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Understanding Interferon Subtype Therapy for Viral Infections: Harnessing the Power of the Innate Immune System

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Abstract

Type I and III interferons (IFNs) of the innate immune system belong to a polygenic family, however the individual subtype mediators of the antiviral response in viral infections have been hindered by a lack of reagents. Evaluation studies using different IFN subtypes have distinguished distinct protein properties with different efficacies towards different viruses, opening promising avenues for immunotherapy. This review largely focuses on the application of IFN-α/β and IFN-λ therapies for viral infections, influenza, herpes, HIV and hepatitis. Such IFN subtype therapies may help to cure patients with virus infections where no vaccine exists. The ability of cell types to secrete a number of IFN subtypes from a multi-gene family may be an intuitive counterattack on viruses that evade IFN subtype responses. Hence, clinical use of virus-targeted IFN subtypes may restore antiviral immunity in viral infections. Accumulating evidence suggests that individual IFN subtypes have differential efficacies in selectively activating immune cell subsets to enhance antiviral immune responses leading to production of sustained B and T cell memory. Cytokine therapy can augment innate immunity leading to clearance of acute virus infections but such treatments may have limited effects on chronic virus infections that establish lifelong latency. Therefore, exploiting individual IFN subtypes to select
those with the ability to sculpt protective responses as well as reinstating those targeted by viral evasion mechanisms may inform development of improved antiviral therapy.

Keywords: Virus; innate cytokines; evasion; immunotherapy; interferons; subtypes

1. Introduction

An inherent form of host protection from viruses lies in the ability to rapidly produce an antiviral class II family of alpha-helical cytokines (e.g. interferon, IFN) in response to virus exposure to immediately minimise damage from invading viruses and induce potent immunity, enabling crosstalk between the innate and adaptive immune systems of vertebrates. This review will focus on the early host immune responses of the type I and type III IFN families and the roles of the different subtype genes in viral infections and disease, highlighting influenza, herpes, human immunodeficiency virus (HIV) and hepatitis viruses.

Cell sensing of viral pathogens involves PRRs, such as Toll- and retinoic acid inducible gene 1 (RIG-I)-like receptors recognising pathogen-associated molecular patterns (PAMPs) [1,2]. Through a variety of mechanisms, the IFNs provide protection of the host with direct impact on viral replication (anti-viral) but they can also directly influence immune responses (immunomodulatory) including dendritic cell (DC), macrophage, natural killer (NK), T and B cell responses [reviewed in Ref. [3]]. IFN signaling pathways cause rapid stimulation of cells within minutes upon pathogen recognition, activating a plethora of interferon-stimulated genes (ISGs). The direct antiviral effects are often associated with the ISGs; 25OAS, PKR, ISG56, RNaseL, IRF7, MHC, CD80, CD86, Mx and iNOS. Whereas additional ISGs modulate the acute innate response and orchestrate adaptive responses, with pleiotropic effects on immune cell activation, maturation, proliferation, migration, survival and apoptosis [4]. However, their indirect long-term effects, dissipated from initial cell stimulation to cytokine network cascades, can last from months to years. Moreover, the timing, duration, strength and cellular context of IFN responses can dictate disease outcome, being either resolved or chronic inflammatory/autoimmune in nature [5].
The biological role of the IFN subtypes represents a longstanding area of intrigue by investigators; why there are so many different subtype genes and whether they act in a non-redundant fashion in different viral infections [6]. A perception is that production and function of all the IFN alpha subtypes are not essential in a cell but included in the genome in case of failure by others due to viral evasion tactics. Therefore, the IFN subtypes represent a repertoire of proteins affording “layers” of protective responses to invading pathogens of different cell types.

