Interleukin-1α: a key player for epithelial-to-mesenchymal signalling in COPD?

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Interleukin-1 alpha released by airway epithelial cells may instruct fibroblasts to become pro-inflammatory in COPD http://ow.ly/CLYK301tyOj

The lungs are continuously exposed to inhaled particles and irritants. Tobacco smoking is the leading cause of several airway diseases, including lung cancer, idiopathic pulmonary fibrosis and chronic obstructive pulmonary disease (COPD). In COPD, repeated exposure to cigarette smoke induces chronic inflammation and structural remodelling of the airways, with peribronchial fibrosis and epithelial-to-mesenchymal transition [1], resulting in (mostly irreversible) airway obstruction. Thus, abnormal airway responses to noxious gases probably results from aberrant signalling and crosstalk between epithelial, mesenchymal and immune cells.

In this issue of the *European Respiratory Journal*, Osei *et al.* [2] describe how epithelial cells signal to fibroblasts through interleukin (IL)-1α, with relevance to COPD. Using co-cultures of human primary cells (bronchial epithelial cells (BECs) and lung fibroblasts) and human cell lines (MRC5 fetal fibroblasts and 16HBE epithelial cells), the authors show that co-culture of BECs and fibroblasts induced the production of heat shock protein (Hsp)70, IL-8/CXCL8 and IL-1β by lung fibroblasts, while decreasing expression of α-smooth muscle actin, transforming growth factor (TGF)-β1 and extracellular matrix proteins. These effects, which were not different between control- and COPD-derived cells, were recapitulated by using BEC (16HBE)-conditioned medium, suggesting the requirement for soluble factor(s). Using neutralising antibodies, the authors went on to demonstrate that release of CXCL8 and Hsp70 by fibroblasts in the co-culture system was independent of IL-1β and prostaglandin E2 but dependent on IL-1α. In addition, IL-1α release by BECs was enhanced in COPD-derived cells by exposure to cigarette smoke extract. Although this *in vitro* model may not completely recapitulate the *in vivo* situation, it provides important new insights regarding the signals delivered by airway epithelial cells and regulating mesenchymal cells.

There is accumulating evidence that BECs are key cells in frontline defence that directly signal to immune cells, in particular antigen-presenting cells [3, 4]. Several previous works identified that BECs shape the immune response engaged by pathogens [5]. For instance, BECs exposed to *Klebsiella pneumoniae* regulate local immune responses notably by acting on the myeloid dendritic cell network [6]. Respiratory syncytial virus-infected BECs regulate $CD8^+$ T-cell activation and antiviral activity, according to changes in epithelial expression of the "checkpoint" immune receptor PD-L1 [7]. BECs also regulate dendritic cell differentiation and maturation as well as responsiveness to lipopolysaccharide [8], and inhibit T-cell recall responses towards common aeroallergens in order to ensure mucosal homeostasis and dampen allergic responses [9]. It has also been shown in asthma that BECs may suppress constitutive and IgE-dependent histamine release by lung mast cells [10], further highlighting the central role of the epithelium in sensing and shaping mucosal danger signalling. We recently showed that BECs from COPD patients also imprint

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B-cells with signals promoting maturation into IgA-producing plasma cells, while cigarette smoke partly counteracts this IgA-promoting effect [11]. This effect was at least partly related to an intrinsic ability of COPD BECs to produce increased amounts of certain cytokines (IL-6 and BAFF; B-cell activating factor) and to induce B-cell expression of TACI (transmembrane activator and CAML interactor). OSEI *et al.* [2] also addressed intrinsic epithelial changes, showing that an amplified IL-1α response to cigarette smoke extract is seen in BECs from COPD patients as compared to cells from controls.

Standing at the interface between the environment and host tissues, the innate immune system may be engaged through several pattern recognition receptors (PRRs) to pathogen-associated molecular patterns (PAMPs), namely Toll-like receptors (TLRs), NOD-like receptors, protein-activated receptors and RIG-like receptors. Ligation of these receptors triggers an immune response, initiated by the release of epithelial cytokines including IL-6, thymic stromal lymphopoietin (TSLP), IL-25 and IL-33 [12]. Upstream of these cytokines, the activation of NOD-like receptor family, pyrin domain containing 3 (NLRP3) inflammasome leads to the release of IL-1α, IL-1β and IL-18, acting as pyrogens and T-cell activators. Activated epithelial cells secrete pro-IL-1β that is cleaved by caspase-1 to produce bioactive IL-1β [13]. Despite recent evidence pointing to the involvement of NLRP3 inflammasome in asthma, COPD and idiopathic pulmonary fibrosis, and its close relationship with IL-1β and the NLRP3 inflammasome, the role of IL-1α in respiratory diseases has long been neglected. IL-1α was described in 1985 when IL-1 was discovered to consist of two distinct proteins [14]. Studies of lung samples from COPD patients and from mice exposed to cigarette smoke as an experimental model of COPD showed increased expression of IL-1α [15–17],

