ABSTRACT (ENGLISH)

Rhinoviruses (RV) and inhaled allergens, such as house dust mite (HDM) are major factors responsible for exacerbations of asthma. When acting in combination they even further increase the risk and severity of exacerbations, and emergency hospitalizations. Not much is known about immune mechanisms underlining such noxious virus-allergen interactions, leading to the lack of efficient prevention and treatment. This is especially important in the times of current severe acute respiratory coronavirus 2 (SARS-CoV-2) pandemic. There are contradictory reports regarding asthma being a risk factor for the development of severe coronavirus disease 2019 (COVID-19). To address these questions, we studied molecular mechanisms of RV, HDM and SARS-CoV-2 interactions in differentiated human primary bronchial epithelium, and upon in vivo experimental RV infection in healthy individuals and asthmatic patients by combination of molecular biology techniques, high throughput transcriptomic and proteomic methods, coupled with confocal microscopy imaging. We found that RV infection in bronchial epithelium was sensed via retinoic acid-inducible gene I (RIG-I) receptor. Activation of RIG-I led to the subsequent apoptosis-associated speck-like protein containing a CARD (ASC) recruitment, its oligomerization, and RIG-I inflammasome activation. This mechanism was significantly increased in bronchial epithelium in patients with asthma. Excessive activation of RIG-I inflammasome was partially responsible for the impairment and persistence of IFN-I/III responses, prolonged viral clearance, and unresolved inflammation in asthmatic bronchi. HDM exposure further increased RIG-I inflammasome activation and subsequently decreased RIG-I-dependent antiviral responses. RV/HDM-induced sustained IFN-I/III responses initially restricted SARS-CoV-2 replication in epithelium of patients with asthma, but even this limited infection with SARS-CoV-2 augmented inflammasome activation and hyperinflammation in the airways. Epithelial RIG-I inflammasome and IL-1β signaling provide a potential therapeutical target to lower burden of RV and SARS-CoV-2 infection in asthma.