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The role of the NLRP3 Inflammasome in the pathogenesis of airway disease ☆

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ABSTRACT

The incidences of respiratory diseases like asthma and Chronic Obstructive Pulmonary Disease (COPD) are increasing dramatically. Significantly, there are currently no treatments that can slow or prevent the relentless progression of COPD; and a sub-population of asthmatics are resistant to available therapies. What is more, currently prescribed medication has only minimal effect on the symptoms suffered in these patient groups. There is therefore an urgent need to develop effective drugs to treat these diseases.
Whilst asthma and COPD are thought to be distinct diseases, it is currently believed that the pathogenesis of both is driven by the chronic inflammation present in the airways of these patients. It is thus hypothesised that if the inflammation could be attenuated, disease development would be slowed and symptoms reduced. It is therefore paramount to determine the pathways driving/propagating the inflammation. Recently there has been a growing body of evidence to suggest that the multimeric protein complex known as the Inflammasome may play key roles in the inflammation observed in respiratory diseases. The aim of this review is to discuss the role of the NLRP3 Inflammasome, and its associated inflammatory mediators (IL-1β and IL-18), in the pathogenesis of asthma and COPD.

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1. Introduction

The incidence of chronic respiratory disease is increasing dramatically, particularly in developing countries around the globe. Asthma and chronic obstructive pulmonary disease (COPD) affect the lives of ~300 and 200 million people respectively worldwide (WHO 2007). What is more the severity and incidence of both these disease are increasing globally. COPD is currently reported to be the fourth leading cause of death worldwide and is predicted to be the third ranked disease in the year 2020 (Lopez & Murray, 1998). In 2005 COPD alone was responsible for 3 million deaths, and asthma claimed a further 250,000 lives (WHO 2007). Both diseases also have massive burdens on healthcare costs globally, where in 2007 alone COPD cost the US economy $47 billion with an additional $19.7 billion attributed to asthma (American Lung Association, 2007). Despite the ever increasing number of patients suffering from COPD there are currently no treatments that can slow or prevent the progression of the disease or provide patients with adequate relief from their symptoms (Stockley et al., 2009). The majority of deaths attributed to asthma occur in patients suffering from the severe form of the disease (5–10% of patients), and these

Abbreviations: AHR, airway hyperresponsiveness; ASC, apoptosis-associated speck-like protein containing a CARD; ATP, adenosine triphosphate; COPD, Chronic Obstructive Pulmonary Disease; CS, cigarette smoke; DAMP, danger associated molecular pattern; HDM, house dust mite; IgG, Immunoglobulin G; IgE, Immunoglobulin E; IL-1β, Interleukin 1 beta; IL-18, Interleukin 18; NLR, Nod-like receptor; NLRP3, NACHT, LRR and PYD domains-containing protein 3; OVA, ovalbumin; PAMP, pathogen associated molecular pattern; ROS, reactive oxygen species; TLR, Toll-like receptor.

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are generally not managed effectively with the current Gold Standard asthma therapies i.e. combination of β_2-adrenoceptor agonists and inhaled corticosteroids (Barnes, 2010). What is more, patients with either of these diseases often suffer acute episodes of worsening of their symptoms (i.e. exacerbations) which are associated with respiratory infections and exposure to airborne pollutants (Johnston, 2007). Therapies for these exacerbations are inadequate and these episodes are associated with much of the morbidity and mortality (Johnston, 2007; Hansel & Barnes, 2009). Therefore finding therapies to aid patients suffering from asthma and COPD is of the utmost importance.

Although much progress has been made over the last half century understanding the features of both diseases, the underlying mechanisms leading to the pathogenesis of asthma and COPD are yet to be determined comprehensively. In the case of both asthma and COPD, the pathophysiological changes seen have been well characterised and are used to diagnose patients. COPD is associated with exposure to inhaled pollutants, primarily cigarette smoke (CS), which is thought to lead to the chronic airway inflammation via the activation of structural and inflammatory cells within the lung (epithelial cells and alveolar macrophages). These in turn release chemotactic mediators which recruit additional inflammatory cells ($CD8^+$ T-cells, neutrophils, monocytes and lymphocytes) into the lung. It is this chronic inflammation that is thought to cause the structural changes in the airway (i.e. emphysema, small airway disease and fibrosis) and the associated symptoms (i.e. cough and shortness of breath) (Stockley et al., 2009). Allergic asthma is also a chronic inflammatory airway disease but has a distinct inflammatory profile (e.g. eosinophils, $CD4^+$ T cells, Th2 cytokine production). Again it is this inflammation that is believed to drive the airway pathology (i.e. increase smooth muscle mass and fibrosis) and increased airway responsiveness (or airway hyperreactivity, AHR) and the associated symptoms of variable airflow limitation, shortness of breath and cough (Bateman et al., 2008).

