Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Interferon Lambda

SS7-1

Differential negative regulation of type I and type III interferons underlies extended antiviral effects of interferon-lambdas

Sergey V. Smirnov [1], Christoph Burkart [2], Wei Li [1], Anita Lewis-Antes [1], Joan Durbin [3], Dong-Er Zhang [2], Sergei V. Kotenko [1], [1] *Department of Biochemistry and Molecular Biology, University Hospital Cancer Center, New Jersey Medical School, UMDNJ, Newark, NJ, USA,* [2] *Moores UCSD Cancer Center, Department of Pathology and Division of Biological Sciences University of California San Diego, La Jolla, CA, USA,* [3] *Department of Pathology, New York University School of Medicine, NY, USA*

Two types of IFNs are produced in response to virus infection and play a crucial role in the establishment of a multi-faceted antiviral response. For decades, classical type I IFNs were considered indispensable and unreplaceable antiviral mediators that evoke the first line of defense against invading viral pathogens. However, recently discovered type III IFNs are challenging the established paradigm and steadily gaining increasing popularity and attention. Although type I and type III IFNs engage distinct receptor complexes, both types of IFNs activate the same signal transduction pathways, induce expression of the same set of genes, and subsequently have very similar biological activities. Therefore, type III IFNs appear to mimic type I IFNs in their expression pattern, signaling pathways and biological activities. Nevertheless, a growing body of evidence suggests that type III IFNs, do not merely serve as a parallel backup mechanism for the type I IFN antiviral system. The first important difference resides in the expression pattern of IFN receptors; whereas type I IFN receptors are expressed in most cell types, IFN-λ receptor demonstrates a more restricted pattern of expression that limits the action of IFN-λs, in contrast to IFN-α/β, to primarily mucosal/epithelial tissues. However, because epithelial cells respond equally well to both types of IFNs, the distinct pattern of IFN receptor expression does not reveal a unique function of type III IFNs in antiviral response in epithelial tissues. We now demonstrate that differential negative regulation of signaling triggered by type I and type III IFNs renders type III IFNs capable of inducing and maintaining a long-lasting antiviral state in epithelial cells. In contrast, antiviral state induced by type I IFNs is transient because cells quickly become insensitive to type I IFNs. Moreover, we uncovered a crosstalk between type I and type III IFNs that balances the action of type I and type III IFNs for the ultimate goal of achieving robust and well-tuned antiviral protection in epithelial cells.

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SS7-2

IFN-λ1 inhibits the human Th2 response

Grant Gallagher, *HUMIGEN LLC, the Institute for Genetic Immunology, Hamilton, NJ, USA*

The type-III IFNs, known variously as IFN-λ1, λ2 & λ3, or IL-29, IL-28A & IL-28B respectively, were first described in 2003. As well as a well-described anti-viral activity, the distribution of these ligands' receptor leads one to infer that they may have a particular role at the interface between the epithelia (and hence the outside of the body) and the immune system. Our laboratory has examined this interaction, with particular focus on the relationship between the type-III IFNs, plasmacytoid dendritic cells and T-cell function. Here, we shall describe the role of IFN-λ1 in modulating the human Th2 response. IFN-λ1 acts directly on CD4+ve T-cells and dentritic cells, especially plasmacytoid DCs. When activated cia CD3 and CD28 in the presence of IFN-λ1, naive CD4+ T-cells fail to upregulate the IL-4 receptor or GATA3. As a consequence, they show a reduced ability to differentiate to IL-4, IL-5 or IL-13 expressing or secreting cells. These effects are not accompanied by a complementary elevation of Th1-like activity (for example, IFN-γ secretion). Interestingly, IL-4 and IL-13 can efficiently upregulate IFN-λ1 secretion by pDC, but not by direct action on these cells. Rather, they act upon monocytes, whose consequent secretion of IL-1 Receptor Antagonist (IL-1RA) stimulates elevated IFN-λ1 secretion from the pDC.

