JEM Journal of Experimental Medicine

VIEWPOINT

COVID-19 and emerging viral infections: The case for interferon lambda

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With the first reports on coronavirus disease 2019 (COVID-19), which is caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the scientific community working in the field of type III IFNs (IFN-λ) realized that this class of IFNs could play an important role in this and other emerging viral infections. In this Viewpoint, we present our opinion on the benefits and potential limitations of using IFN-λ to prevent, limit, and treat these dangerous viral infections.

Infection with SARS-CoV-2 has emerged as a major global threat. First reported in China at the end of 2019, this outbreak rapidly spread throughout the globe and was declared a pandemic by the World Health Organization on March 11, 2020. In the absence of approved therapies or vaccines to prevent or treat this infection, its rapid dissemination has overwhelmed public healthcare systems worldwide, causing severe economic and social distress. The previous high mortality outbreaks caused by SARS-CoV-1 in 2003 and Middle East respiratory syndrome (MERS)–CoV in 2012 illustrate that the emergence of novel viruses is not an isolated occurrence. However, the former outbreaks differed substantively from COVID-19, which can be transmitted by asymptomatic individuals. Currently, the primary tool to mitigate SARS-CoV-2 is social distancing, and an effective antiviral pharmacologic agent would be an important clinical and public health tool.

IFNs as natural broad-spectrum antivirals

A wide spectrum of viruses can directly cause human disease, ranging in severity from asymptomatic to life threatening. Host survival is dependent upon key factors including cellular mechanisms of innate antiviral immune response, intended to counter virus replication until virus-specific lymphocytes can eliminate the infection. Therefore, the development of therapeutic intervention strategies that augment these intrinsic, early broad-spectrum antiviral mechanisms is desirable. Although the biology, life cycle, and pathogenesis of different viruses are widely divergent, IFNs activate protective mechanisms aimed at both virus control and elimination. Administration of IFNs can be used for prophylaxis as well as early therapy, predicated on the principle of supplementing to compensate for insufficient IFN production or activity that might be actively blocked by the virus.

IFN-λ as an antiviral drug

For decades, type I IFNs (IFN-α/β) have been explored as mediators of rapid, innate antiviral protection. In 2003, a novel group of three cytokines, now known as type III IFNs (IFN-λs), was discovered that act independently of type I IFNs to establish antiviral resistance in cells (Kotenko et al., 2003; Sheppard et al., 2003). An additional member of this family (IFN-λ4) was discovered in 2013 (Prokunina-Olsson et al., 2013). Most of the information on the function of IFN-λs has been generated using mouse models and thus has to be critically evaluated in relation to human disease (Ye et al., 2019). The distinctive actions of type I and type III IFNs are achieved through the engagement of separate nonoverlapping heteromeric receptor complexes: IFNAR complex (with IFNAR1/IFNAR2 subunits) for all type I IFNs and IFNL complex (with IFNLR1/IL10R2 subunits) for all type III IFNs (Fig. 1). Signaling pathways and sets of

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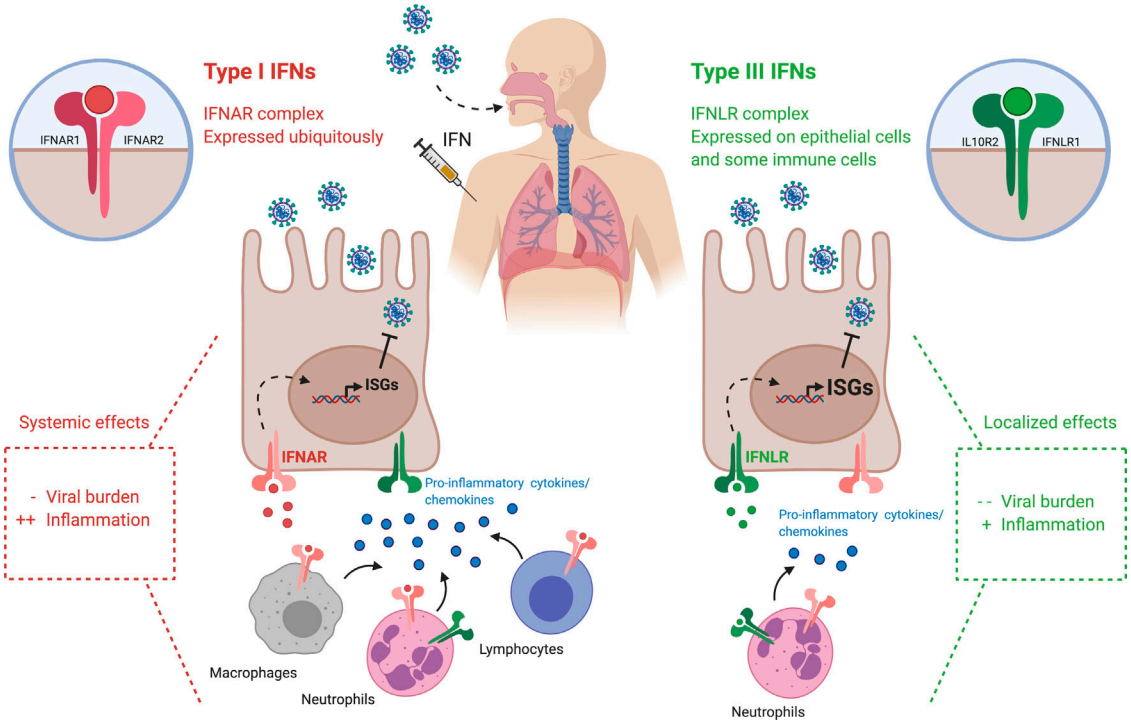

