Review of: "Delayed induction of type I and III interferons mediates nasal epithelial cell permissiveness to SARS-CoV-2"

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Hatton and colleagues from the Duncan lab present an elegant study using cutting-edge techniques such as single-cell RNA-sequencing (scRNAseq) and quantitative mass spectrometry (qMS) to assess the response to SARS-CoV-2 infection in primary nasal epithelial cells differentiated at an air-liquid interface (ALI). This study appears to be the first to report the use of primary nasal epithelial cells in ALI culture thereby demonstrating a more physiologically relevant model of SARS-CoV-2 infection in upper airway cells.

One of the advantages of culturing cells by ALI in this study in contrast to others, is that all SARS-CoV-2 infections were encountered by the nasal epithelial cells via the apical surface thereby closely mimicking the clinical infection in patients. Another advantage of ALI culture for epithelial cells is the role that cell polarization plays in the subsequent innate immune response. It has previously been demonstrated that the high affinity type I interferon (IFN) receptor (IFNAR2) localizes to the basolateral surface of epithelial cells in ALI culture (Ciencewicki et al 2009, Journal of Interferon and Cytokine Research, vol 29, p289-297), so it is likely that different IFN responses would be inducible across the apical versus basolateral surfaces of these cells. This feature of ALI-differentiated epithelial cells is yet to be fully investigated. It would be interesting to determine whether the other IFN receptors are also polarized on differentiated epithelial cells.

While all cell types observed during infection in this study contained at least low-level transcripts for the SARS-CoV-2 nucleocapsid (N) gene, scRNAseq enabled identification of secretory, ciliated and deuterosomal cells as being the most susceptible to SARS-CoV-2 infection. Why only certain cell types are more susceptible is yet to be fully explained.
Utilizing scRNAseq and qMS in this study enabled confirmation of the inhibitory effect SARS-CoV-2 has on the induction of type I and type III IFNs, as reported by others.

As expected, it’s not just the induction of IFNs that are delayed by SARS-CoV-2 infection but expression of the anti-viral proteins that these cytokines induce. Using qMS, this study demonstrated that the most significantly suppressed were known IFN-inducible proteins ISG15, IFIT1, IFIT2, IFIT3, with antiviral proteins

MX, MX2 and OAS1 also highly suppressed. Interestingly, SNX33 was also identified in this proteomic dataset, yet not discussed – while not previously associated directly with viral infection, SNX33 is important for cytoskeletal reorganization and is required for homeostasis and control cell cycle through controlling mitosis and cytokinesis (Zhang et al 2009, Journal of Biological Chemistry, vol284, p 21659-69). Coronaviruses are known to disrupt cytoskeletal rearrangements by high-jacking the cells own machinery for its purposes (Wen et al 2020, Journal of Molecular Cell Biology, vol12, p 968-979). The results of this study are consistent with the ability of SARS-CoV-2 to effect this through suppression of SNX33 production.

Finally, this study also addressed the possibility of using IFNs to prophylactically inhibit or intervene in the progression of SARS-CoV-2 infection. IFNβ and IFNλ1 have been the focus of a number of interventional clinical trials during the COVID-19 pandemic
- https://clinicaltrials.gov/ct2/show/NCT04494399; https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-020-04864-4; https://clinicaltrials.gov/ct2/show/NCT04534673. Demonstrating that exogenous administration of IFNβ or IFNλ1 via the basolateral surface prior to infection or within 6 hours of exposure to the virus induced a protective response in primary ALI-differentiated epithelial cells, this study supports a protective role for these IFNs in SARS-CoV-2 infection. This also showed that while the virus itself inhibits IFN production thereby reducing the host immune response, it also suggests that SARS-CoV-2 does not inhibit IFN responsiveness if it can be delivered prior to or early during infection. A fully comprehensive analysis of the transcriptomic and proteomic differences between IFN administered prophylactically or 6 hours post-infection could be informative for determining the mechanism of SARS-CoV-2 inhibition of the host innate immune response.