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SS7-3

A non-redundant role of IFN-λ in antiviral defense of the intestinal tract

Markus Mordstein [1], Johanna Pott [2], Tanel Mahlakoiv [1], Eva Neugebauer [3], Vanessa Ditt [3], Christian Drosten [3], Mathias W. Hornef [2], Thomas Michiels [4], Peter Staeheli [1], [1] *Department of Virology, University of Freiburg, Germany,* [2] *Institute for Med. Microbiology and Hospital Epidemiology, Hannover Medical School, Germany,* [3] *Institute of Virology, University of Bonn Medical Centre, Germany,* [4] *de Duve Institute, Université catholique de Louvain, Brussels, Belgium*

Virus-infected cells secrete a broad range of interferon (IFN) subtypes which in turn trigger the synthesis of antiviral factors that confer host resistance. IFN-α, IFN-β and other type I IFNs signal through a common universally expressed cell surface receptor (IFNAR), whereas type III IFN (IFN-λ) uses a distinct cell-type-specific receptor complex (IL28R) for signaling. Using mice that lack functional receptors for IFNAR, IL28R, or both, we have recently shown that IFN-λ contributes to resistance against several human pathogenic viruses that infect the respiratory tract such as influenza A virus, respiratory syncytial virus and SARS coronavirus (*Mordstein et al., J Virol 2010*). We now present data indicating that IFN-λ also plays an important role in defense against viruses that infect the intestinal tract. Cells expressing functional IL28R complexes could be visualized throughout the entire intestinal tract. Interestingly, expression of interferon-induced Mx1 protein in these cells was much stronger after treatment with IFN-λ as compared to treatment with type I IFN. Intestinal epithelial cells (IEC) isolated from mice infected with murine rotavirus expressed antiviral genes only at low levels if IFN-λ signaling was impaired. In contrast, antiviral gene expression in IECs of IFNAR-deficient mice was only slightly lower than in cells from wild-type mice. Accordingly, significantly higher levels of murine rotavirus antigen could be detected in the colon of infected IL28R-deficient mice compared to wild-type mice or mice lacking functional type I IFN receptors. Together with our previous findings that functional IFN-λ signaling prevents spread of intranasally applied SARS coronavirus into the mouse intestine as well as virus shedding via the fecal route, our new data strongly suggest that IFN-λ plays a more prominent role in protection of the intestinal tract against viral infections than type I IFN.

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SS7-4

Primary human hepatocytes can produce and respond to interferon-lambda (IFN-λ)

Raymond P. Donnelly, *Division of Therapeutic Proteins, Center for Drug Evaluation & Research, FDA, Bethesda, MD, USA*

Interferon-lambda (IFN-λ) is currently being tested clinically as a novel, anti-viral, therapeutic agent to treat patients with chronic hepatitis C virus (HCV) infection. Liver is the primary target organ for HCV because it preferentially infects and replicates in hepatocytes. Although several reports have shown that human hepatoma cell lines such as HepG2 and Huh-7 can respond to IFN-λ, it is not known whether primary human hepatocytes can respond directly to this cytokine. It has also not been determined if primary human hepatocytes can produce IFN-λ in response to viral infection or TLR agonists such as poly I:C. We found that freshly isolated primary human hepatocytes co-express high levels of type-I (IFN-α and -β) and type-III (IFN-λ) interferon mRNA and protein following treatment with poly I:C *ex vivo*. The induction of IFN-β mRNA expression preceded the peak of IFN-α and IFN-λ gene expression. Furthermore, the elevated levels of type-I and type-III IFN gene expression correlated with expression of the corresponding proteins as measured by specific ELISAs. We also found that primary human hepatocytes express IFN-λ receptors (IL-28R) and can respond well to IFN-λ stimulation. Although the magnitude of IFN-stimulated gene (ISG) expression induced by IFN-λ was generally lower than that induced by IFN-α, the repertoire of genes that are induced by IFN-λ was essentially the same as that induced by IFN-α as determined by comparative cDNA microarray analyses. Activation of hepatocytes by IFN-λ occurs independently of type-I IFNs because treatment with an anti-IFNAR antibody largely blocked induction of ISG expression by IFN-α,