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.

T cells, including 2-hydroxyglutarate (Tyrakis et al., 2016). Second, the authors have so far only used tumor cells that are genetically modified to express the CAR target and xenograft models that lack an immunosuppressive tumor microenvironment. Thus, do CAR^{KR} T cells have improved effector function in models that closely mimic human disease? Third, can this recyclable CAR design benefit the CARs containing other costimulatory or signaling domains, such as ICOS domain and JAK-STAT signaling domain? In other words, can these CARs function through CAR signaling endosomes? Ultimately, these studies will be informative for building better CAR T cells that possess Teff and Tcm cell-like features, thus improving CAR T cell therapy for cancers and other diseases.

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Interferon-λ at the Center of the Storm

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Type I and III interferons (IFNs) drive effective antiviral functions but differentially affect tissue homeostasis. Using mouse models of severe inflammation, Broggi et al. and Major et al. report in *Science* that type III IFNs disrupt epithelial cell proliferation and differentiation in the lung.

A hallmark of successful host restriction of viral infection is the rapid induction of interferons (IFNs) to initiate innate and adaptive immunity. Type I (IFN-α/β) and type III (IFN-λ1–4) IFNs exert collaborative antiviral effects on cells by inducing transcription of hundreds of antiviral IFN-stimulated genes (ISGs) to promote viral clearance. Type I and III IFNs are produced following the detection of viral infection by pattern recognition receptors (PRRs) in host cells. Although every nucleated cell is capable of responding to type I IFNs, type III IFN activity is restricted to epithelial cells, hepatocytes, and some myeloid cell subsets (Hemann et al., 2017). Cell-type-specific expression of the IFN-λ receptor (IFNλR) restricts type III IFN antiviral activity to these sites. IFN-λs are considered milder than type I IFNs, with long-lasting antiviral activities. IFN-λs are indispensable for clearance of acute and chronic viral infections, such as norovirus and hepatitis C virus infection (McFarland et al., 2014; Nice et al., 2015). IFN-λs are pivotal to antiviral immunity against influenza A virus (IAV) infection in the respiratory tract by inducing localized antiviral protection without the damaging inflammation caused by type I IFNs (Galani et al., 2017). Recent work investigating this distinction has indicated temporal antiviral responses are responsible, where type I IFNs transiently induce proinflammatory genes and leukocyte recruitment and type III IFNs induce delayed and prolonged antiviral immunity that promotes a tissue repair gene signature (Forero et al., 2019). IFN-λs also serve as a link between innate and adaptive immune responses by promoting T cell immunity and cross-protection against IAV (Hemann et al., 2019). Interestingly, IFN-λs may prevent viral spread between the upper and lower respiratory tract, as IFN-λs inhibit IAV spread between these compartments (Klinkhammer et al., 2018). Chronic or aberrant exposure of type I IFNs leads to severe interferonopathies; in contrast, type III IFNs have not been associated with tissue pathology. Two recent studies in *Science* now report that prolonged type III IFN exposure interferes with lung repair by reducing epithelial cell proliferation in murine models of severe lung inflammation.

Epithelial cells, which are essential to antiviral immunity and tissue homeostasis, utilize diverse physical and immunological mechanisms to protect underlying tissues and limit immunopathology at mucosal sites. The role of IFNs in the recovery phase of viral infection, epithelial cell growth, and differentiation in the respiratory tract is largely unexplored. Broggi et al. (2020) and Major et al. (2020) investigated the effects of prolonged type I and III IFN exposure on respiratory epithelium homeostasis and barrier function in pulmonary murine models of hyperinflammation. Major et al. show that exogenous administration of type I and III IFNs during the recovery phase of high-dose IAV infection—presumably when viral levels are decreasing and endogenous IFNs have cleared—reduces the number of proliferating epithelial cells in the airways of mice. The number of proliferating epithelial cells is higher in *Ifnar1*$^{-/-}$ and *Ifnlr1*$^{-/-}$ mice than wild-type controls during IAV infection. Similarly, Broggi et al. demonstrate increases in proliferating epithelial cells in the airways of *Ifnlr1*$^{-/-}$ mice continuously administered poly(I:C) intratracheally for 6 days, suggesting that type III IFNs disrupt cellular proliferation of lung epithelial cells. While interesting, high dose IAV or poly(I:C) might not mimic the complex virus-host interactions in the lung. These findings contradict prevailing models that IFN-λ provides robust antiviral protection while simultaneously promoting barrier integrity and limiting tissue damage in other viral infection models (Hemann et al., 2017; Lazear et al., 2015; Wells and Coyne, 2018). Broggi et al. and Major et al. demonstrated that type I and III IFNs impaired cellular proliferation in the presence of severe inflammation and tissue damage, whereas others have shown IFN-λ promotes barrier integrity in the absence of prolonged or preceding inflammation (Forero et al., 2019; Hemann et al., 2017; Lazear et al., 2015; Wells and Coyne, 2018). These discrepancies are most likely due to differences in the models and viruses studied. Interestingly, Broggi et al. (2020) demonstrated no increases in expression of type I and III IFNs in the upper airways of patients infected with SARS-CoV-2 but increased levels of IFNs in bronchoalveolar lavage fluid. These results intriguingly suggest local differences in IFN-λ-mediated antiviral immunity exists between the upper and lower respiratory tract during SARS-CoV-2 infection.

