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Current Opinion in Virology

The unique regulation and functions of type III interferons in antiviral immunity

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Type I interferons (IFNs) were long considered to be the sole IFN species produced by virus-infected cells until the discovery of type III IFNs (IFNλs), decades later. Like type I IFNs, type III IFNs are induced by and protect against viral infections, leading to the initial conclusion that the two IFN species are identical in regulation and biological functions. However, the two systems differ in the tissue expression of their receptor, resulting in different roles *in vivo*. The unique nature of IFNλs has been further demonstrated by recent studies revealing differences in the regulation of type I and III IFN expression, and how these proteins elicit specific cellular responses. This review focuses on the distinctive features of type III IFNs in antiviral innate immunity.

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Current Opinion in Virology 2015, **12**:47–52

This review comes from a themed issue on **Antiviral strategies**

Edited by **Michael Gale** and **Curt M Horvath**

http://dx.doi.org/10.1016/j.coviro.2015.02.003

Introduction

Interferons are secreted proteins that are defined by their ability to confer resistance to viral infections. Historically type I IFNs were thought to be the only species produced by non-lymphoid cells in response to viral infections, and able to activate innate and adaptive immunity. However, many different examples of antiviral signaling occurring in a type I IFN-independent manner have been described [1–6]. The specific mechanisms that govern these processes are unclear but could be explained, at least in part, by the actions of type III IFNs [7••,8••]. The type III IFN family is composed of three genes: IFNλ1 (IL29), IFNλ2 (Il28A) and IFNλ3 (IL28B). A fourth member, IFNλ4, was identified more recently and is a poorly understood frameshift variant of IL28B that predicts Hepatitis C virus clearance and response to IFN therapies [9]. In humans, IFNλ1 is the most prominent and best studied species, but it is a pseudogene in mice [10]. Type III IFNs signal through the IFNλ receptor (IFNλR) which is composed of two chains: IL28Rα, a unique subunit, and IL10Rβ, shared with cytokines of the IL10 family. Like the type I IFN receptor (IFNAR), binding of the IFNλR results in the activation of JAK/STAT signaling, expression of interferon-stimulated genes (ISGs) and induction of an antiviral state. However, unlike IFNAR, which is expressed on virtually all cell types, IL28Rα is only expressed on specific tissues such as epithelia. Initial reports have focused on the similar activities of type I and III IFNs, but recent work has revealed unique properties of IFNλs and have established them as the primary regulators of antiviral immunity at mucosal surfaces, especially in the intestine [11••]. This review focuses on the fundamental differences between type I and III IFN biology.

IFNλR signaling

Similar to type I and II IFNs, ligation of the IFNλR leads to the activation of kinases of the JAK family and phosphorylation of several members of the STAT family of transcription factors [7••,12•,13]. Once phosphorylated, STAT1 and 2 associate with a third protein called IRF9 to form a transcription complex termed IFN-stimulated gene factor 3 (ISGF3). ISGF3 translocates to the nucleus to induce the expression of ISGs [14]. The IL10Rβ chain is shared with cytokines of the IL10 family and signals via Tyk2, leading to the speculation that Tyk2 mediates IFNλ signaling. Original studies on the IL28Rα carried out before the identification of IFNλs concluded that JAK1, but not JAK2, mediate IFNλ signaling [12•]. However, it was recently shown in a more physiological context that JAK2 is indeed phosphorylated by type III IFNs [15••,16•]. In addition, inhibitor and RNAi studies have shown that JAK2 is necessary for STAT1 phosphorylation in response to IFNλs, and that JAK2 mediates antiviral signaling in cells that only produce type III IFNs [15••]. In these studies, JAK1 was confirmed as a mediator of IFNλ signaling, but further work is needed to determine whether Tyk2 is involved in this pathway. Therefore, type I and III IFNs appear to signal via different JAK/STAT pathways, but no unique ISG among the 300 produced by IFNλ has been identified [13,17,18].

