Interferon Responses by Differentiated Primary Bronchial Airway Epithelial Cells to SarsCoV2 Are Less Robust Than to Human Rhinovirus16

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Rationale: Common human alphacoronaviruses and rhinoviruses (HRV) induce IFN I/III responses important to limiting viral propagation in the airway epithelium. In contrast, highly pathogenic human betacoronaviruses (e.g. SARS-CoV, circa 2002) may evade or antagonize RNA-induced IFN I/III responses.

Aim: 1) Compare IFN I/III responses by bronchial AECs from children and adults between infection with SARS CoV2 and HRV-16. 2) Determine if pre-infection of AEC cultures with HRV-16, or pretreatment with IFN-β or IFN-λ, modifies SARS-CoV-2 replication.

Methods: Bronchial AECs from children and adults (n=15; ages 8-75 yrs.) were differentiated ex vivo at an air-liquid interface to generate organotypic cultures. In a biosafety level 3 (BSL-3) facility, cultures were infected with SARS-CoV-2 isolate USA-WA1/2020 or HRV-16 at a multiplicity of infection (MOI) of 0.5. At 96 hrs. following infection, RNA and protein were isolated. Expression of IFNB1, IFNL2, and interferon stimulated genes (ISGs) IFITM1, IFITM3, and OAS1 was measured by qPCR in SARS-CoV-2- infected, HRV-16-infected, and uninfected AEC cultures. In additional experiments AECs were pre-infected with HRV-16 (MOI=0.5), or pre-treated with recombinant IFN-β1 (1ng/mL in media) or IFN-A2 (10ng/mL), 72 hrs. before SARS-CoV-2 infection. Recombinant IFNs were refreshed with each media change. SARS-CoV-2 replication was assessed by qPCR, and quantified as viral copy number/ng RNA. Results: SARS-CoV-2 induced less robust increases then HRV-16 in expression of IFNB1 (median 1.4-fold increase, 95% CI 1.2-1.7, vs. 3.8-fold, 95% CI 2.3-6.6, p<0.01), IFNL2 (median 11-fold increase, 95% CI 3-17, vs. 23-fold, 95% CI 12-62, p<0.01), IFITM1 (median 3-fold increase, 95% CI 2.3-6.6, p<0.01), IFITM3 (median 1.6-fold increase, 95% CI 1.2-2, vs. 2.5-fold, 95% CI 2.2-4, p=0.003), and OAS1 (median 1.9-fold increase, 95% CI 1.4-3.5, vs. 3.8-fold, 95% CI 2.8-7.8, p<0.001). SARS-CoV-2 replication was significantly reduced when AECs were pre-infected with HRV-16 (median 2126 viral copies/ng RNA, 95% CI 204-11,080, vs. 92 viral copies/ng RNA, 95% CI 24-289, p=0.002). SARS-CoV-2 replication was also significantly reduced when AECs were treated with recombinant IFN-β1 (median 2126 viral copies/ng RNA, 95% CI 204-11,080, vs. 81 viral copies/ng RNA, 95% CI 3-172, p=0.005) or IFN-λ2 (median 2126 viral copies/ng RNA, 95% CI 204-11,080, vs. 48 viral copies/ng RNA, 95% CI 26-143, p=0.001).

Conclusion: SARS-CoV-2 elicits a less robust IFN I/III response by primary bronchial AECs than HRV-16. Pre-infection of AECs with HRV-16, or pre-treatment with recombinant IFN-β1 or IFN-λ2 markedly reduces SARS-CoV-2 replication.