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Review

Experimental rhinovirus infection in COPD: Implications for antiviral therapies

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) is a major public health problem and will be one of the leading global causes of mortality over the coming decades. Much of the morbidity, mortality and health care costs of COPD are attributable to acute exacerbations, the commonest causes of which are respiratory infections. Respiratory viruses are frequently detected in COPD exacerbations but direct proof of a causative relationship has been lacking. We have developed a model of COPD exacerbation using experimental rhinovirus infection in COPD patients and this has established a causative relationship between virus infection and exacerbations. In addition it has determined some of the molecular mechanisms linking virus infections to COPD exacerbations and identified potential new therapeutic targets. This new data should stimulate research into the role of antiviral agents as potential treatments for COPD exacerbations. Testing of antiviral agents has been hampered by the lack of a small animal model for rhinovirus infection and experimental rhinovirus infection in healthy volunteers has been used to test treatments for the common cold. Experimental rhinovirus infection in COPD subjects offers the prospect of a model that can be used to evaluate the effects of new treatments for virus-induced COPD exacerbations, and provide essential data that can be used in making decisions regarding large scale clinical trials.

Contents

1. Chronic obstructive pulmonary disease: aetiology and pathophysiology

Chronic obstructive pulmonary disease (COPD) is defined as a treatable and preventable disease characterised by progressive airflow limitation and an enhanced airway inflammatory response (Vestbo et al., 2013). It is the most common chronic respiratory condition in adults and it is estimated that 65 million people have moderate to severe COPD resulting in 3 million deaths in 2005. COPD develops in response to cumulative exposure to inhaled noxious particles or gases that trigger pathological responses in the lungs that eventually lead to the development of the disease. There are a number of aetiological agents that are associated with the development of COPD. In Western countries the prevalence of

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COPD is strongly related to cigarette smoking as tobacco smoke is the main aetiological agent. From surveys carried out in developing nations it has become apparent that the relationship between cigarette smoking and COPD is less strong in these countries (Buist et al., 2007; Menezes et al., 2005), and other risk factors contribute to the development of COPD including exposure to burning of biomass fuels, outdoor air pollution and respiratory infections.

COPD is characterised by a number of pathological changes in the lungs that include parenchymal destruction (emphysema), inflammation of large airways (chronic bronchitis), inflammation and destruction of small airways (bronchiolitis) and mucous hypersecretion (Hogg and Timens, 2009). These pathological changes lead to the characteristic physiological abnormalities of airflow obstruction (manifested by a reduction in the forced expiratory volume in 1 s (FEV_1), and a reduction in the ratio of the FEV_1 to the forced expiratory volume (FVC)), hyperinflation and impaired gas exchange that eventually lead to respiratory failure.

There are three main processes in the lungs that drive development and progression of the disease namely pulmonary inflammation, oxidative stress and protease/antiprotease imbalance. Exposure to inhaled irritants such as cigarette smoke triggers an inflammatory response in the lungs and in those individuals that develop COPD this response is exaggerated. Studies comparing smokers with and without COPD have demonstrated greater numbers of neutrophils, macrophages and CD8+ T cells in the lungs of COPD patients (Decramer et al., 2012; Di Stefano et al., 1996, 1998). These inflammatory cells release a host of biological mediators including proteases such as neutrophil elastase and matrix metalloproteases, whilst at the same time the antiprotease defences of the lung are impaired (Pons et al., 2005). This protease/antiprotease imbalance results in uninhibited proteolytic activity and destruction of lung parenchyma. High levels of reactive oxygen species are generated in COPD from both exogenous sources (tobacco smoke) and endogenous sources (inflammatory cells). When these overwhelm the lungs' anti-oxidant defences oxidative stress results and induces multiple biological effects including induction of pro-inflammatory cytokines and chemokines, mucous hypersecretion, activation of proteases and damage to cellular components including phospholipids, proteins and nucleic acids (Chiba et al., 2012). Therefore the processes of airway inflammation, oxidative stress and protease excess are interlinked and contribute to the development of COPD.