Type III IFN targets and biological activities

Recent studies have revealed important differences in the biological functions of type I and III IFNs. These differences primarily stem from the fact that all cells respond to type I IFNs, while only a small subset responds to type

III. This functional tissue-specificity is due to the expression of the IL28Rα subunit, which is only expressed on epithelial cells of the gastrointestinal, intestinal and reproductive tracts and some immune cells [11••,19,20]. Consequently, type III IFNs are not able to able to confer protection against systemic virus infections. Rather, these IFN are most effective at controlling viral infections at mucosal surfaces [21,22••,23]. Evidence supporting this idea comes from recent work comparing the relative importance of the IFNAR and IFNλR in the control of rotavirus, an RNA virus that primarily infects intestinal epithelial cells. Whereas IFNAR-deficient mice controlled viral replication in the intestine, IL28Rα-deficient intestinal epithelial cells could not mount an effective IFN response and were unable to control rotavirus infection. Furthermore, systemic treatment of infected animals with IFNλ, but not IFNβ, repressed rotavirus infection in the intestine [22••]. *In vitro* studies of human intestinal epithelial cells support the idea that type III IFN induction and responsiveness are key aspects of the biology of these cells. For example, the differentiation state of intestinal epithelial cells dictates the quality of the IFN response, with increasing IFNλ produced as cells polarize [15••], suggesting that epithelial cell biology is intimately linked with the type III IFN system.

Regulation of type III IFN expression

Type I and III IFNs are produced following recognition of viral ligands, most prominently nucleic acids, by a wide range of pattern recognition receptors. On endosomes, viral nucleic acids are recognized by Toll-like receptor (TLR) 3, 7/8 and 9. cGAS and RIG-I like receptors (RLRs) perform the same functions in the cytosol. TLR ligands induce type III IFNs concomitantly with type I, but the pathways activated are unknown [24–27•]. Similarly type III IFNs are induced by, and protect against DNA viruses [28–30], but the precise mechanisms driving these processes have yet to be studied. Type III IFN expression in response to RNA viruses is best understood, and involves RLRs, MAVS and TBK1, like type I IFNs [15••,31–33]. However, the subcellular localization of MAVS determines which IFN species is produced. MAVS is an adapter of the RLR pathway that was first identified as being localized on mitochondria [34] and was later shown to also localize to peroxisomes [1] and mitochondrial-associated endoplasmic reticulum membranes [35]. From peroxisomes, MAVS is able to induce ISGs and control viral infections independently of type I IFNs [1]. Indeed, transgenic cell lines preferentially expressing MAVS on peroxisomes only induced type III IFNs in response to a variety of intracellular ligands [15••]. In addition, the function and abundance of peroxisomes and mitochondria determines the quality of the IFN response. Increasing peroxisomal abundance or inhibiting mitochondrial function favors the expression of type III over type I IFNs. This observation could reflect what happens physiologically in epithelia. Indeed, polarization of epithelial cells increases peroxisome abundance and type III IFN responses to viral infections, while the number of mitochondria and type I IFN expression are unaffected [15••].