The respiratory epithelium is composed of ciliated epithelial cells and mucus-secreting goblet cells connected by junctional complexes that restrict paracellular transport in the airways. Major et al. (2020) studied how IFN exposure affects epithelial differentiation and barrier integrity. Interestingly, the authors observed IFN-β or IFN-λ treatment decreases gene expression of ciliated and secretory cell markers in primary airway epithelial cells grown at the air-liquid interface. However, IFNs appeared to have little effect on the formation of intact barriers in high-density primary AEC cultures *in vitro*, as measured by transepithelial electric resistance—a measure of epithelial barrier integrity. Critically, multiciliated cells were significantly increased in the airways of *Ifnlr1*$^{-/-}$ mice compared with wild-type controls during high-dose IAV infection, suggesting that IFN-λ impairs basal cell differentiation following respiratory virus infection. Follow-up studies are important to test whether the impairment of basal cell differentiation is dependent on viral dose (i.e., low versus high titers), occurs in models of influenza virus re-challenge, or is IFN-dependent during infection with multiple respiratory viruses.

Cell cycle progression is highly regulated in response to cellular stress to maintain genomic integrity, regulate cellular proliferation, and promote tissue repair. The tumor suppressor and transcription factor protein p53 responds to cellular stress and controls cell cycle progression. Major et al. (2020) show IFN-β and IFN-λ impaired growth of *in vitro* primary airway cultures, but the effects were restricted to actively proliferating cultures. Through genome-wide transcriptional profiling, the authors revealed signaling nodes that mediate IFN-induced antiproliferative effects on primary murine airway epithelial cells treated with type I and III IFNs during differentiation. Pathways regulating cell cycle and cell death, including the p53 pathway, were strongly induced following prolonged IFN-β and IFN-λ treatment. *Tp53*$^{-/-}$ airway epithelial cells were not susceptible to the antiproliferative effects of IFN-β and IFN-λ, suggesting p53 signaling is activated by IFN-β and IFN-λ signaling. Consistent with this observation, Broggi et al. (2020) show that genes associated with apoptosis and the p53 pathway were enriched in wild-type compared with *Ifnlr1*$^{-/-}$ epithelial cells from mice treated intratracheally with poly(I:C) for 6 days, suggesting that IFN-λ signaling promotes activation of p53. Interestingly, the least expressed gene in *Ifnlr1*$^{-/-}$ epithelial cells was makorin-1 (*Mkrn1*), which induces p21 degradation. p21 is transcribed in response to p53 activation and mediates p53-dependent G1 growth arrest through its interaction with cyclin-dependent kinases. Taken together, these studies suggest that the p53-p21 signaling axis is activated by IFN-β and IFN-λ signaling (Figure 1). Whether this signaling axis requires canonical IFN signaling pathways or is mediated via different signaling complexes still requires further investigation. These observations open up exciting new avenues of research to study the contribution of IFN signaling to cell cycle progression, which might have implications ranging from antiviral defense to cancer.

Several studies have demonstrated that preceding respiratory viral infections are associated with severe acute and chronic secondary bacterial infections in the airways. Type I and III IFN signaling are largely responsible for these observations in mouse models of pulmonary viral-bacterial coinfection, as *Ifnar1*$^{-/-}$ and *Ifnlr1*$^{-/-}$ mice have reduced bacterial burdens compared with wild-type mice. Moreover, exogenous type I and III IFN exposure is sufficient to impair bacterial clearance in airways. In line with these studies, Broggi et al. (2020) demonstrate that pretreatment with poly(I:C) is sufficient to increase the bacterial burden in airways of wild-type but not *Ifnlr1*$^{-/-}$ mice during *Staphylococcus aureus* infection, providing further evidence that IFN-λ signaling reduces bacterial control in the respiratory tract. Major et al. (2020) observed increased survival in *Ifnlr1*$^{-/-}$ mice reconstituted with wild-type bone marrow, suggesting that IFN-λ signaling in the stromal compartment is required for increased susceptibility to bacterial superinfection. The mechanisms underlying this susceptibility are unclear and recent studies indicate type I and III IFN may impair bacterial clearance through disparate mechanisms. The same group had previously shown that IFN-λ but not IFN-β limits neutrophil activation (Broggi

