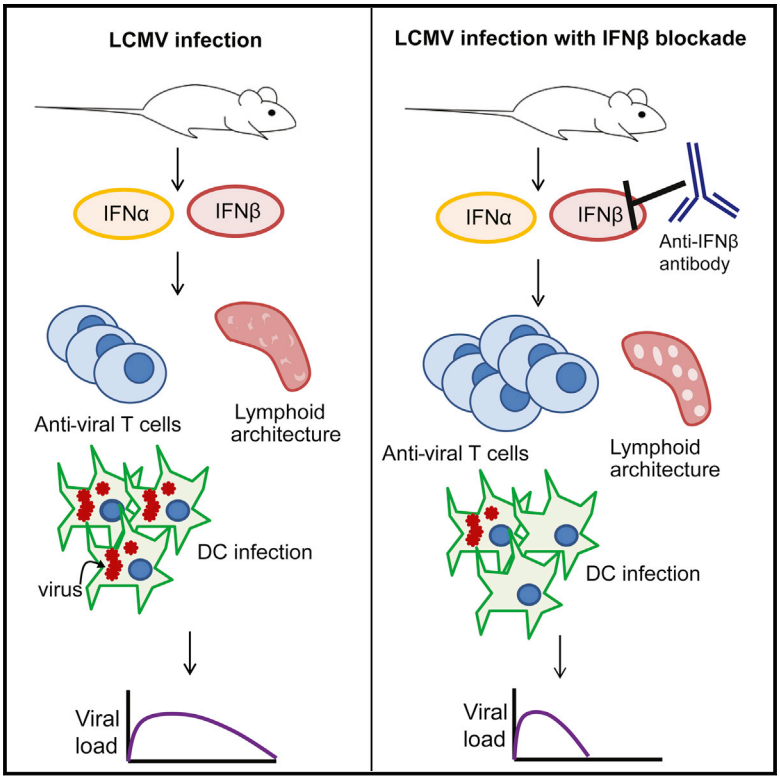
Short Article

Cell Host & Microbe

Blockade of Interferon Beta, but Not Interferon Alpha, Signaling Controls Persistent Viral Infection

Graphical Abstract



Highlights

- IFNα controls early viral dissemination, but does not affect long-term viral control
- IFNβ contributes to disruption of splenic architecture
- Blocking IFNβ improves T cell responses and accelerates clearance of persistent virus
- IFNβ blockade decreases rates of CD8α$^-$DC infection, suggesting a mechanism of action

Authors

Cherie T. Ng, Brian M. Sullivan, ..., Robert D. Schreiber, Michael B.A. Oldstone

Correspondence

mbaobo@scripps.edu

In Brief

Interferon α (IFNα) and IFNβ utilize the same type I IFN receptor to regulate immune responses against microbial infection. Ng et al. show in vivo that IFNβ and IFNα have differential roles in controlling a persistent viral infection, and that IFNβ is the major factor responsible for causing viral persistence.

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Blockade of Interferon Beta, but Not Interferon Alpha, Signaling Controls Persistent Viral Infection

Cherie T. Ng,[1] Brian M. Sullivan,[1] John R. Teijaro,[1] Andrew M. Lee,[1] Megan Welch,[1] Stephanie Rice,[1] Kathleen C.F. Sheehan,[2] Robert D. Schreiber,[2] and Michael B.A. Oldstone[1,*]
[1]Department of Immunology and Microbial Science, The Scripps Research Institute, La Jolla, CA 92037, USA
[2]Department of Pathology and Immunology, Washington University School of Medicine, St. Louis, MO 63110, USA
*Correspondence: mbaobo@scripps.edu
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SUMMARY