2. IFN Responses

2.1. IFN Induction by Viruses

Potent resistance mechanisms to viruses, relying on innate immune activation of macrophages and dendritic cells, are evident throughout evolution, from invertebrates to higher animals. As shown in Fig. 1, there are three major IFN types (Type I, II and III) with multiple proteins that bind their receptors in an autocrine and paracrine manner, leading to expression of thousands of genes, having various biological properties in antimicrobial defense [7]. IFNs are highly conserved across species (e.g. 60–70% homology between human and mouse proteins) highlighting their evolutionary importance in immune defense against pathogens [8]. The evolutionary importance of IFN is underscored by their retention and radiation in fish, amphibian, avian and mammalian species as the primary antiviral mediator in innate immunity. Even in fish species, the IFNs function in host defense by minimising virus infection and spread along with other cytokines (e.g. IL-10, IL-20, IL-24) that activate macrophage and T cell-mediated immune responses but also protect the host from immune-mediated damage. Furthermore, comparative studies of IFN receptor knockout animals with wild-type animals have highlighted the importance of IFN in resistance to virus infection [9–11]. The type I and type III IFNs will be predominantly reviewed here, as they comprise multiple subtype proteins and are induced rapidly, within minutes after virus exposure. It is well established and recognised that they are key players of the first line of host defense in innate immunity.
Stimulation of IFN by virus infection of a cell is found to vary dependent on both cell and virus type [12,13]. Danger signals received by the host upon exposure to viruses are also related to the viral dose and route of infection. As IFNs are themselves ISGs, the IFN subtype genes are transactivated in individual cell types according to competing signaling pathways via strength of receptor binding affinities and activation of STAT phosphorylation [reviewed in Ref. [14]]. The availability of these transcription molecules can also change with the maturation and differentiation of cell types leading to downstream activation of different sets of ISGs. Indeed, the type I and type III IFN signaling pathways converge with both distinct and common ISG subsets [15]. Cell regulation of IFN production is negatively controlled by SOCS, itself an ISG [16]. At the tissue level, expression of ISGs from microarray data sets in transcriptome analyses reveals differences in positive and negative regulation [17]. Cleverly, viruses that manipulate more unphosphorylated ISGF3 in an infected cell can dampen the number of ISGs and hence lower the antiviral activity of normally potent IFNs. The innate IFN subtype responses and their associated protective antiviral states leading to immunity are described below.

### 2.2. Type I IFN subtypes

Most cell types respond to the type I IFN cytokines and likewise most cell types produce these IFNs, including plasmacytoid DCs, macrophages, epithelial cells, fibroblasts, and leukocytes. The human type I IFN family comprises at least 20 intronless cytokine genes clustered on chromosome 9 encoding multiple proteins of approximately 166 aa in average length; including 14 alpha subtypes (and 3 pseudogenes), 1 beta and 1 epsilon. Viruses activate PRRs, which in turn switch on IFN production, with plasmacytoid DCs being the major producers, devoting up to 60% of their transcriptome to express type I IFNs during the first 6 h following TLR7/9 activation [18]. Analysis of the innate interactome, as early as 2 h post-virus infection, shows a strong network linking type I IFN and chemotactant pathways [19].
2.3. Type III IFN subtypes

Unlike the type I IFNs, only limited cell types respond to type III IFN, being of epithelial and hepatocyte lineage, although most cell types produce them. Three IFN lambda genes located on chromosome 19 (murine IL-28a, IL-28b and a pseudogene on chromosome 7) make up the type III IFN subtype family in humans and are also small proteins (174 aa) with antiviral biological function [reviewed in Ref. [20]]. However, unlike the type I IFN genes which do not have introns, the type III IFN genes have five exons interspersed with four introns that require cellular splicing machinery.

In comparison to the type I IFN family, the lambda genes and subtype proteins are fewer in number and have a narrower range of activity in terms of cell types. Furthermore, outcomes of comparative genomic studies have shown that different ISG signatures are induced by specific viruses [12]. Understanding the individual IFN subtypes and their ISG sets is useful for finding biomarkers of immunological signature patterns for viral infections and disease [reviewed in Ref. [3]]. This review focuses on the role of specific IFN subtypes or subsets of IFN proteins as therapeutic responses to virus infections, ultimately harnessing the power of the innate immune system.

