Bronchial epithelial cells: the *key effector cells in the pathogenesis of chronic obstructive pulmonary disease.*

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Abstract

The primary function of the bronchial epithelium is to act as a defensive barrier aiding the maintenance of normal airway function. Bronchial epithelial cells (BECs) form the interface between the external environment and the internal milieu, making it a major target of inhaled insults. However, BECs can also serve as effectors to initiate and orchestrate immune and inflammatory responses by releasing chemokines and cytokines, which recruit and activate inflammatory cells. They also produce excess reactive oxygen species as a result of an oxidant/antioxidant imbalance which contributes to chronic pulmonary inflammation and lung tissue damage. Accumulated mucus from hyperplastic BECs obstructs the lumen of small airways, whereas impaired cell repair, squamous metaplasia and increased extracellular matrix deposition underlying the epithelium is associated with airway remodelling particularly fibrosis and thickening of the airway wall. These alterations in small airway structure lead to airflow limitation, which is critical in the clinical diagnosis of chronic obstructive pulmonary disease (COPD). In this review, we discuss the abnormal function of BECs within a disturbed immune homeostatic environment consisting of ongoing inflammation, oxidative stress and small airway obstruction. We provide an overview of recent insights into the function of the bronchial epithelium in the pathogenesis of COPD and how this may provide novel therapeutic approaches for a number of chronic lung diseases.

Keywords: bronchial epithelial cells, chronic obstructive pulmonary disease, immunity, inflammation, oxidative stress, small airway obstruction.

Introduction

Chronic obstructive pulmonary disease (COPD) represents a syndrome comprising chronic bronchitis (CB) and emphysema characterised by largely irreversible and progressive airflow limitation [1]. More than 200 million people worldwide are currently affected by the disease, which is the fourth leading cause of death worldwide [2] and is projected to be the third leading cause by 2030 [3]. At the pathological level, COPD is associated with chronic pulmonary inflammation in response to environmental insults. This is, in turn, inextricably linked to disturbed tissue repair, increased mucus secretion and epithelial cell hyperplasia with airway wall thickening in the small conducting airways [4]. Bronchial epithelial cells (BECs), which line the airway lumen, are among the first sites of contact for environmental stimuli (microorganisms, gases and allergens) and perform a crucial role in maintaining normal airway function. Studies on human bronchial biopsies in COPD have demonstrated increased inflammatory gene and protein expression and structural alterations in bronchial epithelial cells [5–8] suggesting a causal role of BECs in COPD pathogenesis.

Bronchial epithelial cells (BECs)

BECs are composed of various cell types and may be classified into three categories based on ultrastructural, functional and biochemical criteria: basal, ciliated and secretory cells [9]. Basal cells are ubiquitous in the large (50%) and small airways (81%) [10] but the absolute cell count decreases with airway size [11]. Basal epithelial cells exclusively express hemidesmosomes indicating an important role in the attachment of themselves and more superficial cells to the basement membrane [11, 12]. These cells are also thought to be primary progenitor or stem cells because they can self-renew and give rise to secretory and ciliated epithelial cells in response to epithelial injury [13]. In addition to their structural and progenitor functions, basal epithelial cells also produce various bioactive molecules, including neutral endopeptidase, 15-lipoxygenase products and cytokines [14].

Ciliated epithelial cells are the major cell type within the airways, accounting for over 50% of all epithelial cells [9]. They possess up to 300 cilia per cell and have numerous energy-producing mitochondria adjacent to their apical surface, highlighting the critical function of the cells in clearing mucus out from the airways via directional ciliary beating [15].

Mucus (goblet) cells are large secretory granules containing large quantities of mucin glycoproteins which secrete mucus in order to trap foreign objects in the airway lumen [16]. A balance between the correct amount of mucus production and clearance provides a critical defensive barrier and prevents airway surface desiccation [17]. Mucus cells are also capable of self-renewal and differentiation into ciliated epithelial cells [11].

In humans, non-ciliated secretory cells called Club cells (these were formerly known as Clara cells) exist in the small airways and trachea. These are morphologically identified by their distinctive dome-shaped apical protrusions and molecularly identified by their expression of Clara cell secretory protein [17]. The cells possess several lung protective functions. They regulate bronchiolar epithelial integrity and immunity by producing bronchiolar surfactants and specific anti-proteases; they metabolise xenobiotic compounds by the action of p450 mono-oxygenases [18] and also have an important stem cell function as progenitors for both ciliated and mucus-secreting cells [19].

