ISGs), whose protein products inhibit a variety of steps of virus replication (2). Specific ISG proteins are particularly effective against specific families of viruses, and optimal protection is achieved by the inhibition of more than one step of virus replication by different ISG proteins. Viruses have evolved many mechanisms to evade the antiviral actions of IFNs by blocking their synthesis and/or their actions (3). Thus, in vivo,

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the IFN system is the major mediator of the maintenance of host-virus homeostasis. In addition to their antiviral effects, IFNs affect other functional properties of cells, especially of the immune system; IFN activation of immune cells contributes to the inhibition of viral pathogenesis (4). This article focuses on the antiviral actions of IFNs, especially those mediated by the cell-intrinsic actions of ISG proteins.

INTERFERON CLASSIFICATION AND RECENT DISCOVERIES OF NOVEL INTERFERONS

The classification of IFNs is based on the cell surface receptors to which they bind, to activate intracellular signaling pathways. Type I, II, and III IFNs are distinguished by their distinct IFN receptor complexes (Figure 1) (5). Type I IFNs signal through the dimeric IFN-α/β receptor (IFNAR), consisting of IFNAR1 and IFNAR2; the type I IFNs comprise more than 10 subtypes of IFN-α, named IFN-α1, -α2, etc.; IFN-β, -κ, -ω, -ε; and limitin. Type II IFNs bind to the tetrameric IFN-γ receptor (IFNGR), consisting of two subunits each of IFNGR1 and IFNGR2; IFN-γ is the only known type II IFN. Type III IFNs, comprising IFN-λ1, -λ2, -λ3, and -λ4, trigger the IFN-λ receptor (IFNLR), a heterodimer of IFNLR1 and IL10RB (5–7).

The biological responses to the three IFN types overlap in some aspects, such as their ability to inhibit virus replication in infected cells, but many effects of type I, II, and III IFN signaling are distinct, especially in vivo. These differences are largely based on two properties (Figure 1). First, the expression of an IFN or its cognate receptor is cell type or tissue specific; not all IFNs and all receptors are produced by all cells. Among type I IFNs, plasmacytoid dendritic cells (pDCs) are the dominant IFN-α producers in vivo after microbial infection, whereas IFN-ε is synthesized constitutively in the female reproductive tract (8–10). Whereas IFNAR is ubiquitously expressed, only cells of epithelial origin, as well as a few others, such as hepatocytes, have the ability to respond to type III IFNs (IFN-λ), because they express both IFNLR subunits (11–13). Type II IFNs (IFN-γ) are synthesized by cells of the immune system, mainly natural killer cells, natural killer T cells, B cells, and antigen-presenting cells (5). Such cell type–restricted expression allows for localized, targeted IFN effects and prevents uncontrolled systemic inflammation. Second, different IFN types activate different transcription factors to induce different groups of ISGs (14). These large sets of genes only partially overlap between IFNAR, IFNLR, and IFNGR. IFNAR and IFNLR, although unrelated, use the same intracellular signaling pathway to activate the transcription factor complex ISG factor 3 (ISGF3), and they therefore induce similar sets of genes (15). IFNGR, however, activates the transcription factor gamma-activated factor (GAF), which induces different genes (14, 16). Depending on the cell type, IFNAR signaling triggers activation of additional transcription factors, leading to further differentiation of IFN responses via differential induction of specific ISGs (17).

Type I and II IFNs and their receptors were cloned and sequenced in the late 1980s (18), and enormous research efforts have since elucidated the details of their signaling pathways. IFN-ε, a novel type I IFN, was discovered in 2004 (10); it had probably been overlooked because it is not inducible by microbial infection but is constitutively expressed with tissue

restrictions. In 2003, two research teams independently discovered that a group of cytokines, formerly designated interleukin (IL)-29, IL-28A, and IL-28B, shared several biological properties of type I IFNs (19, 20). These cytokines used their own distinct receptor and hence were a new type of IFN, dubbed type III IFNs; they were later officially named IFN-λ1, -λ2, and -λ3. Because hepatocytes are one of the cell types that express their receptor, IFNLR, the IFN-λs have received a lot of attention in the context of chronic hepatitis C virus (HCV) infections in humans, in which polymorphisms in the IFN-λ gene locus have been found to correlate with treatment success. An additional member of the type III IFN family was discovered in 2013 (21). Surprisingly, not all humans are able to synthesize this novel IFN-λ4, whose gene is located in the same locus on chromosome 19 as those of the other IFN-λs. A two-nucleotide polymorphism (*IFNL4 rs368234815*) in its first exon determines whether or not the transcribed mRNA can be translated into the IFN-λ4 protein. The emerging allele, TT, contains a substitution and an extra nucleotide, leading to a codon frameshift and termination of translation (6, 21). The ancestral allele, −G, which allows for IFN-λ4 synthesis, is maintained especially in Africans as −G/−G or −G/TT but is almost lost in Asians; the inactive TT allele probably emerged in response to selection pressure by some pathogen other than HCV and is not found in other mammals (22).

INTERFERON SYNTHESIS TRIGGERED BY CELLULAR SENSORS OF VIRUS INFECTION

IFNs are highly effective in limiting virus replication and spread, but because they are normally not expressed, IFN synthesis needs to be triggered quickly and strongly upon host contact with the virus. Because all viruses replicate inside host cells, detecting the viral nucleic acids—e.g., RNA or DNA genomes or mRNAs—upon virus entry is an effective strategy for triggering innate immune responses. The viral nucleic acids are recognized by a specialized group of proteins known as pattern-recognition receptors (PRRs) (Figure 2) (23). Nucleic acid PRRs are either endosomal membrane proteins or cytosolic proteins. RNA viruses are recognized by the endosomal transmembrane Toll-like receptors TLR3, TLR7, and TLR8 (24) and by the cytoplasmic RNA helicases RIG-I, MDA5, and LGP2, also known as RIG-I-like receptors (RLRs) (25). DNA viruses are recognized by endosomal TLR9 or several cytoplasmic DNA sensors such as cyclic GMP-AMP synthase (cGAS), IFN-induced 16-kDa protein (IFI16), DDX41, and DAI (23, 26). Some of these receptors are expressed only in specific cell types and recognize specific families of viruses. TLRs are preferentially expressed in myeloid cells, such as plasmacytoid dendritic cells and macrophages, whereas RLRs and DNA sensors are expressed in many cell types, including epithelial cells and fibroblasts (27, 28). TLR3 is a dsRNA sensor involved in recognition of RNA viruses such as influenza A virus (FLUAV) and picornaviruses and DNA viruses such as herpes simplex virus 1 (HSV-1) (29–32). TLR7 and TLR8 are sensors of ssRNA from many viruses, including vesicular stomatitis virus (VSV) and FLUAV (33). RIG-I, MDA5, and LGP2, three closely related RLRs, are the key cytoplasmic sensors of viral RNA species (26, 34). RIG-I recognizes members of a variety of virus families, including paramyxoviruses, FLUAV, flaviviruses such as West Nile virus (WNV), rhabdoviruses such as VSV, and reoviruses. In contrast, MDA5 and LGP2 primarily recognize picornaviruses such as encephalomyocarditis virus (EMCV) (35). These specificities are based on the

different RNA species that are recognized by different RLRs: RIG-I can bind short dsRNA and 5′-triphosphate or 5′-diphosphate ssRNA, generated during viral RNA genome replication as well as from incoming viral genomes (25, 36, 37), whereas MDA5 recognizes long dsRNA species and is also involved in sensing viral mRNAs lacking cap 2′-*O*-methylation (38, 39). The third RLR, LGP2, has a dual role during cytoplasmic RNA recognition: On the one hand, it binds dsRNA in tandem with MDA5 and thereby enhances MDA5 activation (40, 41); on the other hand, it can inhibit RIG-I activation by competing for dsRNA and by direct interaction with RIG-I (42). Viral CpG-containing DNA and genomic DNA from murine cytomegalovirus can be recognized in the endosomal lumen by TLR9, especially in plasmacytoid dendritic cells (43). AT-rich DNA from adenoviruses or herpesviruses is transcribed into RNA by RNA polymerase III, which generates ligands to activate RIG-I (44, 45). Several DNA sensors, such as cGAS, DDX41, and IFI16, use the adapter protein STING for downstream signaling (Figure 3) (26). It is unclear why so many cytoplasmic DNA receptors exist; they may act redundantly, or they may possess specificity for certain cell types or distinct features of DNA ligands (46).

Activation of Pattern-Recognition Receptors

In the absence of virus infection, the PRRs remain in an inactive conformation to block any undesired activation of innate immune responses. Upon binding of viral molecular patterns, the PRRs become activated, leading to conformational changes, often dimerization or oligomerization, and interaction with downstream adapter proteins. We describe below some examples of PRR activation and how these steps are regulated.

