Title: Lung Virome: The Role of Polyomavirus, Torquetenovirus, and Cytomegalovirus in Respiratory Disease

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In recent years, there has been an increasing focus on exploring the role of the global virome in both health and disease. Consequently, investigating the human lung virome could provide new insights into respiratory illnesses. The virome, as an integral component of the microbiome, undergoes continuous changes in composition influenced by factors such as dietary habits, environmental conditions (including smoking), genetic predisposition, and other unpredictable variables. The virome significantly impacts human immune responses and contributes to inflammatory processes. Torquetenovirus (TTV) represents a recent addition to the virome, the exact role of which remains unclear; however, several studies suggest that TTV may trigger inflammasomes, which are intracellular multiprotein complexes crucial for the innate immune system's defense against various pathogens. Moreover, influenza virus (H1N1), cytomegalovirus (CMV), JC polyomavirus (JCPyV), or BK polyomavirus (BKPyV) latent infections are major contributors to variability in respiratory diseases. Chronic obstructive pulmonary disease (COPD) is a significant contributor to global mortality and disability, standing as the third leading cause of death as of 2019. Exacerbations of COPD are often associated with viral and/or bacterial infections. While the exact percentages vary among individual studies, it is generally observed that around 20–50% of patients experiencing acute exacerbations of COPD have detectable viral infections. Although rhinovirus is the primary viral pathogen identified in COPD exacerbations, the detection of viruses during acute COPD exacerbations makes it difficult to establish a causal role in exacerbation pathogenesis. We found that TTV load (>4 log) as well as high CMV serology predict COPD mortality in a sample of 104 patients. Only high CMV serology is associated with an increased risk of dying in COPD current or former smokers. We also observed that the presence of TTV or CMV influences both innate and adaptive immune responses, and its effects on adaptive responses persist long after individuals quit smoking. In conclusion, this study reports a relationship between high TTV load and high CMV serology and the subsequent risk of dying from COPD, thus identifying a novel risk factor for COPD mortality.

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