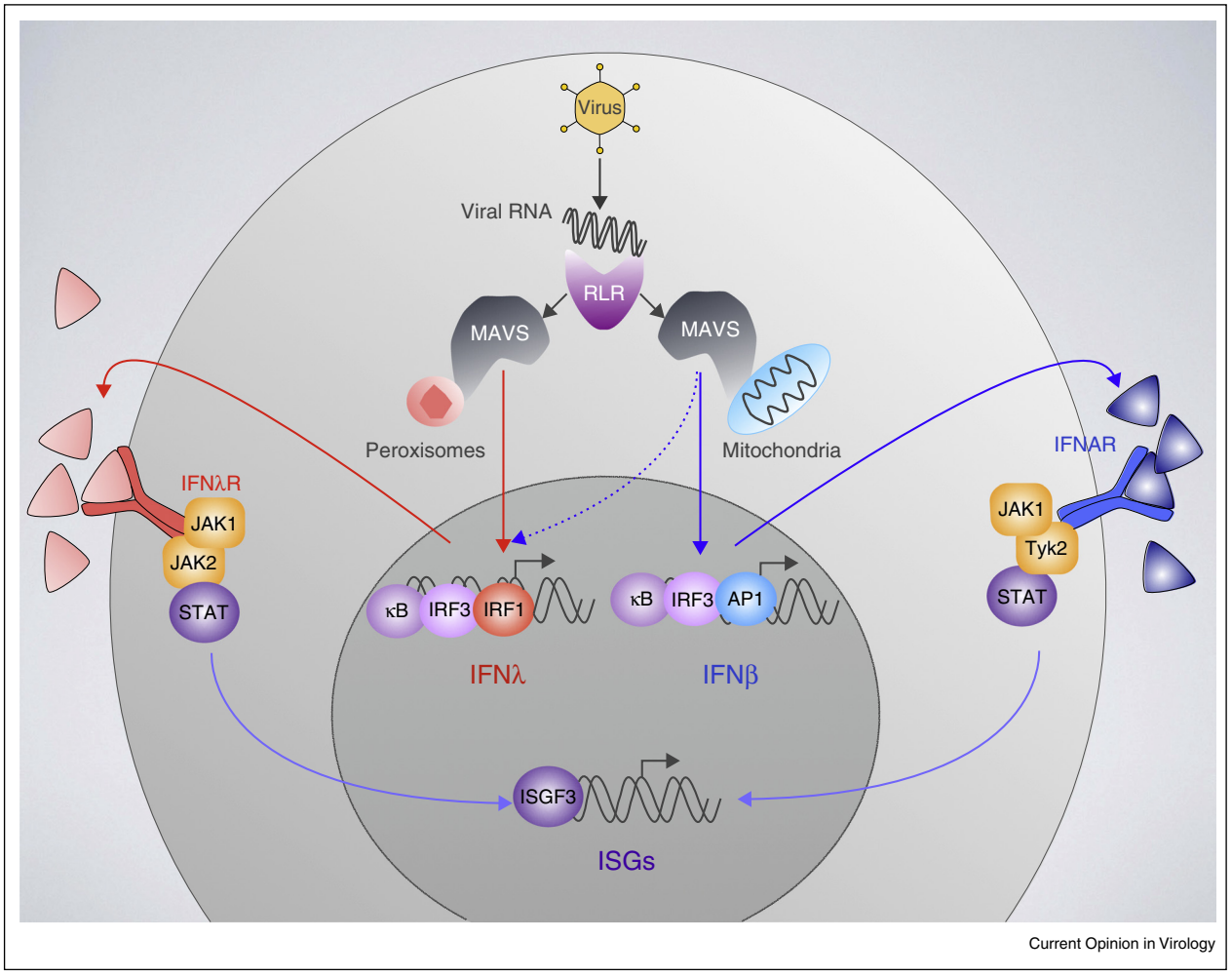
Type I and III IFNs are also differentially regulated at the transcriptional level. IFNβ, the prototypical type I IFN, is induced by the combined actions of the transcription factors AP-1, interferon regulatory factor (IRF) 3 and IRF7 and NFκB. The binding sites for each set of transcription factors are localized in close proximity to each other and IFNβ expression requires the cooperative binding of all activators in a complex termed the enhanceosome [36,37]. The IFNλ1 promoter contains binding sites for the same sets of transcription factors. However, only IRF3, 7 and NFκB are required for type III IFN induction [15••,32,33]. In fact, MAP kinases that activate AP-1 are not required for type III IFN production in response to RNA viruses, demonstrating that AP-1 is dispensable in the IFNλ1 pathway [15••].

Both IFN families also contain binding sites for IRF1, the first IRF identified. Although first reports concluded that IRF1 bound the IFNβ promoter, IRF1 KO mice and cells are unimpaired in their ability to induce type I IFN expression [38]. However, IRF1 is known to be important in antiviral defense, and was thought to act in an interferon-independent manner [1,2]. Recent studies have confirmed that IRF1 does not induce IFNβ [15••], but does instead control type III IFN expression in response to RNA viruses [15••,39,40]. In addition, while IFNβ regulation requires all components of the enhanceosome, it appears that type III IFNs can be induced through the independent action of IRFs and NFκB [41]. This finding has important implications: first, the limited number of transcription factors it requires explains the very high inducibility of type III IFNs. Also, if NFκB and IRFs can independently induce type III IFNs, one can predict that this pathway is less susceptible to be successfully targeted by pathogens. These findings define unique pathways for the induction of each IFN family: IRF3/7 and NFκB are activated by both mitochondrial and peroxisomal MAVS to mediate the expression of both IFN classes. However, MAVS on peroxisomes activates IRF1 to only regulate type III IFNs while MAVS on mitochondria can activate MAP kinases to induce type I IFNs (Figure 1).

Simple tools to study type III IFNs in mouse systems

Most studies on type III IFNs have been carried out in human systems as the tools to study mouse IFNλs are lacking. As type I and III IFNs differ in their ability to activate JAK2 [15••,16•], immunoblotting against phosphorylated JAK2 can report type III IFN signaling in a given experimental system. In parallel, JAK2 RNAi, knockout and/or inhibition with pharmacological inhibitors such as AG490 or 1,2,3,4,5,6-hexabromocyclohexane

Figure 1



Signaling upstream and downstream of type III interferons (IFNs). MAVS on peroxisomes mediates type III IFN (IFNλ) signaling downstream of viral RNA detection by RLRs. IFNλ is expressed by IRF1, IRF3 and NFκB by MAVS on peroxisomes. Type I IFN (IFNβ) is induced by the combined action of IRF3, NFκB and AP-1, downstream of mitochondrial MAVS. Ligation of the type I IFN receptor (IFNAR) activates JAK1 and Tyk2 to induce ISG expression through ISGF3. The type III IFN receptor (IFNλR) probably requires JAK1 and JAK2 to activate STAT phosphorylation.