The TLRs have multiple leucine-rich repeats in their ectodomain, in the endosomal lumen, where they can directly bind to nucleic acids (24). Activation of TLRs requires tyrosine phosphorylation of their cytoplasmic domains (47). For example, TLR3 is activated by tyrosine phosphorylation of two tyrosine residues, Tyr759 and Tyr858, in its cytoplasmic domain (48–50). In resting cells, the cytoplasmic domain of TLR3 remains in a closed conformation to avoid phosphorylation by kinases. Upon binding to dsRNA in the endosomal lumen, TLR3 dimerizes and changes its conformation, which allows the two critical tyrosine kinases, epidermal growth factor receptor (EGFR) and Src, to be recruited to the receptor (51, 52). The sequential recruitment of these tyrosine kinases triggers direct phosphorylation of the two tyrosine residues: EGFR phosphorylates Tyr858 and Src phosphorylates Tyr759. This activated TLR3 is able to recruit the adapter TRIF for downstream signaling (52).

RLRs are activated by dephosphorylation- and ubiquitination-dependent mechanisms (53). They possess a conserved RNA helicase domain for recognition of RNA, and RIG-I and MDA5 (but not LGP2) also possess two CARD domains, which interact with the critical adapter protein MAVS (26). In uninfected cells, phosphorylation of RIG-I CARDs by protein kinase C (PKC) maintains RIG-I's closed conformation (54). Upon binding to viral RNA, RIG-I undergoes dephosphorylation by protein phosphatase 1 (PP1) (55). Then, TRIM25, a ubiquitin ligase, recognizes the dephosphorylated RIG-I and covalently adds ubiquitin moieties onto its CARD, inducing oligomerization and allowing for interaction with MAVS (56). RIG-I is also activated by binding to unanchored ubiquitin chains,

produced by TRIM25 (57). One of several DNA sensors in the cytoplasm, cGAS, upon binding to dsDNA, produces cyclic dinucleotides from ATP and GTP; these cyclic dinucleotides directly bind and activate the endoplasmic reticulum-bound adapter STING, a common signaling platform utilized by DNA sensors (58).

Interferon Induction by Virus-Activated Pattern-Recognition Receptors

Virus detection by PRRs is critical for rapid activation of downstream signaling pathways that lead to the induction of type I and type III IFNs. Induction of *IFN-β* requires the synergistic promoter binding of three transcription factors: IRF-3, NF-κB, and AP1 (59, 60). *IFN-α* subtypes require IRF-7; *IFN*-λs utilize IRF-3, IRF-7, and NF-κB (61–64). These transcription factors are activated upon recognition of virus infection by PRRs. Both dsRNA and dsDNA, present in the endosome or cytoplasm, are capable of activating these transcription factors (Figure 3). Activated PRRs interact with their respective adapter protein: TLR3 uses TRIF, which is recruited to the intracellular domain of TLRs; TLR7, TLR8, and TLR9 use MyD88; RLRs use MAVS, located on the surface of mitochondria or peroxisomes; and several cytoplasmic DNA sensors use STING (65). In the following steps, TRIF and MAVS recruit signaling proteins of the TRAF family of ubiquitin ligases, as well as the IKK*α*/β and TBK1 kinases. These serine/threonine kinases phosphorylate and activate the downstream transcription factors. STING directly recruits the kinases without the need for TRAFs. IRF-3 remains in a closed conformation in the cytosol in uninfected cells, but upon PRR activation, it is phosphorylated by TBK1 on specific serine/threonine residues. This opens up its conformation, causing its dimerization and translocation to the nucleus, where it binds to specific sites, the IFN-stimulated response elements (ISREs), in the promoter regions of target genes such as *IFN-β* and *IFN-λ* (23). Another transcription factor, NF-κB, is activated by phosphorylation-dependent release from its inhibitor IκB to induce target genes, including genes encoding IFNs and proinflammatory cytokines such as interleukins and TNF-*α*. API is activated by all PRRs via mitogen-activated protein kinase (MAPK) pathways (23). Importantly, when IFNs are secreted by infected cells, they act on surrounding and remote cells to induce ISGs; the infected cell, however, benefits from a shortcut to induce ISGs: IRF-3 and IRF-7 can directly induce the transcription of ISGs, without the need for IFN, by binding to the ISREs in the ISG promoters (66, 67).

Interferon-Independent Antiviral Response to Pattern-Recognition Receptor Activation: The RIG-I-Induced IRF-3-Mediated Pathway of Apoptosis

The transcription factor IRF-3, apart from its role in inducing type I and III IFNs and ISGs in infected cells, has an independent additional function in the innate defense against viruses: Activation of IRF-3 by RLR signaling activates a direct proapoptotic effect, which we called the RIG-I-induced IRF-3-mediated pathway of apoptosis (RIPA) (68). RIPA does not require any of IRF-3's transcriptional activities, and it is triggered by RIG-I activation, either directly by viral RNA or by RNA transcribed from viral DNA by RNA polymerase III. RIPA requires a unique set of signaling proteins, such as TRAF2 and TRAF6, to differentially activate IRF-3 for this pathway. In RIPA, IRF-3 directly activates the proapoptotic BH3-only protein BAX, an activator of the intrinsic apoptosis pathway. BAX is activated by its direct interaction with IRF-3 and the concomitant translocation of the IRF-3:BAX complex to the mitochondrial membrane. This causes mitochondrial

dysfunction, release of cytochrome *c* into the cytosol, and subsequent activation of caspase 9 and caspase 3 to induce apoptosis (68). RIPA starts much later than IRF-3's transcriptional activity; in the case of Sendai virus (SeV) infection, this is due to the PI3K/AKT pathway, which stabilizes the cellular pool of the apoptosis inhibitor XIAP. Once XIAP starts to be degraded, RIPA is initiated (69). RIPA provides a defense mechanism to the host: Absence of IRF-3 or caspase 3 causes viral persistence in SeV-infected cells, and RIPA-deficient, *Bax*-deficient cells and mice are highly susceptible to infection by SeV and EMCV (70, 71).

INTERFERON SIGNALING PATHWAYS

Following their synthesis and secretion, IFNs trigger biological effects by binding to their cognate cell surface receptor complex, resulting in conformational changes of the receptor's intracellular domains and giving rise to a cascade of posttranslational modifications of intracellular signaling molecules. The JAK-STAT signaling pathway is the major effector; its main function is the activation of transcription factors that in turn induce transcription of ISGs (Figure 1) (17). The dimeric receptor complex IFNAR is engaged by binding of monomeric type I IFNs, stimulating the intracellular IFNAR-associated Janus kinases JAK1 and TYK2 to autophosphorylate some of their tyrosine residues, followed by tyrosine phosphorylation of the IFNAR subunits; these IFNAR phosphotyrosines create a docking platform for the STAT1 and STAT2 transcription factors. Due to proximity to the JAKs, the STATs are tyrosine phosphorylated (e.g., Tyr701 of STAT1) and dissociate from the receptor. The resulting STAT1-STAT2 heterodimer forms a complex with transcription factor IRF-9. This unique complex, ISGF3, translocates to the nucleus and binds to ISG promoters containing an ISRE to transcriptionally induce the respective genes (17, 72). Surprisingly, although it is unrelated to IFNAR, IFNLR utilizes the same JAK-STAT signaling pathway to induce a similar set of ISGs (15). In contrast, the IFN-γ receptor, IFNGR, cannot recruit TYK2 and therefore does not activate STAT2. In consequence, the STAT1 homodimer, GAF, is the dominant transcription factor activated by type II IFNs and activates the transcription of genes containing a gamma-activated site (GAS) in their promoters (73).

Besides the canonical activation of ISGF3 and GAF, IFNs activate additional signaling pathways that impact gene induction and provide negative feedback regulation of the receptor (17, 74). Figure 4 depicts examples from type I IFN–triggered signaling. Because IFNAR, like IFNGR, engages JAK1, IFNAR signaling activates not only ISGF3 but also GAF. This GAF activation, however, happens to a much lesser degree because the serine kinase IKKε skews the IFNAR pathway toward ISGF3 by serine phosphorylating STAT1, thereby inhibiting STAT1 homodimerization (75, 76). Further diversification of the sets of ISGs induced by type I IFNs occurs via heterodimerization of STAT1 with IRF-1 or subunits of NF-κB, as well as by activation of other STAT family members (STAT3–6), the availability of the latter being cell type dependent (77); all of those complexes can bind to promoters of additional genes that are otherwise not induced by ISGF3. Furthermore, various MAPK pathways are stimulated by type I IFNs, also contributing to the spectrum of induced genes (78). Apart from that, IFN-β can induce several genes that are not inducible by other type I IFNs, such as IFN-α2. This is based on the unique interaction of IFN-β (but not IFN-α2) with IFNAR1, even in the absence of IFNAR2, triggering gene induction via as-yet-unknown signaling pathways (79).

