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Identification of Novel Therapeutic Targets in COPD

Esmaeil Mortaz [1,2], Mohammad Reza Masjedi [2] and Peter Barnes [3]

[1] Division of Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Faculty of Science, Utrecht University, Universiteitsweg 99, Utrecht, The Netherlands, [2]Chronic Respiratory Disease Research Center, National Research Institute of Tuberculosis and Lung Disease (NRITLD), Masih Daneshvari Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran and [3] Cell and Molecular Biology Group, Airways Disease Section, National Heart and Lung Institute, Imperial College London, Dovehouse Street, London, UK

INTRODUCTION

COPD is an important lung and airway disease with an increasing incidence particularly in developing countries. Worldwide, asthma and COPD affect the lives of ~300 and 200 million people, respectively (1). COPD is a chronic inflammatory disease for which smoking is the major risk factor in the developed world and is currently the fourth leading cause of death worldwide. It is predicted to become the third ranked disease by the year 2030 (2, 3). Unfortunately, there are no effective treatments for severe asthma and COPD due to a lack of clarity in disease mechanisms. However, new observations in the areas of signal transduction and epigenetics may provide new understanding of the pathogenesis of lung diseases. Understanding the pathways and mechanisms leading to mediator release may lead to better therapeutic approaches for these diseases. The inflammatory mediators involved in COPD have not been clearly delineated but are thought to include many lipid mediators, inflammatory peptides, reactive oxygen species (ROS) and nitrogen species, chemokines, cytokines and growth factors. These are all involved in orchestrating the complex inflammatory process that results in small airway fibrosis and alveolar destruction occurring in COPD (4-6). Cigarette smoke contains over 4,700 chemical compounds, and both the tar and gas phases contain numerous free radicals and other oxidants present in high concentrations which contribute to the pathogenesis of this condition (7-10). Exposure to cigarette smoke activates an inflammatory cascade in the airways, resulting in the production of a number of potent cytokines and chemokines with accompanying damage to the lung epithelium leading to increased permeability and recruitment of macrophages and neutrophils (11). Free radicals in cigarette smoke activate inflammatory cells which, in turn, generate high levels of ROS and other toxic metabolites. Activation of immune cells by these radicals leads to the production of oxidants and cytokines, such as IL-8, IL-6 and TNF-α (12-19). IL-8 is a powerful chemotactic and paracrine mediator for neutrophils, and infiltration of activated neutrophils is the key in pulmonary inflammation and oxidative injury (20-23). Several

Correspondence to: Prof. Peter Barnes
Email address: p.j.barners@imperial.ac.uk

inflammatory cells and their mediators, both of the innate and adaptive immune system, participate in the inflammatory response in COPD. Macrophages, neutrophils and CD8+ T cells are the cells usually considered the prime effector cells in pathogenesis of COPD (24, 25). The role of neutrophils and macrophages and their product IL-8 has been well established in the slow progression of the disease (26,27). Besides IL-8, it has been shown that fragments of the extracellular matrix, such as collagen fragments, have chemotactic properties to the cells (28, 29). One of these fragments is N-acetylated Proline–Glycine–Proline (N-ac-PGP) and it is shown that injecting N-ac-PGP into the normal rabbit corneas resulted in rapid and severe neutrophil invasion and neutrophil infiltration in the injured eye (30). Interestingly, N-ac-PGP has been found in the sputum of COPD (31) and cystic fibrosis patients (32). Overbeek et al. demonstrated that N-ac-PGP stimulates the neutrophils to release IL-8, which in *in vivo* may lead to a self-perpetuating situation where N-ac-PGP and CXCL8 work in concert, leading to enhanced neutrophil inflammation and lung inflammation (33, 34).

Recent findings concerning the innate and acquired immune responses in COPD have led to the suggestion of a possible autoimmune component contributing to its pathogenesis. This notion is supported by similar pathophysiology between COPD and some autoimmune diseases (35). In this line, the T lymphocyte subset TH17 was shown to play a role in regulating neutrophilic and macrophage inflammation of the lungs (35), suggesting a potential role for TH17 cells in severe, steroid-insensitive COPD (36-39). Thus, the nature of the immune reaction in COPD and increased amounts of IL-17 raise the possibility of autoimmune hypothesis in its pathogenesis.

Potential role of signal transduction pathways as putative therapeutic targets in pathogenesis of COPD

Understanding the pathways and mechanisms leading to mediator release may lead to better therapeutic approaches for this disease. With the complexity of inflammatory signaling networks and the cross talk that occurs between them, it is important to develop a greater understanding of these networks in the pathogenesis of disease. In terms of lung disease, it is still debatable whether these diseases occur as a result of excessive inflammatory drive or a lack of inhibitory feedback loops. However, it is clear that many of these pathways/networks are abnormally activated in COPD and that interference with these signaling pathways could shed light on disease processes and provide novel therapeutic approaches. Among signaling pathways involved in pathogenesis of COPD, Toll Like Receptors (TLRs) and Inflammasome NALP3 signal transduction activation have been described (40-42).

In this regard, increased ROS production by cigarette smoke has been directly linked to oxidation of proteins, DNA, and lipids which may cause direct lung injury or induce a variety of cellular responses through the generation of highly reactive secondary metabolic entities. ROS may alter remodeling of extracellular matrix, apoptosis and mitochondrial respiration, cell proliferation, maintenance of surfactant and the antiprotease screen, effective alveolar repair response and immune modulation in the lungs (43, 44). ROS have also been implicated in initiating the lung inflammatory response through the activation of transcription factors such as NF-κB and AP-1 and the regulation of the expression and activity of histone modifying enzymes and thereby enhancing inflammatory gene expression (45). Activation of ROS pathways in pathogenesis of asthma (46-48) and COPD has been described (49-51).