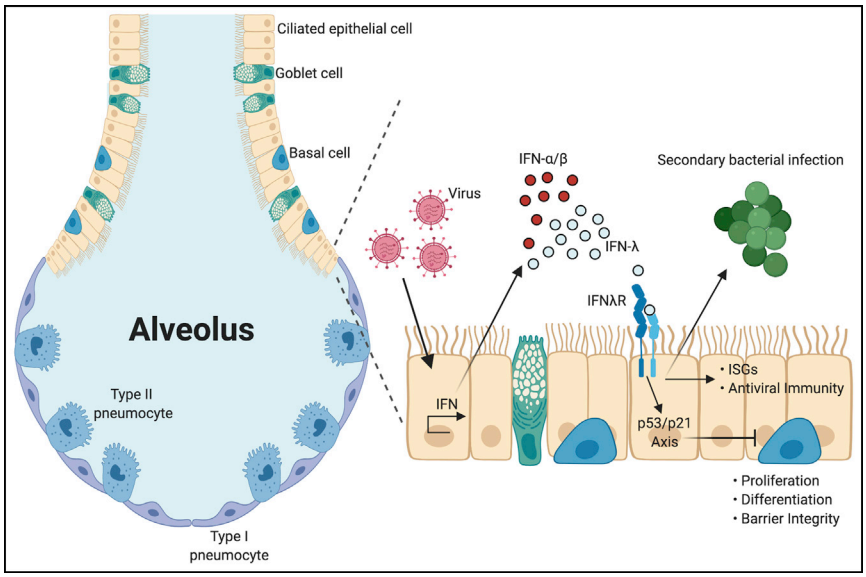

Figure 1. IFN Signaling in the Respiratory Tract

During respiratory viral infection, host cells in the airway sense viral infection through PRRs that activate downstream signaling cascades that culminate in the expression of proinflammatory genes, including type I (IFN-α/β) and type III IFNs (IFN-λ). Type III IFN signals through the IFN-λ receptor (IFNλR) to induce antiviral immunity and ISG expression. The recent studies by Broggi et al. and Major et al. demonstrate activation of the p53/p21 signaling axis in Ifnlr1$^{-/-}$ mice during antiviral immune response in the lung. Importantly, these studies showed IFN-λ signaling promotes secondary bacterial infection. Created with Biorender.com.

et al., 2017). Here, Broggi et al. (2020) show depletion of neutrophils in wild-type mice pretreated with poly(I:C) had no impact on bacterial clearance in the airways. Furthermore, absence of *Ifnlr1* in the stromal compartment, but not hematopoietic compartment, decreased bacterial burden in the airways, suggesting IFN-λ does not promote secondary bacterial infection by inhibiting neutrophil function in this model. These discrepancies may be due to the differences in IFN-λ signaling in neutrophils in the context of virus infection versus poly(I:C)-induced inflammation or the duration of poly(I:C) pretreatment. Another possibility is that IFN-λ may have different effects on neutrophil function or migration in the airways compared with other tissues.

Taken together, both studies highlight that chronic IFN-λ exposure is detrimental to lung epithelial barrier integrity through inhibition of cell proliferation. Follow-up studies need to determine whether the IFN-λ–dependent compromise in barrier integrity may be exacerbated by IFN-independent physiological changes in the airways, which could also impair lung repair and promote secondary bacterial infection. It is also important to consider the differences in IFN-λ receptor distribution and subtypes of *IFNL* genes between humans and mice affecting the outcomes. Better murine models of SARS-CoV-2 infection are required to parse out the role of IFN-λ in the lung during COVID-19 disease progression. Currently, clinical trials are underway to test the benefit of type I and III IFNs on COVID-19 patients. While the jury is still out to determine the therapeutic benefit of IFN-λ, these two studies are a cautionary tale that there might be potential complications of using interferons in general as a therapy to treat patients with severe disease following respiratory viral infection, including in severely ill COVID-19 patients. Overall, these studies highlight the therapeutic challenges for use of IFNs as a treatment for viral infections. These studies open up new avenues of inquiry including understanding the mechanisms of IFN-λ induction and control during resolution of antiviral immunity in the lung, whether prolonged IFN-λ signaling affects cellular proliferation via canonical IFN signaling pathways and if IFN-λ can be used as a therapeutic target to improve outcomes of respiratory viral infections in humans.

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