Type I and other IFN signaling pathways are fine-tuned in many ways, such as by posttranslational modification of their components through acetylation, methylation, SUMOylation, or palmitoylation (reviewed in 72) and by the generation of mRNA splice variants; for example, IFNAR2 also exists as a soluble IFNAR2a, which enhances type I IFN signaling, as well as IFNAR2b, a membrane-bound decoy receptor that dampens IFN responsiveness (80–82). Postactivation silencing of IFNAR signaling is achieved quickly after IFN exposure and is mediated by at least two proteins that are ISGs themselves and therefore accumulate in response to IFN: Suppressor of cytokine signaling 1 (SOCS1) binds and inhibits TYK2, whereas USP18 (UBP43) occupies IFNAR2 and hence blocks JAK1 activation (83, 84). Furthermore, IFN receptors are internalized into endosomes after IFN binding, thereby temporarily reducing IFN responsiveness of the cell (5). However, when STAT1, STAT2, and IRF-9 are abundant in a cell, as a consequence of their induction by IFN signaling, U-ISGF3, which is composed of unphosphorylated STATs and IRF-9, is capable of sustaining the induction of many ISGF3-inducible ISGs, even in the absence of IFN signaling (85).

IFNs have transcription-independent, direct effects on cellular metabolism as well (86). IFNAR engagement entails the activation of mammalian target of rapamycin (mTOR) complexes via the PI3K/AKT signaling pathway. mTOR kinase activity is a major facilitator of cellular translation via at least two routes: Translation initiation factor eIF4E is released from inhibition by 4E-BP1 when the latter is phosphorylated by mTOR, and mTOR-mediated $p70^{S6K}$ phosphorylation stimulates eIF4B. Both mechanisms lead to higher translation rates of capped mRNAs, such as ISG mRNAs synthesized after IFN exposure (Figure 5) (87, 88).

ANTIVIRAL ACTIONS OF INTERFERON-INDUCED PROTEINS

Most IFN effects are mediated by the actions of the proteins encoded by the ISGs, which are transcriptionally induced by IFNs. The composition of specific sets of ISGs induced in a cell depends on the transcription factors activated by a specific type of IFN in that cell type and determines the range of biological effects (Figure 5). IFNs are powerful antiviral cytokines used therapeutically against viruses such as HCV (IFN-α2, IFN-λ1), hepatitis B virus (HBV) (IFN-α), and Kaposi's sarcoma–associated herpesvirus (KSHV) (IFN-α). IFNs block viral pathogenesis by three different means. First, they induce cell-intrinsic innate immunity against viruses, which is the focus of this review. Second, they stimulate innate immune cells such as natural killer cells. Third, they help activate the adaptive immune system by activating B and T cells, as well as antigen-presenting cells, such as macrophages, in which they induce upregulation of major histocompatibility complexes in order to present microbial antigens more efficiently (4, 89). Many proteins that mediate or modulate IFN synthesis and IFN signaling are encoded by ISGs; these are constitutively expressed but induced further by IFN exposure. This family of ISGs includes the genes that encode the viral sensor proteins RIG-I, MDA5, TLRs, and cGAS and the transcription factors IRF-1, IRF-7, IRF-9, STAT1, and STAT2. SOCS1 and USP18, two negative feedback regulators of IFN signaling, are also encoded by ISGs (2). These proteins regulate the magnitude of action of the IFN system but do not affect virus replication per se.

Type I and III IFNs exert their innate antiviral effects through the actions of ISG proteins, which inhibit individual steps of virus life cycles—i.e., entry, genome release, transcription, translation, genome replication, assembly, and egress—within the infected cells (Figure 6) (2, 90). Several key concepts characterize the way these ISG proteins work against viruses. First, the antiviral activity of IFNs against a specific virus is mediated by a number of ISG proteins that act independently, but in concert, to inhibit the virus life cycle at multiple levels (91, 92). Second, different subsets of ISG proteins target different families of viruses (92, 93). Third, some ISG proteins show cell type–specific or tissue-specific antiviral activity; for example, murine Ifit2 inhibits VSV replication in brain neurons but not in lungs, despite being expressed in both organs (94). Fourth, some ISGs exist as small gene families of related members, such as the genes encoding MxA and MxB or IFIT1, IFIT2, IFIT3, and IFIT5. These, however, do not act redundantly; individual members show individual virus and tissue specificity of action. For example, MxA inhibits FLUAV and several other viruses, but only MxB inhibits HIV-1 (95, 96). Cell culture–based screens using overexpression or knockdown of individual ISGs can identify their virus specificity (92, 93, 97, 98), whereas cell type specificities and the biological relevance for disease outcome can be identified only by using individual ISG–knockout mice (94, 99, 100). Valuable insights have been gained from genetic analysis of patients, which demonstrates correlation between mutations in a specific ISG and susceptibility to infection by a specific virus (101). Only representative examples of ISG protein actions are highlighted here; more comprehensive reviews on this topic are available (2, 101).

Three long-known ISGs are the protein kinase PKR, the GTPase MxA, and the enzyme oligoadenylate synthetase (OAS). PKR is constitutively expressed but further induced by IFN; upon binding to (viral) dsRNA, it phosphorylates the translation initiation factor eIF2α, thereby inhibiting translation of cellular and viral mRNAs (102). Human cytoplasmic MxA and murine nuclear Mx1, on the other hand, have a specific spectrum of antagonized viruses and are both key antiviral effectors against influenza viruses; they bind to viral RNA-protein complexes, either trapping them and preventing their cytoplasmic trafficking (MxA) or inhibiting nuclear transcription of viral mRNA (Mx1) (96). OAS, upon binding to dsRNA, produces 2′,5′-oligoadenylates, which activate the latent ribonuclease, RNase L, which then degrades cellular and viral RNAs. Recent evidence suggests that the degradation products of RNase L can activate the RNA sensor RIG-I to enhance IFN induction within the infected cells (103, 104). Another family of ISGs is the IFITs; they are among the most strongly IFN-induced ISGs overall (14, 105, 106). Human IFIT1 and murine Ifit1 recognize viral mRNAs with either incompletely methylated caps (i.e., caps lacking ribose 2′-*O*-methylation) or with a triphosphate at their 5′ ends. This interaction inhibits mRNA translation or sequesters viral RNA, respectively, both of which inhibit the viral life cycle (107–110). Intriguingly, most viruses avoid IFIT1 action; murine Ifit2, however, is quite effective against viruses, strongly protecting against pathogenesis by a number of viruses, such as VSV, WNV, mouse hepatitis virus (MHV), and SeV (94, 99, 100, 111). Several ISG proteins inhibit the entry of enveloped viruses into cells by altering the cell membrane surface, thereby preventing fusion of viral and cellular membranes. This is achieved by cholesterol 25-hydroxylase (CH25H) generating 25-hydroxycholesterol, which presumably changes membrane properties, such as membrane fluidity, and thereby prevents the entry of a broad range of enveloped viruses

(112–114). IFN-induced transmembrane protein 1 (IFITM1) and IFITM3 each inhibit the entry of a specific set of viruses, such as FLUAV, WNV, and Ebola virus, at different stages between receptor binding and entry (95). ISG15 is a small protein which, upon its IFN-induced synthesis, is conjugated to all newly synthesized cellular and viral proteins (a process termed ISGylation) by an enzyme complex similar to the ubiquitin ligases (115, 116). Antiviral effects of ISG15 were observed using *Isg15*-knockout mice infected with influenza or herpes viruses, but the requirement for protein ISGylation versus the action of unconjugated ISG15 was not uniform (117, 118). Inherited *ISG15* deficiency in humans has recently shed new light onto the function of ISG15 during certain virus infections. The lack of ISG15 made patients more resistant to virus infections, because intracellular unconjugated ISG15 serves as a negative regulator of IFNAR signaling. ISG15 prevents degradation of IFNAR's negative regulator USP18, and as a result, type I IFN signaling is strongly enhanced in the absence of ISG15 (119, 120). One example of an IFN-induced viral egress inhibitor is Tetherin (BST2); this transmembrane protein tethers HIV-1 virus particles to the cell surface, preventing their release, the last step of the virus life cycle (121–123).

Type I IFNs can also be detrimental to the host. High type I IFN levels are a major pathogenic factor in systemic lupus erythematosus and in septic shock caused by bacteria (124–126). Strikingly, in certain virus infections, type I IFN action is not protective. For example, it worsens pathogenesis during infections of mice with influenza virus or Sendai virus in the lungs, and it promotes persistent lymphocytic choriomeningitis virus (LCMV) infection (127–130). Furthermore, during influenza virus infection, high type I IFN expression in lungs has long been known to facilitate superinfection with bacteria such as *Haemophilus influenzae* and *Streptococcus pneumoniae* due to suppression of neutrophils and T helper 17 cell responses, among other mechanisms (131, 132).