Figure 1. **Potential benefits of using type III IFNs for prevention and treatment of COVID-19** Type I IFNs (IFN-α/β) signal through a heterodimeric receptor complex, IFNAR, which is comprised of IFNAR1 and IFNAR2 subunits. IFNAR activation induces expression of ISGs and triggers pro-inflammatory responses via the recruitment and activation of immune cells. This promotes an antiviral state in the host, but as IFNAR is expressed on all cells, the administration of type I IFN can have serious systemic side effects. In contrast, type III IFNs (IFN-λ1-4) signal through a distinct receptor complex, IFNLR, which consists of IL10R2 and IFNLR1 subunits. IFNLR1 expression is restricted to epithelial cells and a subset of immune cells, including neutrophils. Therefore, type III IFN administration as a prophylactic treatment or at an early stage of COVID-19 would result in ISG expression and antiviral response localized to epithelial cells, reducing side effects and inflammation associated with the systemic action of type I IFNs.

IFN-stimulated genes (ISGs) induced by these IFNs are remarkably similar but not redundant (Crotta et al., 2013; Galani et al., 2017). IFNAR is expressed on all cells, while IFNLR, limited by IFNLR1 expression, is restricted to epithelial cells and a subset of immune cells, including neutrophils. Due to these specific expression patterns, type I IFNs provide a systemic response, and IFN-λs guard epithelial surfaces (Broggi et al., 2020; Fig. 1).

Type I IFNs have been used to treat chronic hepatitis C virus and hepatitis B virus infection and may have the potential to protect patients during outbreaks of other viruses. However, these treatments have significant systemic side effects due to the ubiquitous expression of IFNAR. In mice, IFN-λ was found to be more effective than IFN-α in preventing and treating influenza virus infection, with no increase in inflammation and tissue damage as compared with IFN-α (Davidson et al., 2016; Galani et al., 2017). IFN-λ was also more potent than IFN-α in restricting viral dissemination from nasal epithelium to the upper respiratory tract (Klinkhammer et al., 2018). Clinical trials of IFN-λ for the treatment of chronic hepatitis C virus infection documented fewer and milder side effects, but equal efficacy, when compared with IFN-α–based therapies (Muir et al., 2014). These studies suggest specific advantages for IFN-λs as antiviral therapeutics at epithelial surfaces.

COVID-19 treatment by IFN-λ: Pros and cons

With no time to spare for new pharmaceutical developments, the race is on for the repurposing of existing drugs. A compelling case can be made for IFN-λ–based therapeutics. Pegylated IFN-λ1 (peg-IFN-λ1) is the only IFN-λ currently available as a therapeutic agent. In vitro, treatment with IFN-λ showed potency against a variety of viruses, including SARS-CoV1 and MERS-CoV. The main function of IFN-λ is to prevent viral infection by establishing an antiviral state and, if infected, to slow viral replication and dissemination. In contrast to IFNAR, the IFNLR is largely absent on resting immune cells in humans and mice (with the notable exception of neutrophils [Blazek et al., 2015; Broggi et al., 2017; Espinosa et al., 2017] and human B cells [Goel et al., 2020]), allowing to avoid or minimize systemic inflammation caused by treatment with type I IFNs (Broggi et al., 2020; Fig. 1). Severe lung inflammation and tissue damage are hallmarks of COVID-19, significantly contributing to mortality from this infection (Mehta et al., 2020); thus, enhancement of inflammation and cytokine storm must be avoided. However, it remains to be elucidated whether IFNLR can be up-regulated upon stimulation or in a highly inflamed environment, increasing the risk of possible adverse effects of IFN-λ on human cells (Espinosa et al., 2017; Goel et al., 2020). The absence of pro-inflammatory effects in the lungs (Davidson et al., 2016; Forero et al., 2019; Galani et al., 2017) is one of the most important arguments for the specific advantage of IFN-λ over type I IFNs as a treatment option for COVID-19. However, it is very important to establish if immune cells are responsive to IFN-λ in COVID-19, as

their activation exacerbates inflammation. It also remains to be seen whether IFN-λ shares the known antiproliferative effect of type I IFNs and whether this could impede repair processes during recovery or sensitize epithelial cells to virus-induced cell death.