2.4. Biological roles of multiple IFN subtypes in viral infections

As many different IFN proteins have been found in vertebrates, one is driven to understand their biological role in host defense. The ability to measure the binding affinity of IFN to its cognate receptor, stability of the ternary complex, expression levels of IFN subtype transcripts, proteins and the subtype specific responses themselves along with expression of the different subtypes has opened wide this field of research. Accumulating evidence now shows that distinct IFN genes, encoding biologically active IFN proteins, can be protective against different pathogens, collectively providing the host with a pool of type I IFN subtypes in controlling microbial pathogenesis [21]. In other words, the host has an armory of different IFN cytokine weapons for its defense. Nonetheless, some viruses in strategic host interplay, orchestrate dysregulation of IFN responses. This in part may explain why some viruses do not elicit equal IFN subtype responses in the infected cell.
Viruses frequently target certain organs and tissues for replication, and those that disseminate to the central nervous system (CNS) can invade the brain, travelling through the spinal cord, brain stem, and cerebellum, often causing fatal encephalitis. Highly specialised cell subtypes in the brain (astrocytes and neurons, microglial cells) have been reported to be protected from a number of viruses by the type I IFNs, which also limit virus spread within the CNS [reviewed in Ref. [22]]. The protective mechanisms were expressed through type I IFN signaling and the levels of ISGs, which interestingly was inversely correlated to age. Here, the use of IFN subtypes may be of benefit to restore cytokine expression that is lost upon aging. Furthermore, refined immunotherapy to target specific regions and virus-infected zones of the brain, or indeed other specific tissues may be possible with direct delivery routes rather than systemic application.

2.5. Viral evasion of IFN responses

Many different virus families have inherent mechanisms for IFN evasion through viral encoded host homologues that block IFN production (Table 1) or inhibit IFN signaling, abrogating immune activation of cells (Table 2) [23]. Certain viral pathogens have co-evolved immune evasion strategies in order to survive the battle within the host, affording a selective advantage [24]. For example, the RNA virus of the orthomyxoviridae family, influenza A encodes the viral protein NS1 specifically as an IFN antagonist, which interacts with the IFN-β signaling pathway, blocking IRF3 and the IFN-β promoter, allowing permissive virus infection in the absence of IFN [25]. A large DNA virus, cytomegalovirus (CMV) that has a predilection for infecting DCs, encodes many viral evasion proteins (e.g. IE1) that manipulate the normally high levels of IFN production in this important antigen-presenting cell [26]. In yet another DNA virus family, herpes simplex virus (HSV), IFN responses are essential to stop acute virus replication disseminating to the central nervous system, in an attempt by the host to prevent ensuing encephalitis. However, HSV-1 encodes several viral proteins to abrogate such IFN responses, including the immediate early protein ICP0 blocking IFN-β stimulation, the late protein γ134.5 inhibiting PKR [27], and ICP27 protein inhibiting STAT1 phosphorylation, all of which allow viral ascension of the spinal cord and establishment of latency in the CNS and brain via transportation through the brain stem [28].
One can learn from focusing on immune evasion tactics of these viruses, which provide insights into effective host immune responses that may otherwise lead to resolution or clearance of the virus infection. Indeed, the primary host defense carried out by innate immune cells is often a central target for subversive efforts by both small RNA and larger DNA viruses. This is highlighted by the fact that IFNs and IFN-producing innate cells are frequently counterattacked by different and diverse virus types, being pivotal to the interplay of innate and adaptive responses in immunity [29–31]. Furthermore, a link between type I and type II IFN pathways portrays antiviral synergism of these networks. IFN activating-pathways are inhibited by viruses at a number of levels; pathogen recognition receptors (PRRs), cytosolic signaling events and host cell transcription. With these multiple target hits by the virus on the early IFN networks, the host immune system is weakened allowing a supportive environment for virus replication. In addition, recombinant viruses, with deleted genes encoding IFN antagonist proteins, are often more immunogenic than wildtype and have been experimentally explored as better vaccine candidates.