ANTIVIRAL ACTIONS OF TYPE III INTERFERONS

Type III IFNs have major roles in specific viral pathogenesis in the intestine, lung, and liver (11). They prevent murine norovirus (MNV) infection in the gut, especially when the commensal bacterial flora has been previously removed by antibiotic treatment; furthermore, type III IFN injections are effective for curing persistent MNV infections(133, 134). The absence of commensal bacteria leads to abnormal intestinal morphology and lymphocyte function; strikingly, these are ameliorated by MNV-induced type I IFN (135). In humans, HCV replicates in hepatocytes. In over 70% of cases, it establishes a persistent infection; a third of these persistent infections progress to chronic liver diseases and carcinoma. Current therapy uses PEGylated IFN-α2 in combination with ribavirin and, more recently, with inhibitors of the viral protease (136). The major problem is a high percentage of IFN-α nonresponders—that is, patients who fail to eliminate the virus during therapy. As a novel alternative, IFN-λ1 has been successfully used in HCV therapeutic trials (137, 138). It may be more effective for two reasons: It has fewer side effects compared with IFN-α because of the cell type–restricted pattern of IFNLR expression (compared with ubiquitous IFNAR expression). Moreover, it has been suggested that, unlike IFNAR signaling, IFNLR signaling is not downregulated during prolonged treatment with IFN (139–141); the silencing of IFN-α2/IFNAR signaling, due to the continuous induction of ISG proteins such as USP18, is a major cause of nonresponsiveness (142). Another more subtle but equally important

determinant of treatment outcome is the overall level of ISG expression in the infected liver before IFN-α therapy starts (Figure 7). Lower ISG expression and, concomitantly, relatively elevated HCV RNA levels in livers before therapy correlate with a higher likelihood of successful therapy and permanent eradication of HCV; similarly, spontaneous clearance of the virus without therapy is more likely with low liver ISG expression levels. On the contrary, high ISG expression levels predict failure of IFN therapy (143, 144). Possible causes for different ISG expression levels have emerged from many independent genetic studies correlating specific polymorphisms (one- or two-nucleotide substitutions) in the *IFN-λ* locus with therapy outcomes. The most conclusive example is the polymorphism *rs368234815*, described above, which determines whether or not the IFN-λ4 protein can be synthesized in infected cells (21, 145). Consequently, the production of IFN-λ4 by infected liver cells is a strong predictor of being an IFN-α therapy nonresponder (Figure 7) (12, 21, 143, 146).

VIRAL ANTAGONISM OF THE INTERFERON SYSTEM

To escape from the multipronged antiviral effects of the IFN system, viruses have evolved a variety of strategies. In fact, viral countermeasures target all levels of the IFN system, preventing IFN synthesis (Figure 8, steps ①–⑦), ablating IFN-stimulated JAK-STAT signaling (steps ⑧-–⑪), and inhibiting and/or evading ISG protein functions (step ⑫). Because several review articles have provided comprehensive accounts of these strategies (3, 147), only a few representative and novel examples are highlighted here.

The induction of IFN synthesis often starts with detection of viral RNA; several viral proteins, such as FLUAVNS1 and Ebola virus VP35, bind to viral RNA and hide it from detection by cellular sensors such as RIG-I (148, 149). RNA viruses in particular proficiently target RLR and TLR signaling pathways to prevent transcriptional induction of IFNs, very often by interfering with IRF-3 or IRF-7 phosphorylation, nuclear translocation, or promoter binding (3). Some examples include the relocation of the signaling components RIG-I, TBK1, and IRF-3 into viral inclusion bodies (bunyavirus NSs protein) (150) or degradation of these proteins within virally formed degradasomes (respiratory syncytial virus NS protein) (151). HCV, using its protease NS3/4A, specifically cleaves and thereby inactivates key signaling intermediates, such as the adapters MAVS and TRIF, blunting the RLR and TLR3 pathways (152). This discovery formed the basis for the development of new HCV protease inhibitors now used for treatment of HCV patients (136). Paramyxoviral V proteins show surprising sophistication in inhibiting virus detection by the sensor MDA5. Not only does V directly bind and inhibit both MDA5 and LGP2, but it also binds the cellular phosphatase PP1, keeping it from dephosphorylating MDA5 and hence maintaining MDA5 in an inactive conformation (153–156). The prime example of a multifunctional antihost protein is FLUAV NS1. It interferes with the ubiquitination of RIG-I by human TRIM25 or by murine Riplet ligases, preventing RIG-I activation (157–159). Also, NS1 functions in the nucleus by binding to CPSF and cellular RNAs to prevent poly(A) tailing and splicing of these RNAs, a generalized mechanism to prevent expression of host genes including *IFN-β* (149). VSV M protein achieves general host gene expression by blocking host mRNA transcription in the nucleus (160).

Signaling by IFNs can be targeted by soluble poxviral IFN decoy receptors, by virus-mediated degradation or relocation of STAT proteins, or by prevention of ISGF3 nuclear import in order to avoid the expression of ISGs in infected cells (3). A final means to antagonize the IFN system is to interfere with the functions of the ISG proteins themselves. An example is the antagonistic function of FLUAV NS1, which directly binds and inhibits PKR (161). Other viruses inhibit PKR by encoding small, partially double-stranded RNAs that stably bind PKR without activating it (Epstein-Barr virus EBER and adenovirus VA1) (162). MHV, a coronavirus, encodes a phosphodiesterase for the purpose of cleaving 2′,5′-oligoadenylates to efficiently prevent RNase L stimulation (163). Lastly, the anchoring of the egressing virus particles to the cell surface by Tetherin is antagonized by HIV, influenza viruses, and Ebola virus (123). The avoidance of ISG protein actions is another effective alternative to actively antagonizing them. The ISG protein IFIT1 inhibits translation of mRNAs lacking cap 2′-*O*-methylation at the first ribose (107–110). Viruses evade this inhibition in at least three different ways: (*a*) Viruses utilize the cellular mRNA capping machinery or transfer cellular 2′-*O*-methylated caps onto their own RNAs; (b) viruses encode a 2′-*O*-methyltransferase of their own (WNV, MHV, vaccinia virus, VSV, etc.); and (*c*) alphavirus mRNAs (Venezuelan equine encephalitis virus, Sindbis virus) form a secondary structure adjacent to the unmethylated cap to sterically prevent murine Ifit1 from binding (164). The evolutionary battle between the host and the virus can extend further; the host can, in turn, antagonize the viral antagonists, as seen with the multifunctional NS1 of FLUAV, which is conjugated to cellular ISG15 and thereby becomes inactivated (165). ISGs even coevolve with viral inhibitors such as the vaccinia virus K3L protein. K3L is a small eIF2α-mimicking PKR-binding protein that blocks PKR kinase function. In several primates, the interacting surface of PKR with eIF2α has changed over time to help overcome competitive binding by viral K3L (166).

FUTURE PERSPECTIVES

In spite of the wealth of knowledge acquired during the more than 50 years of research since the discovery of IFN, much remains to be learned. A major unanswered question is, Why so many type I IFNs? Are they redundant, or do they have different physiological roles? A second, more philosophical question is, If IFNs are antiviral, why do viruses induce their synthesis? In this context, a newly emerging concept postulates that IFNs, rather than protecting the host, may be partners in crime and augment viral pathogenesis (127, 129). A major underexplored research area addresses the nature of cross talk among IFNs and other cytokines that are also induced by virus infection (132). As our understanding of the actions of ISG proteins is increasing, it is intriguing to learn that a specific ISG protein can be antiviral only in a specific cell type (94). This observation suggests that an ISG protein, or its functional analogs, may have a more targeted and selective antiviral effect than an IFN, for therapeutic purposes. The biological implications of protein ISGylation are not yet fully understood. Moreover, it remains possible that not only ISG15 but other small IFN-induced proteins are also covalently linked to cellular and viral proteins. Another significant area of expansion of future investigation is on the role of IFNs in superinfections. There are intriguing reports on how IFNs produced by initial acute virus infection promote secondary bacterial infection (131, 167). In the same vein, it will be interesting to know how low levels

of IFNs produced by chronic virus infection influence susceptibility to other infectious agents. In the recent past, important insights into the functions of specific components of the IFN system have been revealed by genetic analyses of familial cohorts that are susceptible to specific microbial infections (120); one expects that this kind of investigation will be a rich source of new information in the future, as systems analyses are more routinely performed to investigate human diseases.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Glossary

IFN-stimulated gene (ISG)
a gene that is transcriptionally induced or upregulated upon IFN receptor signaling

IFN-α/β receptor (IFNAR)
cell surface complex of IFNAR1 and IFNAR2; activated by type I IFNs

IFN-γ receptor (IFNGR)
cell surface complex of IFNGR1 and IFNGR2; activated by type II IFNs

IFN-λ receptor (IFNLR)
cell surface complex of IFNLR1 and IL10RB; activated by type III IFNs

ISG factor 3 (ISGF3)
transcription factor consisting of STAT1, STAT2, and IRF-9; drives transcription of ISGs with an ISRE promoter

Gamma-activated factor (GAF)
transcription factor consisting of a STAT1 homodimer; drives transcription of ISGs with a GAS promoter

Pattern-recognition receptor (PRR)
cellular sensor protein in the cytoplasm, on the cell surface, or on endosomal membranes; recognizes microbial molecular patterns

IFN-stimulated response element (ISRE)
promoter element responsive to ISGF3 and IRF transcription factors; drives transcription of many ISGs

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SUMMARY POINTS

1. The type I, II, and III IFNs and their cognate receptors form three biologically distinct systems. Their components are expressed with cell type restrictions and activate different transcription factors, inducing overlapping but distinct sets of ISGs.
2. Type I and III IFNs are transcriptionally induced upon detection of viral molecular patterns by cellular sensor proteins and are secreted. They act on the infected cell as well as surrounding and remote uninfected cells.
3. IFNs act through their cell surface receptors to engage the JAK-STAT pathway and other signaling pathways toward transcriptional induction of ISGs.
4. ISG proteins are the mediators of IFN actions.
5. IFNs are protective against most viruses but can be harmful during certain virus infections (e.g., influenza viruses, HCV), bacterial infections, or autoimmune diseases. High levels of type I and III IFN expression are observed in those scenarios.
6. Antiviral effector ISG proteins act in concert to inhibit multiple steps of virus life cycles; some ISG proteins inhibit only specific viruses, whereas some are active only in specific cell types.
7. Viruses antagonize the IFN system at multiple levels, including IFN synthesis, IFN signaling pathways, and the functions of individual ISG proteins.

