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Rhinovirus – not just the common cold

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Summary Rhinoviruses (RV) are ubiquitous respiratory tract pathogens. They affect both the upper and lower respiratory tract and cause colds but have also been associated with wheezing, asthma exacerbations and pneumonia. New blood transcription profiling techniques of the host immune response are becoming available to characterise the pathogenesis of RV in humans. This review will outline the clinical impact of RVs in children.

Background

Rhinoviruses (RV) are small, approximately 30 nm in diameter, viruses consisting of a simple viral capsid and a positive sense single strand of ribonucleic acid (RNA) with a genome approximately 7200 kb in size. The capsid contains four proteins, VP1–VP4, arranged in 60 repeating protomeric units in an icosahedron.[1,2] RVs exhibit considerable genetic diversity.[1,2] They are classified in the order *Picornavirales*, family *Picornaviridae* and genus *Enterovirus*. Within the *Enterovirus* genus there are three RV species; A, B and C.[3] Within each of these species, isolates are subdivided into numeric genotypes that are primarily based on sequence comparisons of the VP1 protein or VP4/VP2 coding region.[4] There are over 100 RV genotypes. The genetic diversity of RVs is continuously changing and consequently the classification of RVs is regularly updated.[3] Within the RV-A species, for example, a discrete "clade D" has recently emerged which may in time be classified separately from RV-A.[4]

RVs enter via the upper respiratory tract and bind to respiratory epithelial cells via several receptors which are different depending on the RV species. RV-A and RV-B bind to the intercellular adhesion molecule 1 (ICAM-1) receptor and low-density lipoprotein receptor (LDLR) and RV-C binds to the newly identified cadherin-related family member 3 receptor (CDHR-3).[5–7] The attachment of RV to its receptor in susceptible patients elicits an innate immune response leading to airway inflammation and remodelling (Figure 1).

RVs are the most common cause of respiratory tract infection in infants and almost all infants develop at least one RV infection in the first year of life.[8] Prematurely born infants and older children with asthma are particularly at risk of developing severe RV infections.

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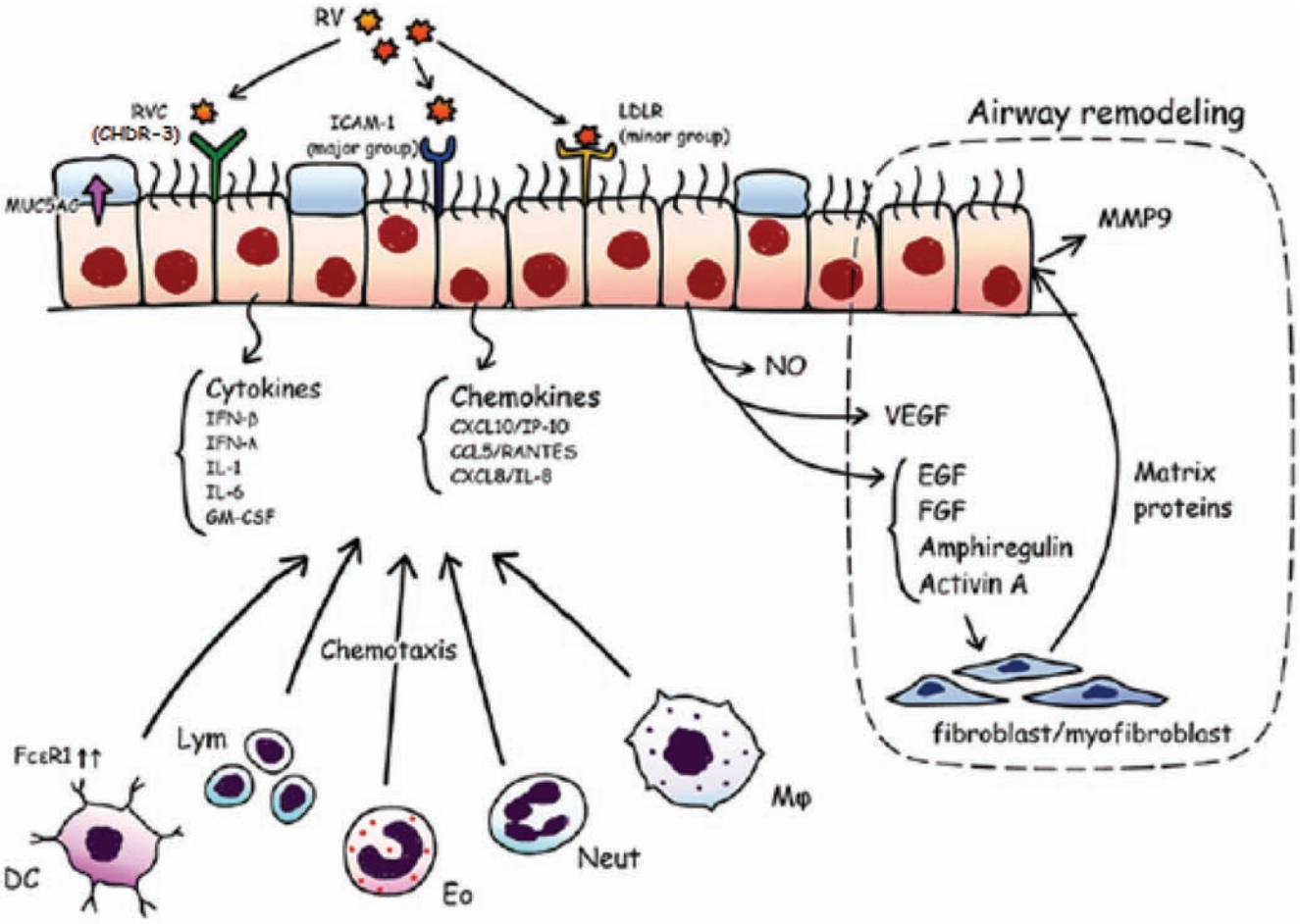