Due to the hypothesis that it is the chronic inflammation which drives the pathogenesis and symptoms of both these diseases, a huge amount of research effort is directed to understanding the mechanism initiating and propagating the inflammation. In this review we present the evidence for a role of the NLRP3 Inflammasome, and its products, in the inflammation observed in COPD and asthma. Often referred to simply as "the Inflammasome", the NLRP3 (NALP3 or cryopyrin) Inflammasome is the most studied of the family of Inflammasome complexes. The Inflammasome has been the subject of many excellent reviews recently (Martinon & Tschopp, 2006; Mariathasan & Monack, 2007; Mitroulis et al., 2010) and so in this review we will limit our description to a brief overview (Fig. 1). Following appropriate stimulation the NLRP3 recruits ASC and pro-caspase 1 to form a multimeric protein complex which leads to the cleavage of the pro-caspase 1 into the active form (Martinon et al., 2002). Caspase 1 can then cleave the pro-forms of two potent pro-inflammatory cytokines IL-1β and IL-18 in the cytoplasm. This has two main effects, firstly it increases the biological potency of the cytokines and secondly in this mature form these cytokines can be released from the cell (Martinon et al., 2002; Mariathasan et al., 2006). Fig. 1 depicts an overview of the various ways the Inflammasome, or its associated cytokines, can be activated/promoted. The primary role of the Inflammasome and its products seems to be as part of the body's innate immune system, in that they can be triggered to assist in defence against invading pathogens. Indeed much of the data published on the Inflammasome/caspase 1 is on its role in the body's response to pathogens such as viruses and bacteria (Brodsky & Monack, 2009; Bryant & Fitzgerald, 2009; Cassel et al., 2009; Franchi et al., 2010; Kanneganti, 2010; Rathinam & Fitzgerald, 2010; Schroder & Tschopp, 2010). Briefly, Inflammasome associated pro-cytokines (and in some instances the Inflammasome/caspase 1 themselves) can be produced (and in some cases activated) by a family of receptors which detect the presence of pathogens through pathogen associated molecular patterns (PAMPs) (Ishii et al., 2008). This family of receptors include Toll-like receptors (TLRs), Nod-like receptors (NLRs), RIG-I-like RNA helicases (RLHs), and C-type lectin receptors (CLRs) (Trinchieri & Sher, 2007). TLRs are known to recognize PAMPs on the cell surface, whereas NLRs sense microbial

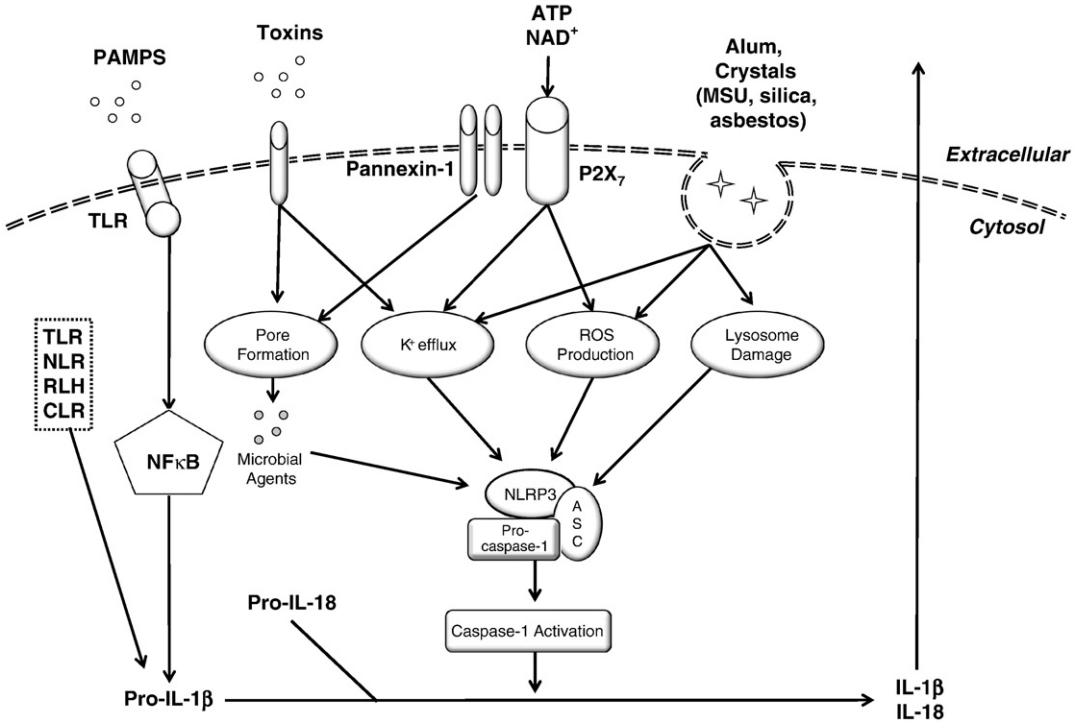

Fig. 1. An overview of the signalling cascade associated with the NLRP3 Inflammasome (adapted from Franchi et al., 2009) illustrates the array of ways it can be activated. The processing and subsequent release of pro-inflammatory cytokines IL-1β and IL-18 via caspase 1 can be dependent on the activation of the NLRP3 Inflammasome.