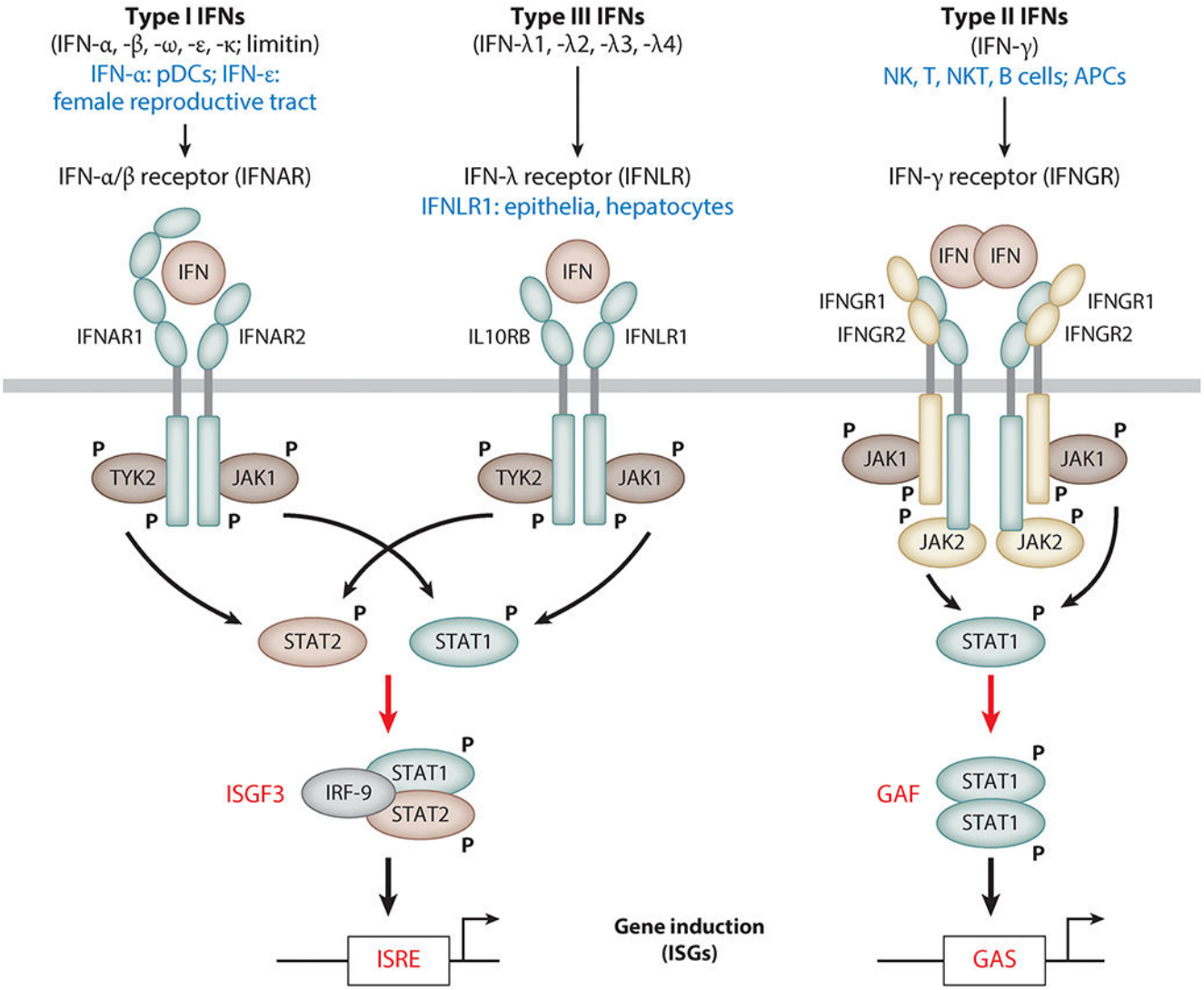

Figure 1.

Major differences between the type I, II, and III IFN systems. Each type of IFN acts through its own cognate cell surface receptor. The Janus kinases JAK1, TYK2, and JAK2 phosphorylate STAT proteins and trigger their transcriptional activity. The three signaling systems are distinguished by their cell type–specific expression of IFNs or their receptor (*blue*), as well as by the different transcription factors they activate (*red*). Abbreviations: APC, antigen-presenting cell; GAS, gamma-activated site; IFN, interferon; ISG, interferon-stimulated gene; ISRE, IFN-stimulated response element; NK, natural killer; NKT, natural killer T; pDC, plasmacytoid dendritic cell. To download a PowerPoint slideshow illustrating further details about each IFN system, click the Interactive Figure button.

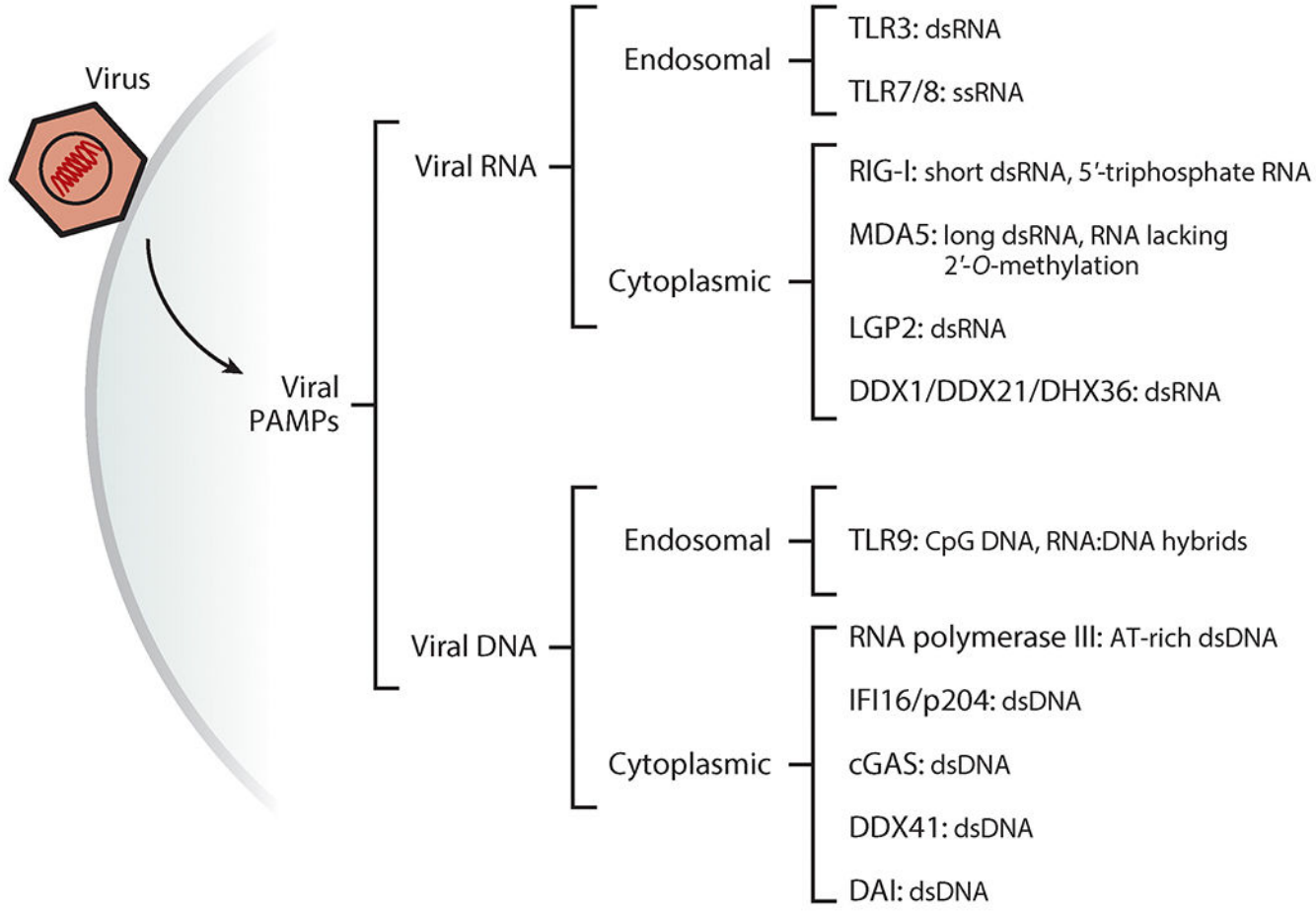

Figure 2.

