Multiple RSV strains infecting HEp-2 and A549 cells reveal cell line-dependent differences in resistance to RSV infection

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Background: Respiratory syncytial virus (RSV) is the major viral driver of a global pediatric respiratory disease burden disproportionately borne by the poor[1]. Thus, RSV, like SARS-CoV-2, combines with congenital and environmental and host-history-dependent factors to create a spectrum of disease with greatest severity most frequently occurring in those least able to procure treatment.

Methods: Here we apply whole genome sequencing and a suite of other molecular biological techniques to survey host-virus dynamics in infections of two distinct cell lines (HEp2 and A549) with four strains representative of known RSV genetic diversity.

Results: We observed non-gradient patterns of RSV gene expression and a single major difference in transcriptional readthrough correlating with a deep split in the RSV phylogenetic tree. We also observed increased viral replication in HEp2 cells along with a pro-inflammatory host-response; and decreased viral replication in A549 cells with a more potent antiviral response in host gene expression and levels of secreted cytokines.

Conclusions: Our findings suggest HEp2 and A549 cell lines can be used as complementary models of host response leading to more or less severe RSV disease. *In vitro* perturbations inspired by actual environmental and host-history-dependent factors associated with greater disease can be tested for their ability to shift the antiviral response of A549 cells to the more pro-inflammatory response of HEp2 cells. Such studies would help illuminate the tragic costs of poverty and suggest public health-level interventions to reduce the global disease burden from RSV and other respiratory viruses.

1. **Shi T, et al.** Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in young children in 2015: a systematic review and modelling study. Lancet. 2017;390(10098):946-58. doi: 10.1016/S0140-6736(17)30938-8. PubMed PMID: 28689664; PMCID: PMC5592248.