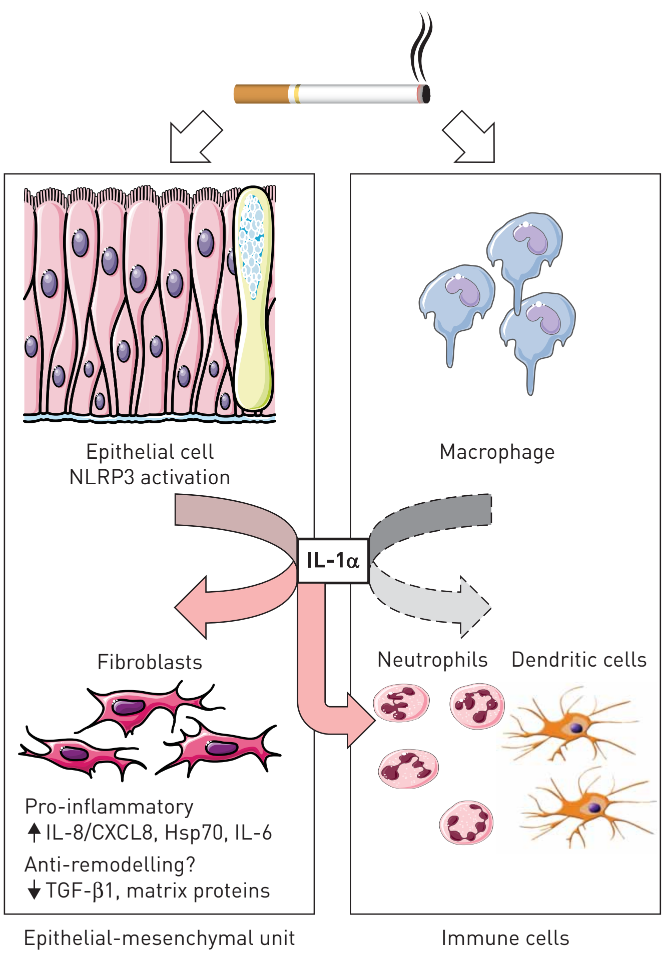

FIGURE 1 Interleukin (IL)-1α as a key mediator of epithelial signalling to mesenchymal and immune cells. In chronic obstructive pulmonary disease, cigarette smoke probably triggers bronchial epithelial cells and alveolar macrophages to release IL-1α following activation of NLRP3 (NOD-like receptor family, pyrin domain containing 3) inflammasome. IL-1α mediates a shift in fibroblast phenotype towards pro-inflammatory fibroblasts releasing increased amounts of IL-8/CXCL8, which in turn attracts neutrophils in the airways. To what extent and how IL-1α also regulates repair responses and matrix deposition [2, 20] remains to be studied, in order to clarify whether (and eventually under what circumstances) this cytokine is pro- or anti-fibrotic in the human lung.

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which mediates accumulation of neutrophils and dendritic cells in the murine model. IL-1α expression was, however, mainly localised to haematopoietic cells such as alveolar macrophages [17, 18] and not to epithelial cells. In asthma, Willart *et al.* [19] demonstrated that epithelial activation by proteolytic allergens triggers the release of IL-1α, which induces, through autocrine IL-1 receptor ligation, the release of pro-Th2 cytokines by BEC, ultimately promoting Th2-biased immune responses.

Osei *et al.* [2] went one step further by providing evidence of a key role for IL-1α in mediating epithelial signalling to fibroblasts. They showed that IL-1α switches on a differentiation programme in fibroblasts towards an inflammatory phenotype (with increased hsp70 and IL-8/CXCL8, and to some extent IL-6), while abrogating their production of matrix proteins. Suwara *et al.* [20] recently showed that human lung fibrobasts also switch towards inflammatory fibroblasts upon incubation with conditioned medium from damaged BECs, increasing their release of IL-8/CXCL8, MCP-1 and IL-6 that was abrogated by anti-IL-1α or anti-IL-1Ra, but not anti-IL-1β, antibodies. The inflammatory phenotype of fibrobasts was accentuated by concomitant activation of TLR3, through nuclear factor κB signalling. Furthermore, a reduced collagen deposition was noticed in IL-1$\alpha^{-/-}$ and IL-1R1$^{-/-}$ mice following bleomycine exposure. The finding of Osei *et al.* [2], *i.e.* a reduced synthesis of matrix proteins upon IL-1α activation, challenges this view of IL-1α as a profibrotic mediator. Thus, whether IL-1α is involved in the loss of small conducting airways or in peribronchial fibrosis observed in COPD [21] remains unclear. In cancer, Bae *et al.* [22] showed that IL-1α may enhance oral squamous carcinoma-associated fibroblast proliferation through the secretion of CCL7, CXCL1 and IL-8/CXCL8 chemokines.

Interactions between epithelial and mesenchymal cells are critical during branching morphogenesis and lung development, and include in the adult lung several aspects including dynamic transition states (epithelial-to-mesenchymal and mesenchymal-to-epithelial transition) and paracrine regulation. In asthma, IL-4/IL-13 activate BECs to release TGF-β2 which, in turn, stimulates myofibroblast transformation and secretion of matrix proteins and vascular mitogens (*e.g.* vascular endothelial growth factor, endothelin-1) [23], leading to the concept of "epithelial-mesenchymal trophic unit". This epithelial-mesenchymal signalling pathway should be further explored in chronic airway diseases such as COPD [24], notably by using multicellular culture models with primary cells as carried out by Osei *et al.* [2].

Altogether, this work illustrates that repeated broncho-epithelial injury by cigarette smoke, in individuals with putative susceptibility factors (which remain largely unknown), may trigger an altered programming of airway epithelial cells resulting in chronic inflammasome activation which includes the release of IL-1α (figure 1). Whereas this cytokine probably contributes to persistent accumulation of neutrophils by instructing a pro-inflammatory programming of fibroblasts, it remains to be determined to what extent it also contributes to altered repair responses and matrix deposition in conducting airways of the human COPD lung. An additional difficulty in COPD is the association in the same disease of opposed features of matrix turnover at different airway levels, namely matrix deposition in some conducting airways (while some other small airways may disappear) and matrix destruction in respiratory parts of the lung, or even between adjacent alveolar zones in the combined emphysema fibrosis phenotype [25]. Nevertheless, manipulation of the epithelial-fibroblast pathway should help the development of new therapeutic strategies, and the recent attempt to target the inflammasome in COPD [26] might open the way to new biotherapies in severe chronic obstructive lung disease.

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