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Virus-induced modulation of lower airway diseases: Pathogenesis and pharmacologic approaches to treatment

Richard Leigh [a,b], David Proud [b,*]

[a] Airway Inflammation Research Group, Snyder Institute for Chronic Diseases and Department of Medicine, University of Calgary Faculty of Medicine, Calgary, Canada
[b] Airway Inflammation Research Group, Snyder Institute for Chronic Diseases and Department of Physiology & Pharmacology, University of Calgary Faculty of Medicine, Calgary, Canada

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ABSTRACT

Uncomplicated upper respiratory viral infections are the most common cause of days lost from work and school and exert a major economic burden. In susceptible individuals, however, common respiratory viruses, particularly human rhinoviruses, also can have a major impact on diseases that involve the lower airways, including asthma, chronic obstructive pulmonary diseases (COPD) and cystic fibrosis (CF). Respiratory virus-induced wheezing illnesses in early life are a significant risk factor for the subsequent development of asthma, and virus infections may also play a role in the development and progression of airway remodeling in asthma. It is clear that upper respiratory tract virus infections can spread to the lower airway and trigger acute attacks of asthma, COPD or CF. These exacerbations can be life-threatening, and exert an enormous burden on health care systems. In recent years we have gained new insights into the mechanisms by which respiratory viruses may induce acute exacerbations of lower airway diseases, as well as into host defense pathways that may regulate the outcomes to viral infections. In the current article we review the role of viruses in lower airway diseases, including our current understanding on pathways by which they may cause remodeling and trigger acute exacerbations. We also review the efficacy of current and emerging therapies used to treat these lower airway diseases on the outcomes due to viral infection, and discuss alternative therapeutic approaches for the management of virus-induced airway inflammation.

Contents

Abbreviations: CCL, chemokine (C-C motif) ligand; CF, cystic fibrosis; COAST, Childhood Origins of Asthma; COPD, chronic obstructive pulmonary disease; CXCL, chemokine (C-X-C motif) ligand; CXCR, C-X-C chemokine receptor; dsRNA, double-stranded RNA; ERK, extracellular-signal-regulated kinase; FADD, fas-associated protein with death domain; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte–macrophage colony-stimulating factor; HRV, human rhinovirus; ICAM-1, intercellular adhesion molecule-1; ICS, inhaled corticosteroids; IFN, interferon; IL, interleukin; iNOS, inducible nitric oxide synthase; IPS-1, interferon-β promoter stimulating protein-1; IRF, interferon regulatory factor; ISG, interferon-stimulated gene; LABA, Long-acting β_2-adrenergic agonist; mda-5, melanoma differentiation-associated gene-5; MMP-9, matrix metalloproteinase-9; MUC5AC, Mucin 5AC; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NO, nitric oxide; OAS, 2′5′-oligoadenylate synthetase; OCT, octamer transcription factor; PAMP, pathogen-associated molecular pattern; PI-3 kinase, phosphatidylinositol-4,5-bisphosphate 3-kinase; PRR, pattern recognition receptors; RIG-I, retinoic acid inducible gene-I; RIP-1, receptor interacting protein-1; RNA, ribonucleic acid; RSV, respiratory syncytial virus; RT-PCR, reverse transcription-polymerase chain reaction; Syk, spleen tyrosine kinase; T helper 2, Th2; TLR, toll-like receptor; TRAF-3, TNF receptor-associated factor-3; TRIF, TIR-domain-containing adapter-inducing interferon-β; VEGF, vascular endothelial growth factor

* Corresponding author at: Department of Physiology & Pharmacology, University of Calgary Faculty of Medicine, HRIC 4AC60, 3280 Hospital Drive NW, Calgary, Alberta T2N 4Z6, Canada. Tel.: +1 403 210 3816; fax: +1 403 270 0692.
E-mail address: dproud@ucalgary.ca (D. Proud).

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1. Introduction

Upper respiratory tract viral infections are one of the most common acute respiratory illnesses experienced by humans. In healthy individuals, such infections are usually self-limiting and are associated with the relatively mild symptoms of the clinical syndrome referred to as the common cold. According to the Centers for Disease Control and Prevention, colds result in 22 million lost school days each year in the United States alone. Moreover, Americans experience more than 500 million upper respiratory tract viral infections per year (excluding infections due to influenza) leading to a total annual economic impact estimated at $40 billion in 2003 (Fendrick et al., 2003). A number of different viral types, including coronaviruses, respiratory syncytial virus (RSV), and parainfluenza viruses can induce upper respiratory symptoms, but more than half of all colds are caused by human rhinovirus (HRV) infections (Arruda et al., 1997; Makela et al., 1998).