Importantly, growing evidence indicates a role for ROS in the activation of TLR pathways (52-54) and NALP3 inflammasome (55- 57).

Besides ROS, increased ATP levels in in-vitro, in-vivo models and preclinical smoke-exposure models have been reported (58, 59). ATP can activate the NLRP3 Inflammasome through the P2X7 receptor (60-62) and, in addition, regulate neutrophil chemotaxis and activation through P2Y receptors (63, 64).

Finally, the expression of the NLRP3 Inflammasome-associated cytokines IL-1β and IL-18 is increased in the lungs of COPD patients and animals exposed to cigarette smoke (65, 66). IL-1β levels are increased in airway secretions during COPD exacerbations (66) and correlate significantly with disease severity and other inflammatory mediators such as TNF-α and IL-8 (67). Furthermore, IL-1β can induce the release of M-CSF and GM-CSF from inflammatory cells (68) which in turn potentiates induction of chronic inflammatory diseases (Figure 1).

GENERAL CONCLUSIONS

Taken together, we conclude that a key process in the pathogenesis of COPD involves ROS/ATP-mediated activation of the NALP3 inflammasome and TLRs leading to prolonged, inflammatory responses.

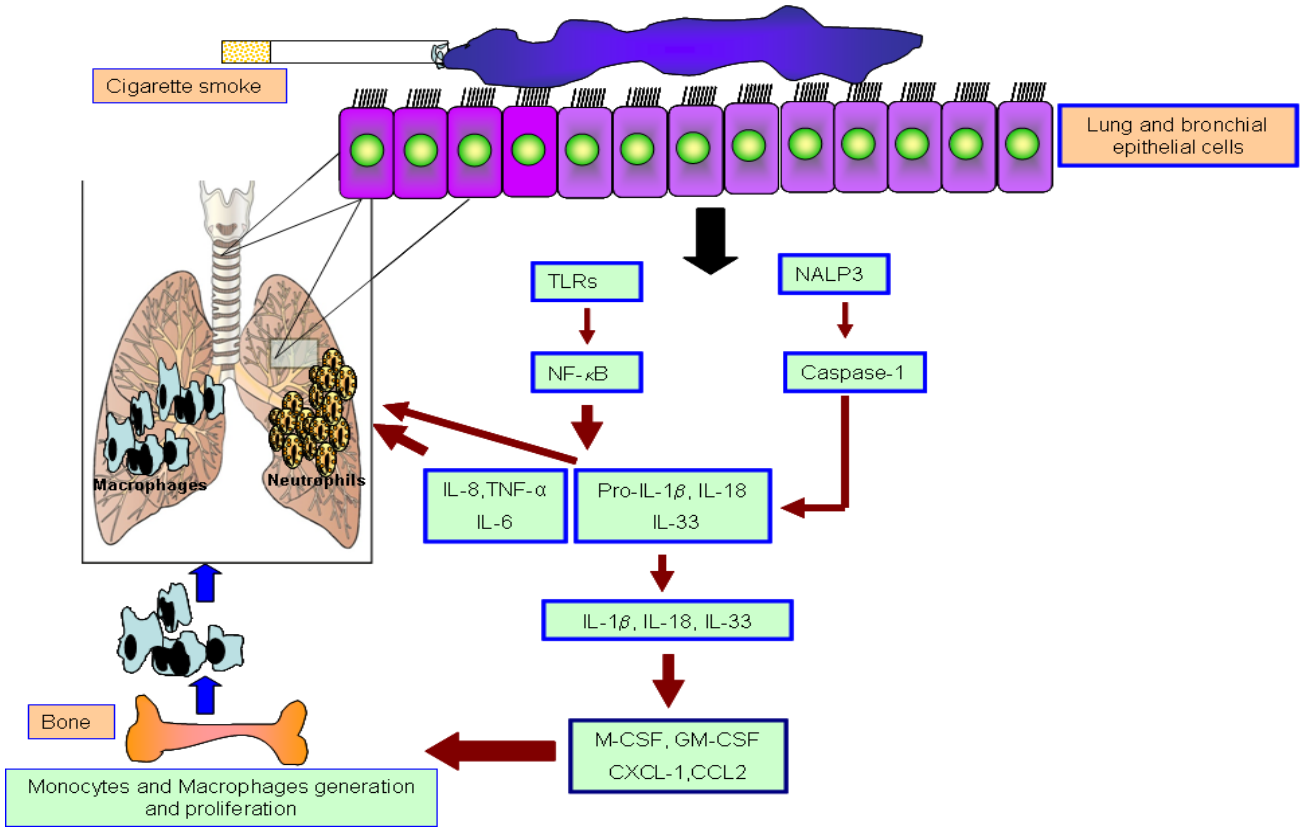

Figure 1. Role of inflammasome and TLRs signaling in pathogenesis of COPD. An overview of the signalling cascade associated with the NLRP3 Inflammasome and TLRs in pathogenesis of COPD. The Interactions between Epithelial cells (EP) and Dendritic cells (DC) in the airways and lungs when they exposed to allergen or cigarette smoke. DCs sample the airway lumen by forming dendritic extensions in between epithelial cells.

Abbreviations
ATP, adenosine triphosphate
COPD, Chronic Obstructive Pulmonary Disease
CS, Cigarette smoke
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
ROS, reactive oxygen species
TLR, Toll-like receptor

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