Considering the critical functions of BECs in maintaining the normal structure and function of the airways it is not surprising that dysregulated BECs may contribute to the pathogenesis of many lung diseases such as COPD. In this review we address the evidence for a critical role of dysfunctional BECs in the pathogenesis of COPD.

BECs initiate and regulate immune responses

The lungs are persistently exposed to environmental insults, but rarely show signs of infection, implying the existence of effective host defence mechanisms. The host is protected against various stimuli by a multi-layered defence system consisting of a combination of physical barriers, as well as innate and adaptive immune mechanisms

[20]. The importance of numerous immune cell types in COPD has been stressed for many years [21]. Vareille et al. [22] summarised the important functions of BECs in response to respiratory viruses and these can be categorised on several different levels. Firstly, BECs form an efficient physical barrier function against viral invasion by exhibiting cell–cell junctions, including tight junctions, adherens junctions, gap junctions and desmosomes [23]. Ciliated and mucus cells together enable the formation of a mucus barrier that traps and clears approximately 90% of inhaled particles [24]. Secondly, BECs rapidly recognise molecules that are exclusive to microbes, namely, pathogen-associated molecular patterns (PAMPs), via expression of pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs). This recognition enables BECs to subsequently interact with, guide, activate and modulate other immune cells [25]. Thirdly, BECs produce various antiviral substances and release chemokines and cytokines that are important in both innate and adaptive immune processes upon viral recognition.

Cigarette smoke (CS) is the main etiological factor for COPD. CS can disturb immune homeostasis in the lungs and change airway host defence mechanisms leading to COPD [26]. CS induces dramatic alterations in the airway epithelial architecture and impairs barrier functions of BECs by increasing the permeability of the airway epithelium, impairing cilia beat ability and reducing mucociliary clearance [27, 28]. This barrier dysfunction, which is often found in COPD [29, 30], can increase viral binding and entry into cells, further impairing barrier function [31–33]. CS also inhibits the production of interferons (IFNs), important antiviral substances, by BECs upon stimulation with a viral double-stranded RNA mimic, polyI:C [34], indicating that BECs have an impaired immune defence against viral infections.

In addition to the compromised immune barrier function following chronic CS exposure, altered BECs also show disproportionate immune responses to other environmental hazards. CS and other inhaled toxic agents cause direct damage to BECs leading to the release of endogenous molecules called damage-associated molecular patterns (DAMPs) [35]. Concentrations of high-mobility group box 1 [36], uric acid and extracellular ATP [37], which are important DAMPs, are shown to be

increased in bronchoalveolar lavage fluid of patients with COPD compared with smokers without COPD. Similar to PAMPs, these signals are identified by PRRs, such as TLR4 and TLR2 on BECs [38] and can subsequently trigger a non-specific inflammatory response [39]. Release of early cytokines and chemokines [such as tumour necrosis factor α (TNF-α) and interleukin (IL)-1 and IL-8/CXCL8] by BECs elicits the recruitment of macrophages, neutrophils and dendritic cells (DCs) to the site of inflammation [40, 41]. These cells, in turn, secrete proteolytic enzymes and reactive oxygen species (ROS), causing lung tissue damage [42].

DCs are specialised antigen-presenting cells that have a central function in the initiation of innate and adaptive immune responses [43]. By integrating multiple signals from the local microenvironment, DCs promote $CD4^+$ T helper cell differentiation and $CD8^+$ cytotoxicity [35], which are both associated with more advanced stages of airflow limitation and emphysema in COPD [44]. Considering the close proximity of BECs and DCs, DCs are likely to be receptive to local signals derived from epithelial cells. Several studies have demonstrated that DC migration, maturation and activation is regulated by BEC-secreted chemokines [45, 46]. For example, MIP-3α/CCL20, the unique ligand for CCR6 released by BECs in response to CS exposure, can facilitate the recruitment of DC subsets to the airway epithelium [41, 45]. BECs not only help promote terminal differentiation of B-cells oriented towards polymeric immunoglobulin-A (IgA) production by producing different cytokines, such as TGF-β, IL-5 or IL-10 [47], but also mediate IgA transportation [48]. Thus, we suggest that BECs can both initiate and regulate the innate and adaptive immune systems involved in COPD pathogenesis **(Figure 1).**