Although type I interferon (IFN-I) is thought to be beneficial against microbial infections, persistent viral infections are characterized by high interferon signatures suggesting that IFN-I signaling may promote disease pathogenesis. During persistent lymphocytic choriomeningitis virus (LCMV) infection, IFNα and IFNβ are highly induced early after infection, and blocking IFN-I receptor (IFNAR) signaling promotes virus clearance. We assessed the specific roles of IFNβ versus IFNα in controlling LCMV infection. While blockade of IFNβ alone does not alter early viral dissemination, it is important in determining lymphoid structure, lymphocyte migration, and anti-viral T cell responses that lead to accelerated virus clearance, approximating what occurs during attenuation of IFNAR signaling. Comparatively, blockade of IFNα was not associated with improved viral control, but with early dissemination of virus. Thus, despite their use of the same receptor, IFNβ and IFNα have unique and distinguishable biologic functions, with IFNβ being mainly responsible for promoting viral persistence.

INTRODUCTION

Type I interferon (IFN-I) is a key element in the innate and adaptive response against host infection. Important functions of this family of cytokines include inducing an antimicrobial state, moderating innate immunity, and activating adaptive immunity. Although IFN-Is have generally been thought to be beneficial to the immune response against microbial infections, recent research has shown that IFN-I signaling may be detrimental in several pathogenic infections (Davidson et al., 2014; Harris et al., 2010; Mayer-Barber et al., 2014; Teijaro et al., 2013; Teles et al., 2013; Wilson et al., 2013). Further, persistent viral infections such as HIV, SIV, and HCV are characterized by high interferon signatures suggesting that high levels of IFN-I signaling may play a role in disease pathogenesis (Bolen et al., 2013; Hardy et al., 2013; Sedaghat et al., 2008; Stylianou et al., 2000). Previously, we reported that blockade of IFN-I signaling led to the accelerated clearance of persistent infection with the clone 13 (Cl-13) strain of lymphocytic choriomeningitis virus (LCMV) (Teijaro et al., 2013). IFN-I signaling was associated with several factors that correlated with an immune-suppressive environment including the following: (1) induction of negative immune regulators (NIRs) interleukin-10 (IL-10) and programmed death ligand-1 (PD-L1), (2) disruption of splenic architecture, and (3) alteration of lymphocyte migration within the spleen. Blockade of IFN-I signaling corrected these defects, resulting in improved viral control. Although the IFN-I pathway was identified as a master regulatory pathway involved in persistent LCMV infection, it is unknown whether a specific species of IFN-I is responsible for these phenomena.

The IFN-I family consists of a dozen IFNα subtypes, IFNβ, as well as IFNε, IFNω, and IFNκ, which are induced after the detection of pathogens by pattern-recognition receptors. All IFN-I utilize the same heterodimeric receptor composed of IFNAR1 and IFNAR2; however, IFN-I subtypes have different signaling activities. Structured analysis has revealed that functional differences between IFNs are linked to their unique receptor binding strengths and dissociation rates, which combine to determine their ability to induce conformational change in the receptor. These ultimately control signal generation and downstream gene expression (Piehler et al., 2012; Thomas et al., 2011). Importantly, IFNβ has the highest binding affinity of the IFN-I family (Piehler et al., 2012).

The LCMV Cl-13 virus induces a persistent viral infection in adult immunocompetent mice (Ahmed and Oldstone, 1988; Oldstone, 2002; Oldstone and Campbell, 2011). During Cl-13 infection, IFNβ is produced at high levels within the first 18–24 hr after infection. Comparatively, only a minimal amount is detected during infection with the Armstrong 53b (ARM) strain of LCMV, which only differs by three amino acids from Cl-13, but causes an acute infection (Bergthaler et al., 2010; Sullivan et al., 2011). IFNα is detected in both Cl-13 and ARM infection; however, Cl-13 infection induces approximately 3-fold more IFNα (Teijaro et al., 2013). The presence of robust levels of IFNβ during infection with Cl-13 and its relative absence during ARM infection suggests that IFNβ may play a major role in IFN-I mediated viral persistence. Based on these observations, we sought to determine the in vivo contribution of IFNβ, as well as IFNα, to persistent LCMV infection using deletion mutants and antibody blockade. We found that early blockade of IFNβ alone does