### 2.6. Current IFN Treatment for Virus Infections

Most clinical treatments have predominantly used IFN-α2 or IFN-β, likely due to manufacturing and production limitations of recombinant IFN and purification from human leucocytes or B lymphoblastoid cell lines. It is noteworthy however that there is no biological context where either IFN-α2 or IFN-β is specifically produced in the host response to an invading pathogen as an isolated single subtype [32]. Such treatments with these limited subtypes overlook the possible therapeutic potential of the other natural IFN subtypes with divergent biological functions. Furthermore, although most IFNs are biologically active in the picomolar range, conventional IFN treatment uses systemic administration of extraordinary high doses, often associated with severe side effects including neurological toxicity limiting treatment efficacy [7,33,34]. Alternative treatment regimes using low dose IFN application, directed to the mucosal immune system, have shown improved clinical efficacy against virus infection in an experimental setting [34–37]. Therefore, exploitation of the dose and delivery modes of the full suite of IFN subtypes for disease control warrants further investigation.
Antiviral activities of different IFN types and subtypes have been demonstrated for a wide range of viruses, including laboratory-adapted strains of influenza, CMV and HSV and clinical isolates of hepatitis C and E viruses, HIV-1. Evidence for non-redundant functions of IFN subtypes for influenza, CMV, HSV-1, HIV-1, HCV and HEV infections using experimental models (Table 3) is described hereafter.

3. Novel Interferon Subtype Therapy

3.1. Influenza Virus

As influenza virus infections are acute in nature, they stimulate IFN expression in the host for a few days only. Type I IFNs are the predominant innate stimulus directly affecting B cells in the mediastinal lymph nodes within the first 48 h post-infection [9]. Select IFN subtypes have been shown to enhance antibody class switching to protective antiviral IgG2a in the mouse model of influenza [38]. IFN-α5 and IFN-α6 were shown to decrease pulmonary virus replication with IFN-α1 the least effective in H1N1 influenza A virus-infected BALB/c mice [39]. Moreover, clinical score, weight loss and lung pathology were absent or significantly reduced in effective IFN subtype-treated mice. Others have demonstrated a role for IFN-β in driving an early Th1 response to acute influenza virus infection, which otherwise shifts to a Th2 response with eosinophilia in the lungs after the first week [40]. However, in C57BL/6 mice, lack of IFN-α/β signaling decreased morbidity and reduced host susceptibility to acute severe influenza [41]. Thus host genotype plays an important role in disease control and subsequent outcome of virus infection.

3.2. Herpes viruses (CMV, HSV-1)

CMV is a ubiquitous species-specific herpesvirus and can cause a myriad of diseases (e.g. hepatitis, encephalitis, retinitis, myocarditis) with no current vaccine available. IFN treatment of mice infected with murine CMV (MCMV) has been evaluated using oral-mucosal delivery of low dose IFN [42]. Reduction of virus load in target organs of virus replication (liver, spleen) was observed to be
equivalent to protection from acute virus infection with systemic delivery of high dose IFN (20,000 IU). In fact low doses of 10 IU/day were optimal for inhibition of MCMV infection in vivo and this antiviral effect was independent of the mouse genotype. Furthermore, IFN-α1 was shown to be superior to IFN-α4 and IFN-α9 against MCMV infection in vivo using transgene delivery for IFN expression in situ [43].

Post-viral myocarditis develops following exposure to CMV and can lead to chronic disease with end stage dilated cardiomyopathy and congestive heart failure [44]. The disease is associated with autoantibody production to heart antigens (e.g. cardiac myosin) and can be exacerbated in otherwise resistant mouse strains with administration of lipopolysaccharide and tumour necrosis factor with MCMV infection [45]. Cardiac inflammation ranges from focal to diffuse cell infiltration of the myocardium and pericardium with degenerative changes in myofibres and irreversible fibrosis. Interestingly, resolution of chronic inflammation is dependent on host genetic factors despite clearance of infectious virus during the acute phase in both susceptible and resistant mouse strains, implicating a chronic autoimmune nature of this disease. Again, divergent IFN subtype functions have been reported with IFN-α6, −α9 and −β subtype therapy providing increased protection from MCMV-induced myocarditis over IFN-α1, −α2, −α4 and −α5 subtypes [46,47].