In addition, bacterial superinfections can be associated with severe cases of COVID-19 (Zhang et al., 2020 *Preprint*), although this varies between clinical studies. Type I IFNs are known to be detrimental in select bacterial infection models (Davidson et al., 2015). For example, *Ifnlr*$^{-/-}$ mice show improved bacterial control in virus–bacteria superinfection models (Planet et al., 2016), and ectopic induction of IFN-λ production proved to be detrimental in mice previously infected with influenza (Rich et al., 2019). While type I IFNs often suppress antibacterial action of immune cells, IFN-λ may employ other routes to facilitate bacterial superinfection, such as reduction in neutrophil recruitment (Blazek et al., 2015; Rich et al., 2019) and/or neutrophil bactericidal activities (Broggi et al., 2017). Although mouse models do not fully recapitulate human diseases with respect to IFN-λ activities, animal studies give a mandate to carefully evaluate the use of IFN-λ as a therapeutic agent against COVID-19.

Although the restricted expression pattern of IFNLR1 may be advantageous in potentially deleterious pro-inflammatory effects of IFN-λ, it may come at the cost of efficacy. Indeed, IFN-λ will only induce an antiviral program in cells expressing IFNLR1. For SARS-CoV-2, it is still debated whether alveolar macrophages or endothelial cells are productively infected and could serve as a virus reservoir not accessible to IFN-λ antiviral action for lack of IFNLR1. While IFN-λ may be better suited than type I IFNs as host-directed anti–SARS-CoV-2 therapy, studies are needed immediately to assess possible detrimental effects that should be factored into further use of IFN-λ.

Although not yet used in active COVID-19 disease, no increased risk of lung infections has emerged from the 19 clinical studies of in over 3,000 patients who were treated for up to 48 wk with peg-IFN-λ1. Potential adverse effects might also be minimized by the shorter duration of treatment. For example, the proposed Phase III clinical trial for chronic hepatitis D virus will be dosed once weekly for 48 wk, as it was in the preceding Phase II study (ClinicalTrials.gov identifier: NCT02765802). However, in the case of acute COVID-19, one or two doses of peg-IFN-λ1 are deemed sufficient in the currently designed randomized clinical trials. This approach could provide immediate protection to healthcare workers and other persons at high risk of being infected or during early stages of infection, while patients show no sign of an inflammatory reaction, especially in the lungs.

There are many outstanding questions in relation to COVID-19 and IFN-λs. We need to understand whether the virus induces the endogenous expression of IFN-λ and/or blocks IFN-λ responses. Is there an age difference in the expression of IFN-λ or its receptors that can explain the more severe disease in older patients? What are the effects of IFN-λ on inflammatory responses and mechanisms of tissue damage and repair and how these activities should be measured in the clinical trials with peg-IFN-λ1 in development for COVID-19? We also advocate for open access for the scientific community to the results of clinical trials to ensure their expert interpretation that can inform further measures. The COVID-19 pandemic illustrates the unmet need for prophylactic and rapid-response measures to boost the antiviral host response. IFNs, and IFN-λ specifically, might address this need for broad-spectrum antiviral biologicals that could help not just this pandemic outbreak, but also future viral threats.

Acknowledgments

We would like to acknowledge the input of other members of the interferon lambda community who participated in discussions on this topic: Evangelos Andreakos, Francine Baker, Connor Bamford, Raymond Donnelly, Darragh Duffy, Adriana Forero, Amariliz Rivera-Medina, Ram Savan, and Nikaia Smith. The Viewpoint was also inspired by the guest session on type III IFNs at the American Association of Immunologists 2020 meeting, which was canceled due to COVID-19; we appreciate the support for this session provided by the Interferon and Cytokine and Interferon Society. The figure was created using BioRender.com.

L. Prokunina-Olsson, O.O. Onabajo, and T.R. O'Brien are supported by the Intramural Research Program of the National Cancer Institute/National Institutes of Health. H.M. Lazear is supported by National Institutes of Health grant R01AI39512. H. Piontkivska is supported by National Institutes of Health grant R21AG064479-01 and a Brain Health Research Institute Pilot Award from Kent State University. C. Odendall is supported by a Sir Henry Dale Fellowship from the Royal Society and the Wellcome Trust (206200/Z/17/Z). A. Wack is supported by the Francis Crick Institute, which receives its core funding from Cancer Research UK (FC001206), the UK Medical Research Council (FC001206) and the Wellcome Trust (FC001206). R.E. Dickenson is supported by a studentship from the UK Medical Research Council. N. Alphonse is supported by a studentship from the King's College London/Francis Crick Institute partnership. I. Zanoni is supported by National Institutes of Health grants 1R01 AI121066, 1R01DK115217, and NIAID-DAIT-NIHAI201700100. The content of this publication and the opinions expressed reflect those of the individual authors solely and do not necessarily reflect the views or policies of the US Department of Health and Human Services, the National Institutes of Health, or corresponding research institutes.

L. Prokunina-Olsson and T.R. O'Brien are coinventors on patents related to IFN-λ4 that are held by the National Cancer Institute. J.S. Glenn is the founder and a board member of Eiger BioPharmaceuticals, Inc., which produces peg-IFN-λ1. S.V. Kotenko is an inventor on patents and patent applications related to IFN-λs that are held by Rutgers University. Other authors declare no competing financial interests related to this work.

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