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Review

Immune and inflammatory response in bronchiolitis due to respiratory Syncytial Virus and Rhinovirus infections in infants

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EDUCATIONAL AIMS

The reader will come to appreciate that:

- Currently, there is no etiologic therapy nor safe and effective vaccine available.
- Viral bronchiolitis is related to long term respiratory morbidity including asthma and recurrent wheezing.
- The pathogenesis of these sequelae may be explained by the different mechanisms of immune and inflammatory responses following infection with Respiratory Syncytial Viruses and Rhinoviruses.
- The knowledge of the response may be used to develop effective antiviral therapies and preventive options against these two viruses.

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SUMMARY

Bronchiolitis is a common disease in infancy, mostly due to *Respiratory Syncytial Virus* and *Rhinovirus*. In addition to acute infection, viral bronchiolitis is responsible for sequelae including recurrent wheezing and asthma. The analysis of the viral characteristics and of the pathogenesis of the infection shows differences between the two viruses that may be helpful for the development of therapies and preventive strategies.

INTRODUCTION

Bronchiolitis is a common disease in infancy with considerable impact on healthcare during the acute illness. Moreover, it is responsible for long term respiratory sequelae, which may further increase clinical and economic impact of these infections. Several studies have clearly demonstrated that previous severe *Respiratory Syncytial Virus* (RSV) bronchiolitis is related to persistent wheezing and asthma [1] while *Rhinovirus* (RV), is more frequently involved in wheezing exacerbations in later childhood [2]. The main differences between RSV and RV are summarized in Table 1.

RSV

RSV is the most significant cause of bronchiolitis in infants younger than 2 years with a hospitalization rate 5.2 per 1000 infants, and it is involved in up to 80% of all hospitalizations due to bronchiolitis [3]. In addition to the acute symptoms, RSV infection may have respiratory sequelae and has been strongly associated with mid-to long-term lung function decline, recurrent wheezing and asthma development in childhood [4]. This concern is strongly relevant in toddlers with underlying comorbidities as well as in infants born prematurely. Two hypotheses have been postulated [5] to clarify the pathogenesis of these sequelae: first, RSV bronchiolitis may interfere with lung development or immune

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Table 1
Comparison between RSV and RV.

	RSV	RV
Epidemiology	Bronchiolitis and LRTI in infants < 2 years Clinical course conditioned by pre-existing risk factors	URTI Second commonest cause of viral bronchiolitis in infants < 2 years Clinical course conditioned by presence of allergy
Virology	RNA Virus (*Paramyxovirus)* 5 structural proteins 2 serotypes (A and B)	RNA Virus (*Picornaviridae)* 160 serotypes grouped into 3 species
Mechanism of infection	Direct cytopathic effect with epithelial necrosis Immune mediated effect	Absence of direct cytopathic effect in the respiratory epithelium
Mediators of inflammation	IL-1β, Type 1 IFN, IL-8, TNF-α, IL-4, IL-10, IL 9, IL-13, IFNγ	Type 1 IFN, RANTES, IP-10, IL-6, IL-8, ENA-78, TNF-α, IL-4, IL-5, IL-13
Humoral immune response	Syntesis of protective IgA and IgG (limited protective effect)	Serotype specific antibody development
Cell-mediated immune response	Shift from Th1 to Th2 immune response involved in the severity of the disease	Th2 response involved in the pathogenesis of subsequent wheezing

maturation. Secondly, RSV infection may be the earliest stimulus for wheezing in children with genetic susceptibility or preexisting abnormal lung function at birth.

RSV is highly contagious and it is spread easily in homes, nurseries and hospitals via airborne transmission from an infected person through coughing or sneezing, creating virus-containing droplets that directly contact airways of other people [6,7]. Indirect transfer can also occur through contaminated surfaces, furnishings, medical devices and hands.

RSV is an enveloped virus of the *Paramyxoviridae* family with a single-stranded negative-sense RNA genome of 15.2 kb [8]. There are five detectable RSV proteins: the nucleocapsid N protein that tightly encapsidates genomic RNA; the large L protein of the major polymerase subunit; the P phosphoprotein that is an essential cofactor in RNA and the M2-1 and M2-2 proteins, respectively, are involved in transcription and in modulating the balance between transcription and RNA replication. Four other proteins are associated with the lipid bilayer: the matrix M protein, the heavily glycosylated G, the fusion F and the transmembrane surface glycoproteins G. Moreover, two small hydrophobic SH proteins are the only antigens involved in the virus neutralization and in the attachment to the target cells. The virus has a single-serotype with two antigenic subgroups (A and B); the most divergent surface protein between serotypes A and B is the G protein. Both serotypes circulate during epidemic seasons with an alternate predominance every one or two years [7].