Although most healthy individuals experience simple common colds, a relatively small percentage of cases develop complications including acute sinusitis or otitis media (Arola et al., 1990; Turner et al., 1992; Gwaltney et al., 1994). More serious complications, however, can occur in subjects with pre-existing lower airway diseases, such as asthma, chronic obstructive pulmonary disease (COPD) or cystic fibrosis (CF), where upper respiratory virus infections are a major trigger for acute disease exacerbations that can be life-threatening and are a major cause of emergency room visits or hospitalizations. Moreover, there is now considerable evidence that virus induced wheezing illnesses in early childhood are a major risk factor for the subsequent development of asthma. These latter observations have also prompted investigations into whether respiratory viral infections may also contribute to the development of the structural changes, referred to as "airway remodeling", that occur in the airways of subjects with asthma. The fact that several viruses are able to exacerbate lower airway diseases suggests that common mechanisms underlie the pathophysiology of these effects. Recently, new insights have been gained into pathways mediating the effects of viruses on lower airway diseases. This review places particular emphasis on how components of these pathways may provide possible new targets for therapeutic interventions. As will be discussed, new therapeutic approaches are clearly required, as currently available medications for the treatment of lower airway diseases are less than optimal for the treatment of viral exacerbations of lower airway diseases. Moreover, none of our current treatment options prevent the development of airway remodeling in asthma or reverse existing features of remodeling.

2. Viral wheezing as a risk factor for asthma development

Respiratory viral infections are the major trigger for episodic wheezing in children. Although a number of virus types, including parainfluenza, metapneumovirus and influenza can trigger bronchiolitis and wheezing (Heymann et al., 2004; Jartti et al., 2004; Williams et al., 2004), initial studies focused on RSV as the major cause of bronchiolitis in young infants, particularly during the winter months. These studies showed that children who develop RSV induced bronchiolitis in early childhood have impaired lung function in later life (Strope et al., 1991). Such children also were at increased risk for recurrent wheezing and development of asthma by ages 6–10 (Stein et al., 1999; Sigurs et al., 2000). Although data from the Tucson Children's Respiratory Study showed that this risk decreases progressively with age and was no longer significant by age 13 (Stein et al., 1999), other studies indicate that RSV bronchiolitis that is severe enough to cause hospitalization in infancy is still a risk factor for asthma into adolescence (Sigurs et al., 2005). While these studies focused on RSV, the improved sensitivity of viral detection that resulted from the introduction of reverse transcription-polymerase chain reaction (RT-PCR), has generated strong evidence for a much greater role for HRV-induced wheezing illnesses in infancy as a major risk factor for the subsequent development of asthma than was previously appreciated. Outside of the winter months, and in children older than 6 months of age, HRV appears to be the dominant viral pathogen associated with wheezing illnesses (Heymann et al., 2004; Jartti et al., 2004; Korppi et al., 2004). It has been reported that children hospitalized with HRV-induced bronchiolitis are at particularly high risk for the subsequent development of asthma (Reijonen et al., 2000; Kotaniemi-Syrjänen et al., 2003). In addition, a series of publications from the high risk **C**hildhood **O**rigins of **Ast**hma (COAST) birth cohort study, showed not only that HRV induced wheezing illness during the first year of life was the strongest predictor of subsequent wheezing in the third year of life (Lemanske et al., 2005), but also that 90% of children who wheezed in the third year of life had confirmed asthma by age 6 (Jackson et al., 2008). Interestingly, in both of these studies, children who wheezed with rhinovirus-associated illnesses had a significantly higher risk of developing chronic wheeze or asthma than those who wheezed due to illnesses associated with RSV. Moreover, there is now clear evidence that children can experience recurrent respiratory illnesses due to serial HRV infections (Jartti et al., 2008).

Although viruses can induce wheezing illnesses in children that predispose to development of asthma, all children experience RSV infections before age 2, and all children experience repeated HRV infections. What renders a subset of children susceptible to developing wheezy bronchiolitis and subsequent asthma is not yet entirely clear. There is undoubtedly a genetic component to asthma susceptibility, and genome wide association studies have identified multiple candidate genes/loci linked to asthma (Ober & Yao, 2011). It is clear, however, that the underlying genetic susceptibility is complex, with heritability accounting for as little as 10–35% of disease according to some estimates (Ober & Yao, 2011). Thus, it seems likely that additional environmental factors play a role in determining susceptibility to asthma development. This has led to the paradigm of a "two-hit" or, conceivably, a "multiple-hit" thesis for the development of asthma, in which recurrent viral infections in the setting of an additional risk factor(s) may be necessary to trigger the subsequent development of asthma. Other relevant factors in early childhood that could contribute to regulating susceptibility to developing asthma include impaired lung development and reduced lung function (Martinez et al., 1988; Gern et al., 2005), living on a farm (von Mutius & Vercelli, 2010), cigarette smoke exposure (Gilliland et al., 2006), daycare attendance in early life (Nystad, 2000), breastfeeding (Gdalevich et al., 2001), antibiotic use (Kozyrskyj et al., 2007) and allergic sensitization (Rakes et al., 1999). Although the concept that two (or more) independent risk factors may interact to induce the development of asthma is attractive, we have limited understanding of the importance of the relative timing and duration of exposures in regulating asthma susceptibility. In the case of allergic sensitization and viral-induced wheezing, which are recognized as independent risk factors for asthma development (Jackson et al., 2008), a recent study examined the temporal relationship between these risk factors in the COAST study birth cohort (Jackson et al., 2012). Markov modeling of the data indicated that allergic sensitization increased the risk of developing HRV-induced wheezing, but did not alter the risk of RSV-induced wheezing. By contrast, viral wheeze did not lead to increased risk of subsequent allergic sensitization. While these data could be interpreted to suggest that allergic sensitization must precede viral wheezing in the development of asthma, a note of caution is warranted.