Temperature-dependent innate defense against the common cold virus limits viral replication at warm temperature in mouse airway cells

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Most isolates of human rhinovirus, the common cold virus, replicate more robustly at the cool temperatures found in the nasal cavity (33–35 °C) than at core body temperature (37 °C). To gain insight into the mechanism of temperature-dependent growth, we compared the transcriptional response of primary mouse airway epithelial cells infected with rhinovirus at 33 °C vs. 37 °C. Mouse airway cells infected with mouse-adapted rhinovirus 1B exhibited a striking enrichment in expression of antiviral defense response genes at 37 °C relative to 33 °C, which correlated with significantly higher expression levels of type I and type III IFN genes and IFN-stimulated genes (ISGs) at 37 °C. Temperature-dependent IFN induction in response to rhinovirus was dependent on the MAVS protein, a key signaling adaptor of the RIG-I–like receptors (RLRs). Stimulation of primary airway cells with the synthetic RLR ligand poly I:C led to greater IFN induction at 37 °C relative to 33 °C at early time points poststimulation and to a sustained increase in the induction of ISGs at 37 °C relative to 33 °C. Recombinant type I IFN also stimulated more robust induction of ISGs at 37 °C than at 33 °C. Genetic deficiency of MAVS or the type I IFN receptor in infected airway cells permitted higher levels of viral replication, particularly at 37 °C, and partially rescued the temperature-dependent growth phenotype. These findings demonstrate that in mouse airway cells, rhinovirus replicates preferentially at nasal cavity temperature due, in part, to a less efficient antiviral defense response of infected cells at cool temperature.

greatly diminishes the antiviral defense response elicited by RV infection in airway epithelial cells, and that host cells genetically deficient in the innate immune signaling molecules that mediate this response support robust RV replication at 37 °C.

Results

Mouse-Adapted RV-1B Exhibits Robust, Temperature-Dependent Growth in Mouse Epithelial Cells. To study viral infection using genetic knockouts and diverse types of primary cells, we chose to investigate temperature-dependent replication of RV using a mouse model system. To do this, we created a mouse-adapted variant of the minor-group rhinovirus RV 1B (RV-1B). Minor-group rhinoviruses, which use the LDL receptor and related receptors for cellular entry, have been shown to enter mouse cells and undergo limited replication, which can be improved by serial passage in mouse cells (8–10). Consistently, we found that RV-1B replicated to a limited extent in the mouse airway epithelial cell line (LA-4) but that replication efficiency was dramatically improved following serial passage of the virus 27 times

Significance

Rhinovirus is the most frequent cause of the common cold, as well as one of the most important causes of asthma exacerbations. Most rhinovirus strains replicate better at the cooler