Cellular sensors detecting viral RNA and DNA. Viral nucleic acids are the key pathogen-associated molecular pattern (PAMP) for cells to recognize the presence of viruses. A large number of sensor proteins (pattern-recognition receptors) bind specific forms of nucleic acids in endosomes and in the cytoplasm and trigger signaling to elicit innate immune responses such as the induction of interferons.

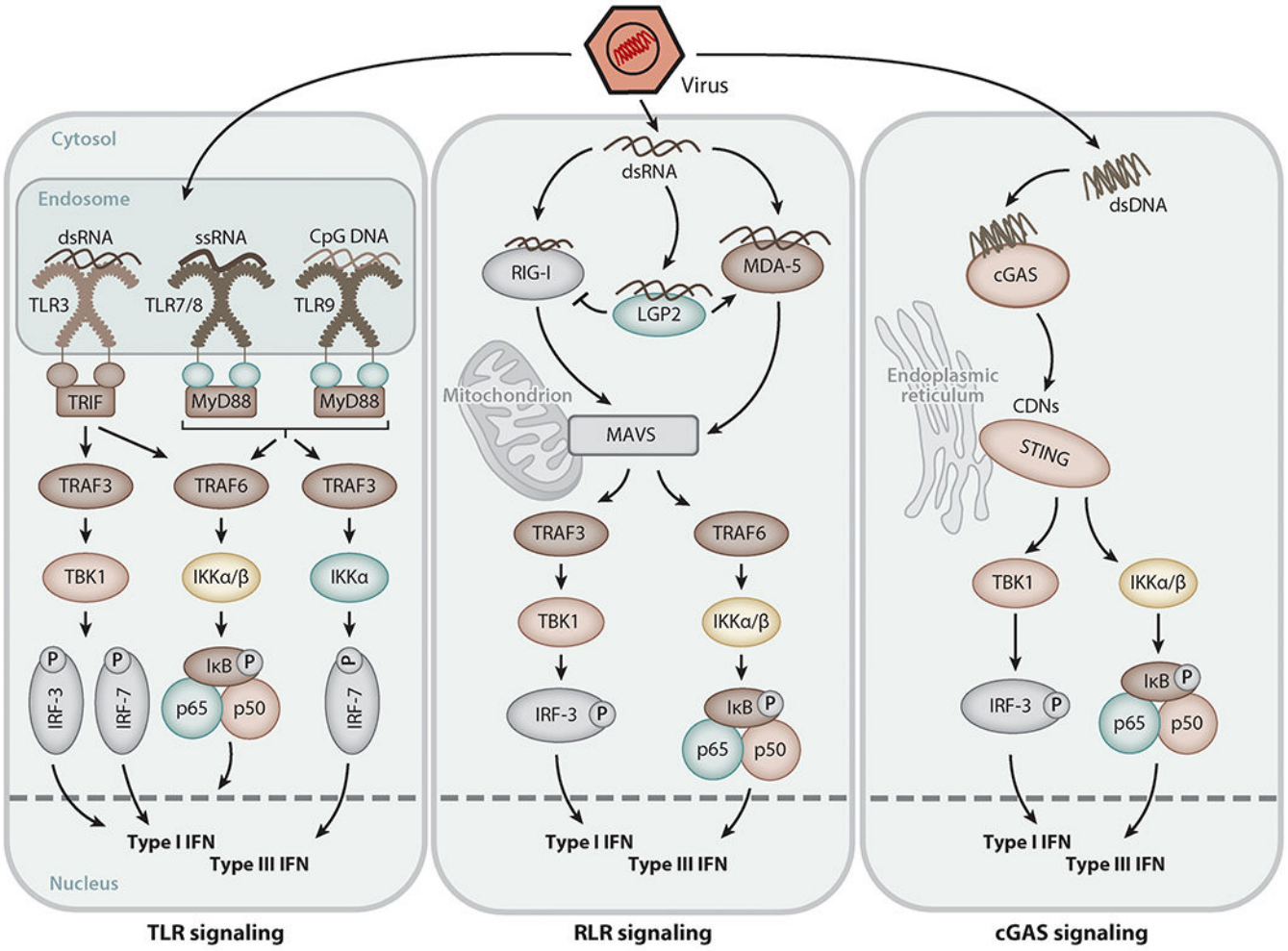

Figure 3.

Signaling pathways for type I and III interferon (IFN) induction triggered by viral nucleic acids. Upon virus entry, viral RNA or DNA in endosomes or the cytoplasm is detected by receptor proteins [e.g., Toll-like receptors (TLRs), RIG-I-like receptors (RLRs), cyclic GMP-AMP synthase (cGAS)], which trigger signaling via adapter proteins such as TRIF, MyD88, MAVS, and STING to activate transcription factors of the IRF family as well as NF-κB, leading to induced transcription of the type I and type III IFN genes.

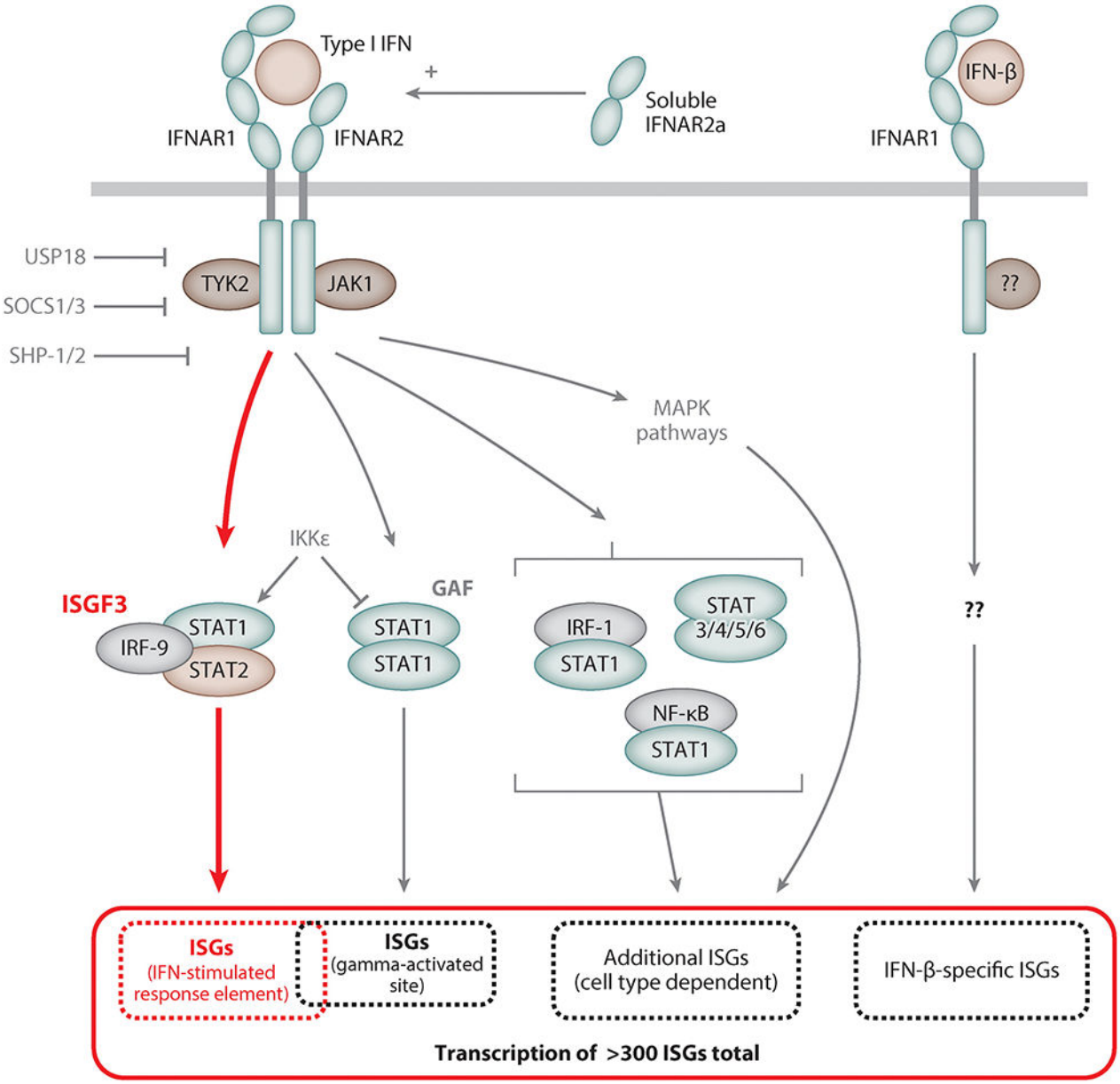

Figure 4.