Figure 1 The pathogenesis of RV infection. Adapted with permission from Saraya et al.[5]

Rhinovirus: a lower respiratory tract pathogen

Until relatively recently RVs were thought to only infect the upper respiratory tract and not result in lower respiratory tract infection (LRTI). Most RVs replicate best at 33–35°C and although the core lung temperature is 37°C, the airways are cooler.[9] The lower respiratory tract, therefore, provides the ideal environment for RVs to flourish. Using viral culture it has been shown that RVs replicate as well as, or better in lower respiratory tract cells compared with upper respiratory tract cells.[9] In addition, in an experimental model of RV infection of the upper airway in adults, RV has been subsequently recovered from the lower respiratory tract and the amount of RV detected in sputum was often higher than that detected in the upper airways.[9] RV can also be detected in the lower airways in children with tracheostomies where there is no risk of the results being affected by sample contamination from the upper airways.[10]

In vitro studies have demonstrated that bronchial epithelial cells are susceptible to RV infection.[11] Compared with the suprabasal fraction, basal cells in mature airway epithelium show increased ICAM-1 expression, RV viral capsid protein (VP2) staining and RV RNA copies per cell, demonstrating their susceptibility to infection by RVs. In addition, epithelial injury has been shown to allow greater RV replication, perhaps explaining the more severe disease seen in children with pre-existing lung disease such as asthma or bronchopulmonary dysplasia.[11,12]

Although the ICAM-1 receptor and LDLR on epithelial cells are well known targets for RV-A and RV-B,[13] the target for RV-C, CDHR3, has only recently been identified by gene expression analysis.[6,14] Expression of eight genes, including those coding for CDHR3, which were common to the plasma membrane and receptor, were significantly higher in cells which were susceptible to RV-C versus those which were non-susceptible. A recent study[6] demonstrated a single nucleotide polymorphism, C529Y, in the gene coding for the CDHR3 protein was associated with increased expression of the CDHR3 protein resulting in increased RV-C binding to the epithelial cells and subsequent progeny yield. A Danish GWAS study identified CDHR3 as a susceptibility locus for asthma exacerbations. Children 2–6 years old with the AA genotype of the CDHR3 gene had an increased risk of severe asthma exacerbations compared with those with the GG genotype. Together these studies suggest RV-C acts via this receptor to cause asthma exacerbations in susceptible children.[7]

Are RVs frequent aetiological agents of acute respiratory tract infections?

In the Childhood Origins of ASThma (COAST) high risk cohort (at least one atopic parent), RVs were detected in over