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Commentary

Macrophage function in chronic obstructive pulmonary disease: The many faces of notch signalling

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Chronic obstructive pulmonary disease (COPD) is a major health problem that was the third cause of death worldwide in 2016, claiming 3.0 million lives [1]. Smoking tobacco cigarettes is the main risk factor for the development of COPD, but environmental exposures resulting from air pollution and burning biomass fuel also contribute [2]. COPD is characterized by progressive airflow limitation that is poorly reversible, and that results from airway wall remodelling and alveolar destruction (emphysema). Chronic inflammation in lung tissue, but also (low-grade) systemic inflammation are observed, and periods of an acute increase in symptoms and inflammation (exacerbations) that are frequently accompanied by respiratory tract infections, contribute to disease progression. Unfortunately, there is little progress in the development of disease-modifying therapies that affect disease progression and mortality. Therefore, more insight into the mechanisms involved in COPD development and progression are needed, but studies in this area are complicated by the fact that COPD is a heterogeneous disorder.

Inflammation resulting from cigarette smoking, tissue destruction and infections plays a central role in COPD. A large number of different cell types have been implicated in the pathogenesis of COPD, including neutrophils, macrophages, $CD8^+$ T cells and B cells [3]. Macrophages not only directly contribute to COPD by producing pro-inflammatory mediators and tissue-destructive proteases, but also indirectly through defective phagocytosis of bacterial pathogens and defective clearance of apoptotic cells (efferocytosis; reviewed in [4,5]). Based on these specific alterations in macrophage function in COPD, it has been proposed that macrophages from COPD patients do not fit into the proposed phenotypes of macrophage differentiation, suggesting the existence of a specific COPD macrophage phenotype [4,6].

In this article of *EBioMedicine*, Ballester-López et al. [7] provide new insight into the role of macrophages in COPD. Based on information from two independent genome-wide association studies (GWAS), they focussed on the Delta/Notch-like epidermal growth factor related receptor (DNER, suggested to be a non-canonical Notch ligand), that was identified as a potential genetic risk in those GWAS studies. They demonstrated higher *DNER* expression in pro-inflammatory macrophages in lung tissue from COPD patients compared to controls and showed increased expression of *DNER* in monocyte-derived macrophages treated with LPS and an aqueous extract of cigarette smoke. Using a murine COPD model of chronic cigarette smoke exposure, they went on to study the role of DNER in murine macrophages and showed its involvement in IFN-γ expression by macrophages. Importantly, DNER deficiency in mice was found to provide protection against smoke-induced emphysema development and lung function impairment in the mouse COPD model. Their finding that use of inhaled corticosteroids (ICS) did not appear to affect *DNER* expression is important, since ICS have a limited or no effect on most parameters of COPD in the majority of patients. Since not all smokers do develop COPD, in human COPD studies it is essential to differentiate between mechanisms that are modified by smoking alone and those that are specifically related to reduced lung function in COPD. The authors based their conclusion that DNER in macrophages contributes to lung function decline in COPD on their mouse studies and on the results of the afore-mentioned GWAS studies. Additional detailed studies are required to investigate the exact link between DNER and COPD, such as its link to disease severity or COPD phenotype.

The Notch signalling pathway is a highly conserved mechanisms that serves multiple functions in a wide range of cell types. It has been reported that Notch signalling is decreased in the airway epithelium of COPD with lower expression of Notch-related genes in smokers with COPD than in asymptomatic smokers [8], which may be highly relevant in view of its role in airway epithelial cell differentiation [9]. In apparent contrast, Notch signalling was also implicated in rhinovirus-induced mucin production in cultured airway epithelial cells from COPD patients [10]. As discussed by Ballester-López et al. in this article of *EBioMedicine*, Notch signalling has been implicated in various inflammatory mechanisms, including macrophage function and polarization, and the function of DNER is poorly understood. Their own findings provide further insight into the complex role of (non-canonical) Notch signalling in COPD, and this insight indicates that targeting Notch signalling as a therapy for COPD or other inflammatory diseases will be challenging.

Author contribution

Pieter S. Hiemstra wrote the commentary.

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Declaration of interests

The author has no conflict of interest to declare.

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