Interestingly, individual IFN-α subtypes have been shown to provide various degrees of protection against different types of HSV infections [48]. IFN-β significantly reduced viral expression of immediate early, early and late genes in vitro over other IFN-α subtypes, indicating differential downstream events from IFN receptor signaling to the antiviral state. In vivo mouse studies revealed differential effects of IFN subtypes in preventing mucosal HSV infection with IFN-α1 and IFN-β more effective than other subtypes [49,50] and IFN-β superior to IFN-α6 at inhibiting ocular HSV-1 infections [51].

3.3. Human Immunodeficiency Virus-1

Whereas with HIV-1, the role of IFN may extend beyond the direct antiviral functions observed in acute virus infection. In studies using the Friend retrovirus mouse model, the antiviral effects of
individual IFN-α subtypes differed greatly in vivo [52]. Treatment with IFN-α1, −α4, or −α9 but not IFN-α6 resulted in a significant reduction in viral load. Protection with IFN-α1 correlated with an expansion of virus-specific CD8+ T cells and NK cells in the spleen, whereas IFN-α4 and IFN-α9 treatment exclusively correlated with NK cell activation, demonstrating distinct biological effects of the subtypes. However, chronic HIV-1 infection stimulates prolonged IFN expression with more subtypes being produced leading to detrimental ISG sets with an associated longer duration, which does not return to baseline levels [53].

In a recent study it was reported that IFN-α2, although currently in human clinical trials for HIV-1 patients, does not consistently reduce viral loads and is not the most effective subtype against HIV-1 in vitro[54]. In humanised mice, the human IFN-α14 subtype was more potent than IFN-α2 in antiviral activity when used in postexposure prophylaxis and treatment of acute viral infection with better regulation of immune hyperactivation [55]. Distinct from IFN-α2, which elicited higher CD8+ responses, IFN-α14 therapy was associated with increased innate immunity (significantly higher induction of tetherin and MX2, increased APOBEC3G signature mutations in HIV-1 proviral DNA, and higher frequencies of TRAIL+ NK cells). Unlike antiretroviral drugs, the ability of IFN-α14 to reduce both viremia and proviral loads suggests that it has strong potential as a component of a cure strategy for HIV-1 infections.

As seen in the clinical HIV-1 setting, systemic immune activation via IFN stimulation of monocytes is a hallmark characteristic regardless of successful anti-retroviral treatment in suppressing plasma levels of HIV RNA [56,57]. In fact, HIV-1-induced immune hyperactivation is associated with increased prevalence and earlier onset of co-morbidities (cognitive decline, diabetes, liver disease, cardiovascular disease), signifying disease progression in HIV-1 patients. Three plasma biomarkers of monocyte activation and IFN signaling (CXCL10, sCD163 and sCD14) were shown to have distinct correlations with aspects of HIV infection and treatment [58], including cardiovascular disease risk factors [59]. Although viraemia is suppressed with anti-retroviral therapy, residual virus levels, including integrated virus and smoking elevate the risk of mortality. Thus here IFN is a double-edged sword and therapeutic strategies targeting inhibition of IFN pathways during chronic infection rather
than stimulation could reduce immune activation and lower the progression to age-related disease and mortality with prognostic value in HIV-treated patients.

3.4. Hepatitis viruses (HCV and HEV)

Experimental *in vitro* studies of viral RNA replication in human hepatoma cells have shown inhibition by IFN-α and IFN-λ3 to be notably weaker for HEV than HCV [60], with both viruses downregulating ISG expression. Furthermore, out of 13 different IFN-α subtypes, IFN-α2a and IFN-α2b were superior to IFN-α1, −α16 and −α21 against HEV and HCV replication and correlated with upregulation of IFIT3. In an earlier study, IFN-α17 was shown to have enhanced anti-HCV effects compared to that of IFN-α2a in a different experimental model [61]. Future clinical trials to establish efficacy of combinations of different IFN subtypes with and without standard antiviral therapy for patients coinfected with different viruses (*e.g.* HIV-1 and HCV) is warranted.