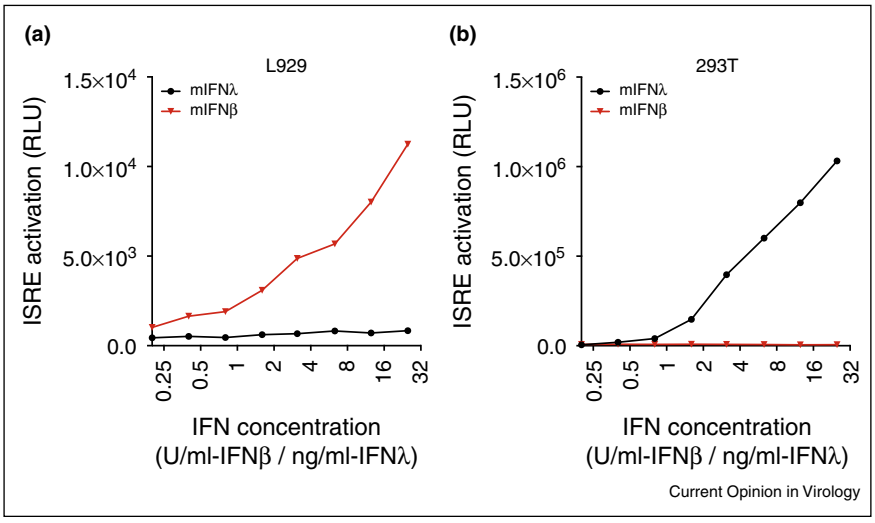
[42] will specifically block type III IFN signaling without affecting type I [15••].

As a complementary method, we have developed a very simple bioassay that enables the quick and distinct detection of mouse type I and III IFNs. Our system utilizes human 293T and mouse L929 cells that express luciferase under the control of an ISRE promoter, the sequence activated by type I and III IFNs. L929 readily respond to mouse IFNβ in a dose-dependent manner but they do not respond to IFNλ2 (Figure 2a). Therefore, these cells can be used to detect IFNβ without detecting IFNλ. To selectively detect IFNλ we took advantage of the fact that IFNβ cannot signal across species while IFNλs do (Figure 2b). Therefore human 293T-ISRE cells can be used to specifically detect mouse type III IFNs, without detecting type I. These bioassays are simple and inexpensive, and are very efficient at detecting specific IFN species.

Conclusions

Recent studies have revealed that the transcriptional regulation of type I and III IFNs are fundamentally different, and that the cellular signaling pathways that drive expression of each subtype can also differ. But perhaps the most fundamental difference between the two systems is their physiological functions *in vivo*, with type III IFNs being the main drivers of antiviral immunity at mucosal surfaces. This tissue-restricted function of type III IFNs has implications in IFN-mediated therapies. PEGylated IFNα has long been used to treat chronic viral infections such as Hepatitis B/C, which infects

Figure 2



Bioassays to specifically detect IFNβ and IFNλ in mouse cells. L929 cells do not respond to mouse IFNλ2 but enable the detection of increasing concentrations of mouse IFNβ **(a)**. As IFNλs are able to signal across species but IFNβ is not, human 293T cells are able to detect mouse IFNλ2 but not IFNβ. Units are in ng/ml (IFNλ2) or in units/ml (IFNβ).

hepatocytes. However, this treatment is associated with side effects that limit its use. As human hepatocytes express IFNλR but most cells in the body do not, IFNλ clinical trials have been very promising in both effectiveness and limitation of side effects [43].

The innate immune system is often described as the first line of defense against pathogens. Among this first line of defense, the first soldiers exposed to pathogens are epithelial cells that constitute the barrier between us and the outside world. The fundamental role of type III IFNs in this tissue therefore makes them an essential weapon in our arsenal against pathogens.

Acknowledgements

JCK is supported by NIH Grants AI093589, AI072955, AI113141-01, and an unrestricted gift from Mead Johnson & Company. Dr. Kagan holds an Investigators in the Pathogenesis of Infectious Disease Award from the Burroughs Wellcome Fund. CO is supported by a Fellowship from the Crohn's and Colitis Foundation of America.

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- •• of outstanding interest

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