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"Compartmentalized response of type I and type III interferons"

by
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ABSTRACT

Interferons (IFNs) are a class of defense molecules produced in response to pathogens. There are three types of IFNs: type I (α/β), type II (γ) and the more recently discovered type III (λ) IFNs. Type I and type III IFNs play a major role in antiviral defense. Type I and type III IFNs signal through their independent receptor complexes. Canonically, most nucleated cells are thought to respond to type I IFNs while restricted cell types that express IFN-λ receptor are responsive to type III IFNs including epithelial cells, human hepatocytes, plasmacytoid dendritic cells (pDCs), and neutrophils. The compartmentalization of type I and type III IFN responses has been clearly demonstrated in the gastrointestinal (GI) tract where intestinal epithelial cells respond only to type III IFNs, whereas type I IFNs act primarily of cells residing in lamina propria. Our previous studies also showed that sensitivity of epithelial cells to type I IFNs is age dependent since the epithelium in neonatal mice, while initially responsive to type I IFNs, loses responsiveness with age. In addition, *in vivo* studies have shown a preferential production of IFN-λs at mucosal surfaces during viral infection in the lung and the intestine, mainly by the epithelial cells. IFN-λs have also been implicated at the maternal-fetal interface during Zika infection. More recently, studies revealed an unexpected role of IFNs in tissue repair, wound healing and homeostasis of the GI tract. Although the compartmentalization of IFN response in the GI tract is now well appreciated, it remains to be evaluated in other organs and tissues. Therefore, mapping IFN responses *in vivo* is crucial to advance our understanding of the complex role of IFNs in regulating the dynamics of innate immunity.

In this study, using single cell RNA sequencing (scRNAseq) we have shown that the lung is also compartmentalized with respect to IFN response and that type III IFNs play a major role in antiviral defense against respiratory infection with influenza A virus. We identified major epithelial cell populations in the distal lung space and characterized their IFN response. We also demonstrate the compartmentalization of IFN response in the female reproductive tract (FRT) in mice with no dependence on the estrus cycle as previously reported. Our results also suggest that human and mouse placenta respond differently to IFNs, while no response to or production of type III IFNs was detected in the human placenta *ex vivo*, *in vivo* experiments revealed selected cell populations in the mouse placenta responding to both type I and type III IFNs. We also show that the sensitivity of epithelial cells to type I IFNs varies strongly between experiments conducted *in vivo*, *ex vivo* or *in vitro*, demonstrating that the IFN response is highly context dependent and highlighting the necessity to investigate the regulatory pathways and molecular mechanisms governing responsiveness of cells to IFNs. Overall, these results continue to expand our current understanding of the unique contributions of type I and type III IFNs to innate defense mechanisms at mucosal barrier surfaces.