4. IFN Therapy for Acute and Chronic Virus Infections

An advantage of IFNs is that they are antigen non-specific and can be functional against multiple virus species even from a different order, family and genus. Therefore, IFNs have been proposed for use in broad passive immune prophylaxis, providing therapeutic responses against viral infections and their associated diseases. Even actual IFN inducers *per se* have been considered for the treatment of patients with viral infections. However, excessive IFN signaling may become unregulated in certain viral settings, exacerbating immunopathology leading to chronic inflammatory disorders.

Manipulating the immune system through exogenous cytokine delivery, in the absence of the viral insult, should be heeded with caution as interfering with host immunity may generate long-term inflammatory side effects. The main goal is to achieve full protection by initiating immune responses against the virus-infected targets with the subsequent inflammatory responses returning to baseline levels, restoring homeostasis in tissues and organs [62], as unresolved inflammation with disturbed baselines post virus infection may perpetuate chronic inflammatory disease [63]. On a cautionary note, there are important implications for potential therapeutic use of IFNs in acute versus chronic
virus infections. The value of such non-specific clinical therapies to protect against acute and chronic types of virus infection is discussed below.

### 4.1. Acute Virus Infections

Some virus infections cause acute illness, such as influenza. Influenza virus is usually cleared by the body after 10-14 days, with peak pulmonary anti-viral CD8+ T cells responses shown at day 6-7 post-infection (later for highly pathogenic viruses) [64]. However, in the absence of virus-specific antibodies, normally directed towards the HA molecule, immunity is impaired and tissue necrosis and inflammation can lead to pneumonia and acute respiratory distress syndrome. Indeed, highly pathogenic influenza A viruses (e.g. avian H5N1, H7N9) have a high mortality rate in naïve humans (around 60%). In the mouse model, extreme pathogenicity of H5N1 has been shown to be linked to high steady-state viral titres in the lungs, despite the development of an antiviral CD8+ T cell response [64]. The concept that effective IFN subtype therapy rapidly reduces virus replication and shedding accounts for the fact that potential treatments using IFN subtypes, or synergistic effects of multiple IFN subtypes, for such virulent viruses may exist. Although the exact dosage and timing of treatment in regard to established infections remains questionable, IFN subtype therapy has been medically recognised in emergency treatment of patients during future influenza pandemics [65].

### 4.2. Chronic Virus Infections

On the other hand, control of virus infections that involve a variety of cells and a state of latency presents a different challenge. Reactivation of latent viruses has been linked with disease pathogenesis. Although IFNs antagonise viral gene expression, aiming to ultimately protect the host and are seen as key in controlling viral-mediated morbidity and mortality, they may in part be responsible for co-morbidities seen with some chronic virus infections. Chronic HIV-1 infection is positively correlated with elevated plasma IFN levels and sustained expression of ISGs, that can be utilised as biomarkers of inflammation and disease progression to AIDS [53]. Paradoxically, therapeutic IFN-α administration significantly reduces plasma HIV-1 viral loads in infected patients [53].
Transcription of herpes viruses is regulated in tempo with sequential immediate early, early and late viral gene expression. Indeed, the immediate early ICP0 gene product of HSV-1 directly counteracts the type I IFN pathway in a strong attempt of the virus to override innate immunity [66]. Underlying chronic inflammatory diseases such as HIV and HCV project heavy burdens on the host that may not be easily lifted with existing treatments. It has been reported that collectively these viruses have evolved up to ninety evasion strategies of innate immunity facilitating the establishment of chronic inflammation that fuels virus replication [24]. Thus improved therapies, taking into consideration such immune activation sequelae, are urgently needed. Novel therapeutic IFN subtype strategies may reveal insights into both disease pathogenesis and prognosis. For example, IFN-λ therapy for HCV shows promise but other type I IFN subtypes such as IFN-α17, displaying the highest anti-viral activity [61], may also prove to be innovative.