Although COPD develops in response to inhaled noxious agents, once the disease has developed it appears to be autonomous of the original stimulus. Studies of ex-smokers with COPD have demonstrated that the airway inflammation is indistinguishable from COPD patients who continue to smoke (Gamble et al., 2007). Therefore it has been suggested that other mechanisms such as autoimmunity and infection may perpetuate the on-going inflammation in COPD, even after exposure to the initiating agent has been removed (Decramer et al., 2012).

2. Public health importance of COPD and its current and future economic impact

COPD is an enormous public health problem and its impact is expected to increase in the future. In 2002 COPD was the fifth leading cause of death worldwide and is predicted to be the 4th leading cause of death by 2030 (Mathers and Loncar, 2006). COPD develops after many years of exposure to the relevant aetiological agent and therefore the current prevalence of COPD reflects exposure to risk factors that has occurred in previous decades. In Western countries the prevalence of COPD is expected to remain stable for some years despite reductions in smoking rates. This reflects previous smoking rates, an ageing population and improvements in therapies for respiratory and cardiovascular diseases that have reduced mortality in COPD (Feenstra et al., 2001). Much of the increase in the global prevalence of COPD in the future is expected to occur in middle-income countries with large populations such as China, India, Turkey, South Africa and Indonesia. Smoking rates in these countries remain high, and there is also a high burden of other risk factors such as use of biomass fuels, outdoor pollution and respiratory infections. Therefore in these countries a 'perfect storm' of risk factors will contribute to a continuing global epidemic of COPD for the foreseeable future (Finney et al., 2013; van Zyl Smit et al., 2010).

3. COPD exacerbations

COPD patients experience a varying level of chronic symptoms punctuated by periods of sustained acute deterioration during which they experience increases in dyspnoea, sputum production, sputum purulence and cough. These episodes are termed 'acute exacerbations' and are associated with increased airflow limitation and dynamic hyperinflation which can result in respiratory failure. The occurrence of exacerbations increases with increasing severity of the disease and some patients experience frequent exacerbations (Hurst et al., 2010). Exacerbations have considerable impact on patients and healthcare providers both during and after the acute episode, and reduction of exacerbations is a key therapeutic goal in COPD. COPD exacerbations are associated with considerable mortality with exacerbations requiring hospital admission having an in-hospital mortality rate of 11–24% (Almagro et al., 2002; Connors et al., 1996; Groenewegen et al., 2003), and 2-year mortality rates ranging from 22% to 49% (Almagro et al., 2002; Connors et al., 1996; Groenewegen et al., 2003). Exacerbations are associated with falls in lung function that are frequently prolonged and lung function may not return to baseline values for several weeks in some patients (Seemungal et al., 2000a). Frequent exacerbations are associated with an accelerated decline in lung function (Anzueto et al., 2009; Celli et al., 2008; Donaldson et al., 2002; Kanner et al., 2001), impaired quality of life (Seemungal et al., 1998) and increased likelihood of becoming housebound (Donaldson et al., 2005).

The healthcare costs and economic impact of COPD exacerbations are enormous. In the United States COPD exacerbations accounted for 1,254,703 hospitalizations in 2006 with an estimated cost of US$11.9 billion (Perera et al., 2012). Therefore prevention of COPD exacerbations is a major therapeutic target and a major unmet need in COPD management. Non-pharmacological treatments for prevention of exacerbations include smoking cessation, influenza and pneumococcal vaccination and pulmonary rehabilitation. The mainstays of pharmacological therapy are inhaled bronchodilators and inhaled corticosteroids (ICS). Clinical trials have demonstrated that these treatments reduce exacerbations (Calverley et al., 2007; Wedzicha et al., 2008), although the efficacy of ICS continues to be debated (Barnes, 2010; Suissa and Barnes, 2009). These treatments are not without adverse effects and there is some evidence to suggest that ICS use is associated with an increased risk of pneumonia in COPD (Barnes, 2010; Cates, 2013; Singanayagam et al., 2010). Treatment of the established exacerbation includes bronchodilators, systemic corticosteroids and antibiotics but their clinical benefits are modest and they are associated with considerable side effects. Therefore more effective treatments for both prevention and treatment of COPD exacerbations are urgently needed.

4. Pathophysiology of exacerbations

The pathological features of stable COPD are well described but the pathology of exacerbations is less well defined. Exacerbations