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Mini review

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.

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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

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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

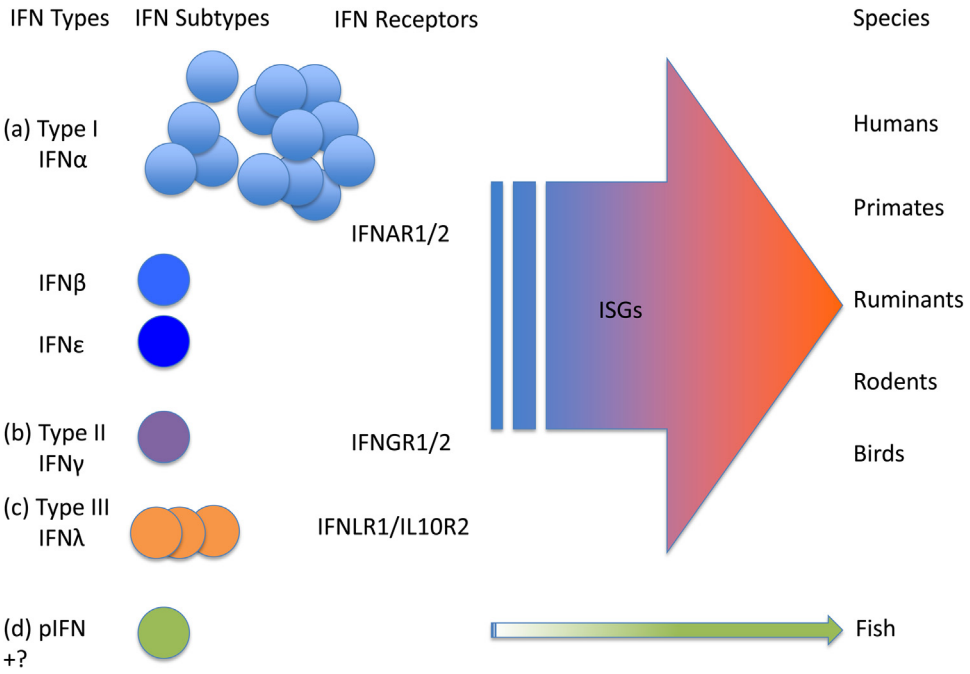

Fig. 1. Speciation pattern of IFNs functioning in antiviral host defense.
The IFN family subtype proteins are rapidly induced by invading viruses and bind to cognate IFN receptors on cell surfaces. Distinct and overlapping interferon stimulated genes (ISGs) are transcribed downstream of IFN signaling pathways, dependent on both virus and cell type. The IFNs are evolutionary 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.

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