The detrimental host effect of certain viruses to induce post-viral autoimmune disease is a serious concern and may ultimately lead to transplantation before end-stage organ failure in some chronic disorders (e.g. post-CMV myocarditis progression to dilated cardiomyopathy). It is interesting to note that the ability of some viruses to antagonise the IFN system may possibly have a payoff for the host in protection from activated IFN pathways triggering autoinflammatory diseases (e.g. diabetes, rheumatoid arthritis, systemic lupus erythematosus) shown experimentally using nucleic acid-sensing antagonists [4]. Furthermore, type I IFN signatures have also been linked to disease pathogenesis in chronic bacterial infections such as tuberculosis and leprosy. Nonetheless, treatment with IFN-β is effective therapy for inflammatory bowel disease and multiple sclerosis with autoimmune natures. Thus, complex IFN-associated inflammatory conditions and recent monogenic interferopathies, with ISG subset signatures linked to immune suppression, represent unmet medical needs and challenges in IFN regulation (either blockade or stimulatory therapy) [5].
5. Conclusion

As the multiple IFN subtypes are naturally high in potency and functional against different viral infections, being evolutionary conserved throughout lower invertebrates to primates and humans, they appear to be directly targeted in immune evasion by pathogenic viruses. Restoration of the antiviral immune response with select IFN subtypes may provide the essential key to rescue protective immunity necessary for health. However, heed must be taken as chronic inflammatory conditions maintained by low viral loads present a different disease pathogenesis with disturbed baseline IFN levels. Acute and latent/chronic virus infections characterise major viral diseases that require novel control approaches after stratification of patients for type I IFN signatures. IFN subtypes tailored for virus virulence, host genotype and disease patterns may represent the new frontier in viral medicine, expanding the therapeutic value of this multi-gene family of innate cytokines to better predict patient prognosis.

Conflict of interest disclosure

The author declares no competing financial interests.

References


The IFN family subtype proteins are rapidly induced by invading viruses and bind to cognate IFN receptors on cell surfaces. Distinct and overlapping interferon stimulated genes (ISGs) are transcribed downstream of IFN signaling pathways, dependent on both virus and cell type. The IFNs are evolutionarily conserved amongst species from human/primates to birds and function in host defense against invading pathogens. Piscine IFN proteins occur in fish species with antiviral biological properties.

Fig. 1. Speciation pattern of IFNs functioning in antiviral host defense.
Table 1. Diverse viral evasion mechanisms through antagonist proteins that inhibit IFN production.

<table>
<thead>
<tr>
<th>Virus</th>
<th>Viral antagonist</th>
<th>IFN signaling site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza</td>
<td>NS1</td>
<td>indirectly inhibits RIG-I</td>
</tr>
<tr>
<td>Paramyxovirus</td>
<td>V</td>
<td>indirectly inhibits RIG-I, inhibits MDA5 and interferes with STAT phosphorylation</td>
</tr>
<tr>
<td>HBV</td>
<td>X</td>
<td>degrades proteasomal MAVS</td>
</tr>
<tr>
<td>HCV</td>
<td>NS3-4A</td>
<td>cleaves MAV</td>
</tr>
<tr>
<td>Mumps</td>
<td>V</td>
<td>decoy for IKKe phosphorylation of TBK1</td>
</tr>
<tr>
<td>HPV-16</td>
<td>E6</td>
<td>inhibits IRF-3</td>
</tr>
<tr>
<td>HCMV</td>
<td>pp65</td>
<td>decreases IRF3 phosphorylation and inhibits IRF3 nuclear translocation</td>
</tr>
<tr>
<td>MCMV</td>
<td>pM27</td>
<td>degrades STAT2</td>
</tr>
<tr>
<td>EBV</td>
<td>BGLF4</td>
<td>decreases active IRF-3 levels</td>
</tr>
<tr>
<td>HSV</td>
<td>ICP0</td>
<td>inhibits IRF3 nuclear translocation</td>
</tr>
<tr>
<td></td>
<td>γ134.5</td>
<td>inhibits PKR</td>
</tr>
<tr>
<td></td>
<td>ICP27</td>
<td>inhibits STAT1 phosphorylation</td>
</tr>
<tr>
<td>Ebola</td>
<td>VP35</td>
<td>inhibits IRF3 phosphorylation</td>
</tr>
<tr>
<td>Rhabdovirus</td>
<td>P</td>
<td>inhibits IRF3 phosphorylation</td>
</tr>
<tr>
<td>Nipah</td>
<td>W</td>
<td>blocks nuclear sequestration of active IRF3</td>
</tr>
<tr>
<td>Measles</td>
<td>C</td>
<td>blocks nuclear sequestration of active IRF3</td>
</tr>
<tr>
<td>Adeno</td>
<td>E1A</td>
<td>competes with IRF3 binding site on promoter</td>
</tr>
<tr>
<td>HIV-1</td>
<td>Vif, Vpr</td>
<td>blocks TBK1 phosphorylation</td>
</tr>
</tbody>
</table>