The tropism of the virus is exceedingly high for superficial cells of the respiratory tract eliciting an immune response that can be at the same time both protective and pathogenic. After the viral replication, the peribronchial tissue becomes the target of a massive cellular infiltration (neutrophils, monocytes, NK and T lymphocytes cells) with a damage of the bronchiolar structure (cellular necrosis and proliferation) and consequent intraluminal obstruction [9]. Although syncytia, polynucleotide cells derived from the fusion of infected cells, are sometimes observed in the bronchiolar epithelium, they are not common.

Several genetic polymorphisms of the genes involved in the immune response (innate defense, host cell receptors, neutrophil response, Th1/Th2 response, adaptive immunity) have been identified as significant factors in the severity of RSV disease [7]. Besides viral, individual and environmental factors such as prematurity, being of young age at onset of the RSV season, daycare attendance; presence of siblings and crowded living conditions, and lack of breastfeeding [10,11], and the immune response play a critical role in the onset of the disease.

Airway inflammation is initially caused by the necrosis of airway epithelial cells due to the direct cytopathological effect of RSV [6], then the immune response to RSV may damage the airways through inflammatory processes. When RSV infects the respiratory epithelial cells and the pulmonary macrophages, the response induces the up-regulation of cytokines and chemokines (IL-8, IP-10, MCP-1, MIP-1α, MIP-1β, RANTES, IL-6, TNF-α, IL-1αβ and IFN-αβ) [12,13] promoting inflammation and the recruitment of innate immune cells into the lungs, such as eosinophils, neutrophils and monocytes. The innate immune response is amplified by IL-1β, synthetized by airway epithelial cells and macrophages as an immature form. This is achieved through 2 signals: first, stimulation of a pattern of recognition receptor ensures expression of pro-IL-1β (the IL-1β precursor) and inflammasome components; second, the inflammasome complex, a multiprotein cytoplasmic complex which activates one or more caspases with subsequent processing and secretion of cytokines, assembly and caspase-1 activation to cleave pro-IL-1β into IL-1β. IL-1β works in an autocrine and paracrine way, and ultimately causes the expression of a number of NF-κB-dependent cytokines and chemokines [14]. Respiratory epithelial cells upregulate the expression of the CD161 ligand LLT1 following detection of viral infection via the pattern recognition receptor TLR3 and following stimulation by the proinflammatory cytokines TNF-, IL-1β, and type I IFNs, which are released early following respiratory virus infection [15].

Furthermore, both RSV infected epithelial cells and dendritic cells (DCs) secrete type-I IFNs, regulating and activating the response of the innate immune system. The signal through the IFN receptor (IFNAR) induces the expression of proteins important for limiting viral replication and directing immune responses. This reveals a dual role for type I IFNs during RSV infections: limiting viral replication and regulating the cytokine expression. The demonstration that type I IFNs can amplify lung inflammation when given exogenously may have applications in the design of vaccines or therapeutics [16]. These findings show that the interaction of RSV with human cells leads to a cytokine expression contingent on cellular cross-talk and the presence or absence of specific antibodies. CD14 monocytes have a key role [17] in the control of antiviral type I IFN responses to RSV via a direct antibody mediated and an indirect mechanism (infection mediated). Since RSV specific antibodies are transmitted from mother to child during pregnancy and via breastfeeding, the role of these antibodies should be carefully evaluated with respect to their effect on innate immune responses when new vaccine candidates are tested. RSV infection in a neonatal mouse model [18] induced limited type I IFN and DC responses. IFN-α treatment was observed to decrease the Th2-biased immunopathogenesis during reinfection. These data suggest that IFN-α is a promising target for future RSV vaccine design.

Neutrophils are the main cells found in the airways [19], since their prevalence in samples of respiratory secretions of RSV infected patients was observed to be 93% in the upper airways and 76% in the lower airways, respectively. Similar to other respiratory inflammatory diseases such as asthma, neutrophils are gathered in