Type I interferon (IFN)-stimulated signaling pathways. Binding of type I IFNs to the dimeric type I IFN receptor, IFNAR, triggers activation of intracellular tyrosine kinases such as JAK1, TYK2, and MAPKs. These in turn activate transcription factor complexes containing STAT proteins, predominantly ISGF3, and others, depending on the cell type. MAPKs activate transcription factors of the ATF/JUN families. IKKϵ serine phosphorylates STAT1 and inhibits its dimerization in favor of ISGF3 formation. A unique interaction of IFN-β with IFNAR1 induces an additional set of genes not induced by other type I IFNs. The soluble splice variant IFNAR2a can enhance type I IFN signaling. Negative regulation of IFNAR signaling is provided by the IFN-stimulated gene (ISG) products USP18 and SOCS,

which bind to IFNAR2 and TYK2, respectively, and the tyrosine phosphatases SHP-1 and SHP-2.

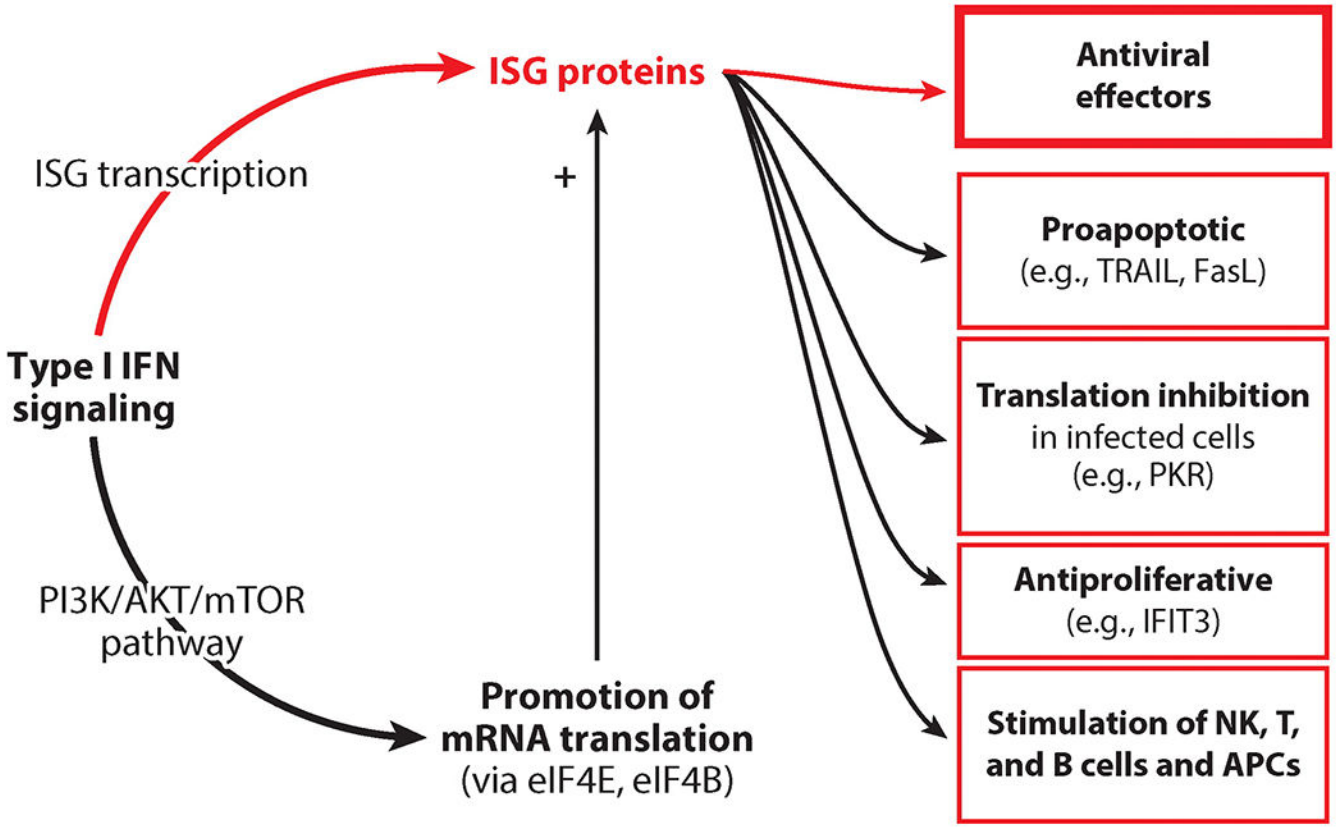

Figure 5.

Interferon (IFN)-stimulated genes (ISGs): the mediators of the biological effects of IFNs. Type I IFN signaling transcriptionally induces ISGs, whose protein products are the effectors of IFN actions that inhibit virus life cycles. Other ISG proteins mediate proapoptotic effects or general inhibition of translation. Certain cell types show slowed proliferation after continuous IFN exposure. IFN action on immune cells, such as natural killer (NK) cells, T cells, B cells, and antigen-presenting cells (APCs), is important for shaping the innate and adaptive immune responses extrinsic to the infected cells. A transcription-independent effect of IFNs is the activation of mTOR kinase via the AKT pathway, a major promoter of translation.

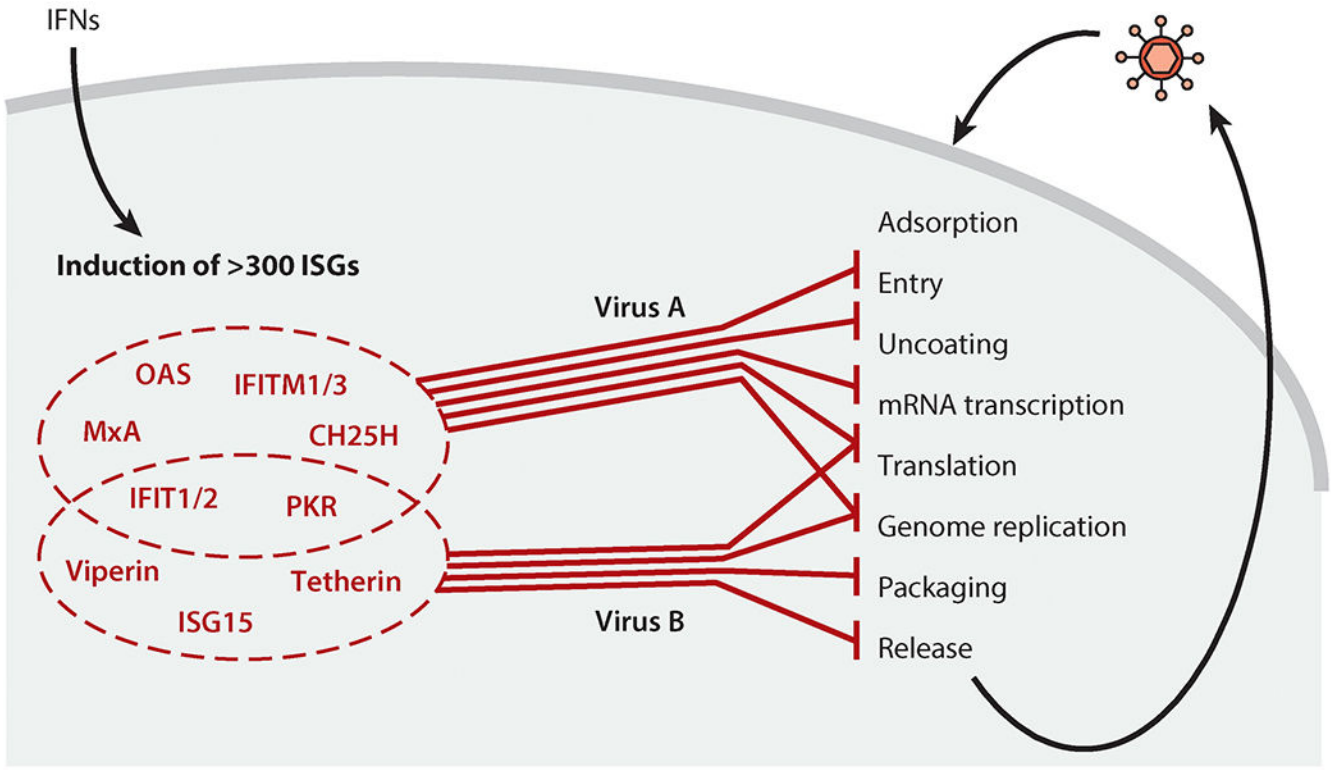

Figure 6.

Inhibition of specific viruses by specific combinations of interferon (IFN)-stimulated genes (ISGs). IFNs induce the expression of hundreds of ISG proteins. Upon subsequent virus infection, a specific subset of ISG proteins inhibits multiple steps of the specific virus's life cycle; each mechanism contributes to the overall inhibition. Additionally, some ISG proteins are inhibitory only in specific cell types. To download a PowerPoint slideshow illustrating further details about this process, click the Interactive Figure button.