*EBV, Epstein Barr virus; HBV, hepatitis B virus; HCMV, human cytomegalovirus; HCV, hepatitis C virus; HIV-1, human immunodeficiency virus type 1; HPV, human papilloma virus; HSV, herpes simplex virus; MCMV, murine cytomegalovirus.
Table 2. Viral antagonism of Type I and III IFN signaling.

<table>
<thead>
<tr>
<th>Virus a</th>
<th>Viral protein</th>
<th>IFN signaling site</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV-16</td>
<td>E7</td>
<td>inhibits ISGF3 nuclear translocation</td>
</tr>
<tr>
<td>HPV-18</td>
<td>E6</td>
<td>blocks TYK2 and STAT1/2 phosphorylation</td>
</tr>
<tr>
<td>EBV</td>
<td>LMP-1</td>
<td>blocks TYK2 and STAT1/2 phosphorylation</td>
</tr>
<tr>
<td>Marburg</td>
<td>VP40</td>
<td>inhibits JAK1 and STAT1/2 phosphorylation</td>
</tr>
<tr>
<td>Measles</td>
<td>V</td>
<td>inhibits JAK1 and STAT1/2 phosphorylation and degrades STAT3</td>
</tr>
<tr>
<td>Ebola</td>
<td>VP24</td>
<td>inhibits phosphorylated STAT1/2 nuclear translocation</td>
</tr>
<tr>
<td>Mumps</td>
<td>V</td>
<td>degrades STAT1 and STAT3</td>
</tr>
<tr>
<td>Dengue</td>
<td>NS5</td>
<td>degrades STAT2</td>
</tr>
<tr>
<td>Adeno</td>
<td>E1A</td>
<td>inhibits STAT1 and IRF9 nuclear translocation</td>
</tr>
</tbody>
</table>

aEBV, Epstein Barr virus; HPV, human papilloma virus.
Table 3. Antiviral efficacies of Type I IFN subtypes in *in vivo* models.

<table>
<thead>
<tr>
<th>Virusa</th>
<th>Strain</th>
<th>IFN subtype antiviral efficacy</th>
<th>Model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Greatest</td>
<td>Least</td>
</tr>
<tr>
<td>Influenza A/PR8/34</td>
<td>murine α5, α6</td>
<td>α1</td>
<td><em>in vivo</em></td>
</tr>
<tr>
<td>MCMV K181</td>
<td>murine α1</td>
<td>α4, α9</td>
<td><em>in vivo</em></td>
</tr>
<tr>
<td>HSV HSV-1</td>
<td>murine α1, β</td>
<td>α6</td>
<td><em>in vivo</em></td>
</tr>
<tr>
<td>Friend retrovirus</td>
<td>murine α1, α4, α9</td>
<td>α6</td>
<td><em>in vivo</em></td>
</tr>
<tr>
<td>HIV HIV-1</td>
<td>human α14</td>
<td>α2</td>
<td><em>in vivo</em></td>
</tr>
<tr>
<td>HCV</td>
<td>human α17</td>
<td>α2a</td>
<td><em>in vitro</em></td>
</tr>
<tr>
<td>HEV</td>
<td>human α2a, α2b</td>
<td>α1, α16, α21</td>
<td><em>in vitro</em></td>
</tr>
</tbody>
</table>

*MCMV, murine cytomegalovirus; HSV, herpes simplex virus; HCV, hepatitis C virus; HEV, hepatitis E virus, HIV; Human immunodeficieny virus.*