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Short Communication

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Transmission of Rhinovirus infection highly influenced by immune system related genetic polymorphisms

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Abstract

Rhinovirus are picornavirus with over 150 serotypes and 3 species. Although usually causing common colds, in Asthma, COPD and elders it may cause life-threatening disease. Both environmental and genetic susceptibility factors may play a role in rhinovirus epidemiology. In the present study we evaluated the influence of immune-system related genetic variations (TOLLIP rs5743899, IL6 rs1800795, IL1B rs16944, TNFA rs1800629) in the modulation of rhinovirus infection susceptibility. Blood samples and monthly nasal swabs were collected from 89 volunteers. DNA and RNA were purified with Qiagen column based kits. Viral RNA was quantified by RT- qPCR on Light cycler 1.1 (Roche). Polymorphisms were genotyped by PCR-RFLP. TOLLIP and IL6 polymorphisms (but not IL1B and TNF) were found to influence rhinovirus nasal detection. TOLLIP-G individuals were more often year-long rhinovirus free ($p<0.028$). This fully agrees with molecular mechanisms as free Rhinovirus particles, are detected by TLR2 which is inhibited by TOLLIP. TOLLIP-G decreases TOLLIP expression, increasing TLR2 and protecting from Rhinovirus infection. TOLLIP G also sustains production of IL6 needed for viral clearance post-infection. However, in the absence of the TOLLIP G allele, and of the IL6-C allele there is low IL6 production leading to a poorer Immune response and higher viral titres.

Rhinovirus (RV) infection increases neutrophilic airway inflammation and triggers asthma exacerbations in both children and adults, but the underlying mechanisms are not completely understood. Toll-interacting protein (Tollip), an adaptor protein, serves as a negative regulator of Toll-like receptor (2, 4) and IL-1 receptor signalling. Tollip inhibits IL-1 and LPS-induced NF-κB activation and proinflammatory cytokine responses. In humans, the Tollip rs5743899 single nucleotide polymorphism has been associated with increased susceptibility to tuberculosis infection and cutaneous leismaniasis. Our research group has shown that Tollip rs5743899 is associated with reduced Tollip expression in human airway epithelial cells and worse lung function in asthmatic subjects. However, the mechanisms whereby Tollip regulates airway inflammation during RV infection in asthma or allergic airway diseases remain to be fully established. Asthma is mainly driven by type 2 immunity, as both IL-13 and IL-33 play key roles in the disease. While Tollip inhibits IL-1R-mediated signalling, IL-33 enhances this signalling pathway and drives type 2 as well as non-type 2 (e.g., neutrophilic) inflammation. The receptor of IL-33 consists of ST2 (IL-1RL1) and IL-1 receptor accessory protein (IL-1RAP). ST2 exists in two major isoforms: membrane ST2 (ST2, ST2L) and soluble ST2 (sST2), both arising from a single gene (Il1rl1) by alternative splicing. Polymorphism in the Il1rl1 gene is associated with an increased risk of asthma, and epithelial ST2 expression is increased in severe asthma in association with type 2 inflammation.

Interestingly, Tollip-deficient mice under intranasal IL-13 challenge develop excessive eosinophilic airway inflammation through a mechanism that involves ST2 signalling in lung macrophages.

Furthermore, IL-13 has been reported to increase ST2 expression in human airway epithelial cells, and we have previously shown that Tollip deficiency in airway epithelial cells promotes IL-8 production in response to IL-13 especially during RV infection. Nonetheless, the functional role of Tollip in airway inflammation (e.g., regulation of epithelial sST2) during viral infection remains unclear. In response to RV, airway epithelial cells also secrete CXCL-1, CXCL-8, and CXCL-10 which are potent chemoattractants for neutrophils and immature monocytes, the latter cell type express high amounts of IL-6, CXCL-8, and IFNs in response to RV when co-cultured with epithelial cells. Although the role of neutrophils in viral clearance is not known, neutrophils suppress IL-6 and CXCL-8 secretion from monocytes therefore, neutrophils may limit RV-induced overt inflammation in vivo. Nasal epithelial cells express programmed death ligand (PD)-L1 and PD-L2 in response to RV. These ligands are co-stimulatory molecules and upon ligation to its receptor PD-1 inhibit activation of T and B cells. In a co-culture model of airway epithelial cells and T cells, the airway epithelial cells express PD-L1 and PD-L2 in response to RV, this in turn inhibits T cell activation and expression of IFN-γ, which is indeed necessary for killing virus-infected cells. Nasal mucosal epithelial cells express IL-15 following experimental RV infection in humans, which in turn activates CD8+ and natural killer cells to promote the expression of IFN-γ that may contribute to viral clearance. We have demonstrated that in the absence of TLR2 signalling, RV stimulates exaggerated CXCL-10 expression in airway epithelial cells via activation of IL-33/ST2 signalling axis. COPD airway epithelial cells show heightened CXCL-10 expression in response to RV and this can be attributed to attenuated TLR2 signalling

Because Tollip interacts directly with IRAK1 and inhibits its activation, deficient Tollip expression in epithelial cells could lead to increased IRAK1 signalling under type 2 cytokine stimulation and RV infection, which would increase IL-8 (a neutrophil chemokine) production and promote excessive airway inflammation. Therefore, we hypothesized that Tollip down regulates RV-mediated IL-8 production in a type 2 cytokine milieu by modulating the IL-33/ST2 signalling axis (e.g., sST2 expression and IRAK1 activation) in human airways. Human primary airway epithelial cell cultures and mouse models were used to test our hypothesis in order to provide a novel mechanism detailing how Tollip inhibits IL-8 production to limit excessive inflammation during RV infection in a type 2 cytokine milieu that is reflective of a subset of asthma.

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