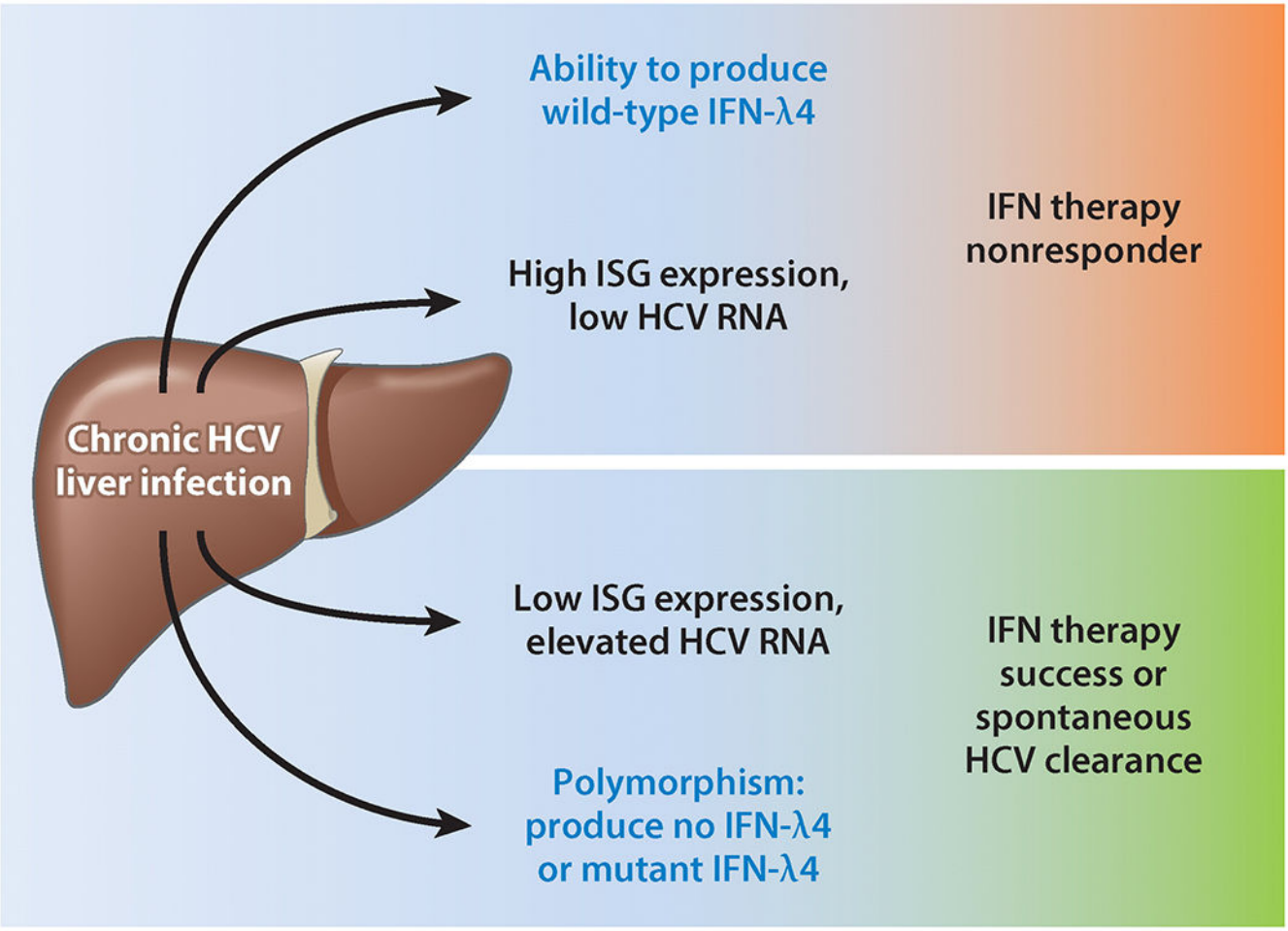

Figure 7.

Interferon (IFN)-λ4 as a predictor of responsiveness to IFN-α therapy of chronic hepatitis C virus (HCV) infection. During chronic HCV infection, expression of IFN-λ4 or relatively high IFN-stimulated gene (ISG) expression levels in the liver before treatment correlates with a lack of response to IFN-α2 therapy (i.e., HCV cannot be cleared permanently from the liver). Inversely, being unable to produce IFN-λ4 or having low ISG expression levels makes spontaneous HCV clearance or successful therapy likely. Whether IFN-λ4 is responsible for elevated ISG expression levels is unknown.

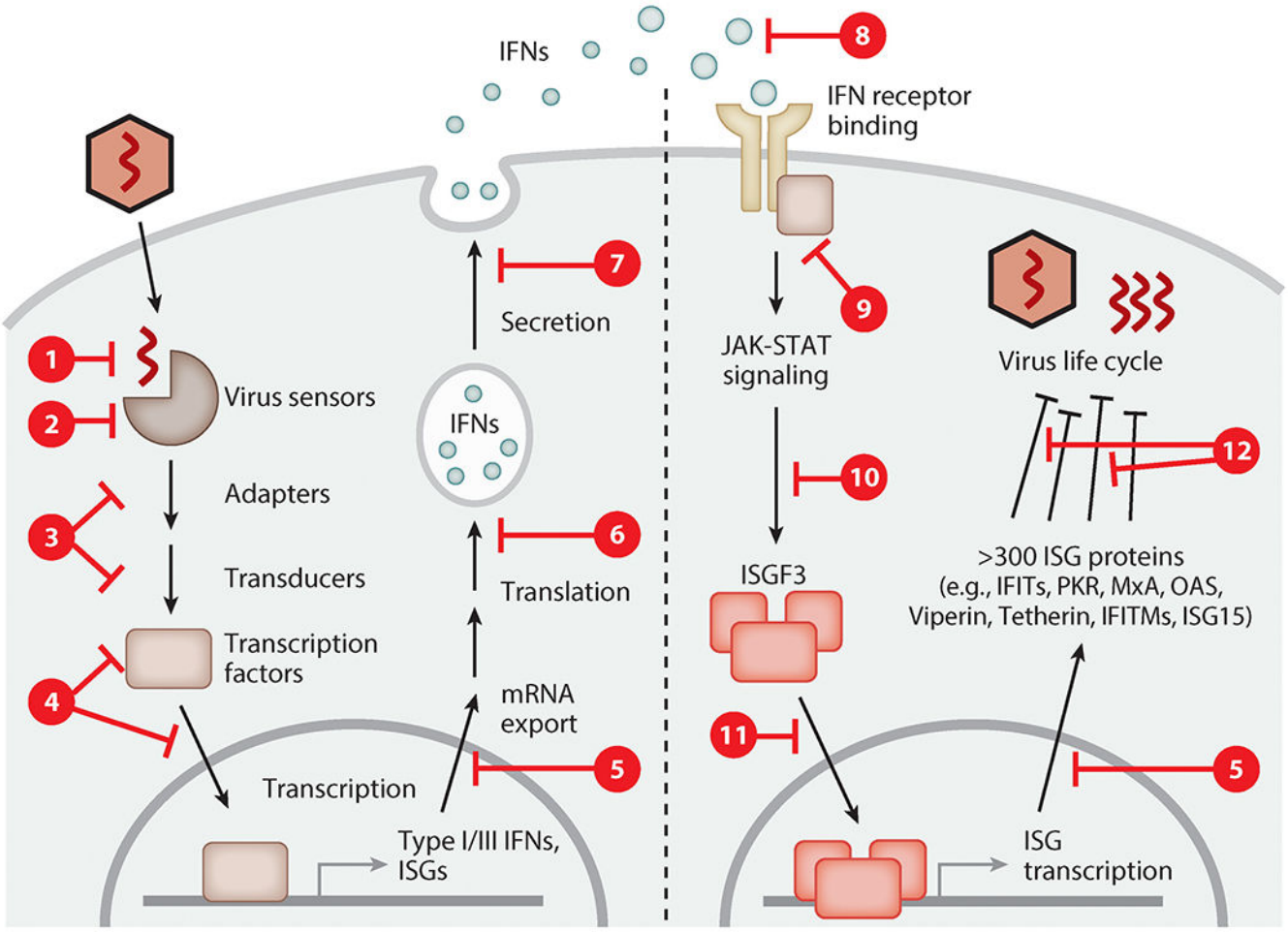

Figure 8.

Principles of viral antagonism of the interferon (IFN) system. All mammalian viruses evolved to counteract one or multiple phases of the IFN system. The synthesis of IFNs is prevented by viruses by masking their nucleic acid (step ①), inactivation or cleavage of cellular recognition receptors or their adapter proteins (steps ② and ③), inhibition or degradation of key transcription factors such as IRF-3 (step ④), and generalized inhibition of host gene transcription, protein translation, or protein secretion (steps ⑤, ⑥, and ⑦). IFN signaling is blocked by viral expression of soluble decoy receptors (step ⑧), inhibition of Janus kinases (step ⑨), STAT protein sequestration or degradation (step ⑩), or prevention of transcription factor nuclear translocation (step ⑪). Lastly, the actions of antiviral interferon-stimulated gene (ISG) proteins are counteracted by direct antagonism or evasion (step ⑫). To download a PowerPoint slideshow illustrating further details about each step, click the Interactive Figure button.