BECs act as both targets and potent effector cells in chronic pulmonary inflammation

Chronic inflammation contributes to airflow limitation in COPD [1, 49]. Chronic inflammation in COPD is mainly characterised by the accumulation of neutrophils, macrophages, B cells and $CD8^+$ T cells, especially in small airways [50]. Various inflammatory mediators also have important functions in the pathogenesis of the

disease. BECs serve as a barrier to noxious stimuli and produce mediators and enzymes to maintain normal airway homeostasis. Respiratory viruses rapidly stimulate epithelial cells to secrete a wide range of pro-inflammatory mediators, such as IL-6, IL-8 and granulocyte-monocyte colony-stimulating factor (GM-CSF) [51, 52]. These early activated cells cause changes in endothelial cell physiology and further induce migration and infiltration of inflammatory cells to the airways [52–54]. Under normal conditions, the inflammatory cells in airways kill and eliminate inhaled foreign matter by secreting cytotoxic mediators and proteases, employing phagocytosis and a respiratory burst. However, sustained deleterious environmental stimuli, such as CS, may cause injury and alterations in defence mechanisms in BECs. The bronchial epithelium not only serves as a target of environmental stresses, but also works as a major effector to propagate the inflammatory process [55]. BECs produce primary inflammatory mediators, such as IFN-γ, TNF-α and IL-1, which then trigger the release of secondary mediators by BECs, including other cytokines, lipid mediators, growth factors, proteases and ROS [35, 56, 57]. A summary profile of the mediators produced by BECs potentially involved in COPD is shown in **Table 1**, with further details on major mediators provided in the following section.

Lipid mediators, including prostaglandins (PGs), leukotrienes (LTs) and platelet-activating factor (PAF), are produced by BECs in response to various stimuli [58, 59] and act in an autocrine or paracrine manner to trigger the production of more lipid mediators [60, 61]. These mediators are chemotactic for neutrophils and macrophages and can alter vascular and epithelial permeability [62]. PAF and LTs can induce airway mucin secretion and cause bronchoconstriction [60, 61]. When oxidant exposure (e.g., chronic CS exposure) is continuous, oxidant species are especially important in the lung epithelium. Reactive species, such as hydrogen peroxide (H_2O_2), superoxide anion radicals ($O_2\bullet$), hydroxyl radicals (i.e., $OH\bullet$), nitric oxide (NO) and peroxynitrite (ONOO), change cell functions in the lungs. The oxidants released by BECs [63, 64] either directly injure the airway epithelium or alter the expression and activation of redox-sensitive pro-inflammatory signalling pathways including nuclear factor-κB (NF-κB) and activation protein (AP)-1 [65], thereby amplifying

inflammatory cell influx. Cytokines are pluripotent proteins that are produced and released by various cell types, including human BECs [66]. Primary pro-inflammatory mediators such as IL-1 and TNF-α are produced rapidly by BECs upon stimulation and can feedback on the same cells to up-regulate the expression and secretion of secondary cytokines including IL-6, IL-8/CXCL8 and GM-CSF [35, 56, 57, 66]. In addition, BECs are a major source of numerous chemokines such as CXCL1, CXCL5, CXCL10, CCL11, CCL2 and CCL5 [67] which facilitate the recruitment and activation of different inflammatory cells within the airways. These recuited inflammatory cells can release various proteases, including neutrophil elastase and matrix metalloproteinases (MMPs), which break down connective tissue components, particularly elastin, in lung parenchyma to produce emphysema.

Exposure of BECs to cigarette smoke results in the activation of numerous redox-associated intracellular signalling pathways including MAPKs, NF-κB and AP-1 [68, 69]. Other transcription factors, including cAMP response element-binding protein, CBP [70], CCAAT/enhancer-binding protein-b [71] and peroxisome proliferator-activated receptor [72], are also activated by CS exposure. These all contribute to varying degress to the expression of inflammatory mediators in BECs.

BECs contribute to the oxidant/antioxidant imbalance in oxidative stress

Increasing evidence showed that oxidative stress is an important feature in COPD [73, 74] because of excess ROS in the antioxidant defence mechanisms in the airways. BECs can produce increased amounts of ROS in response to different stimuli [75]. The airways are exposed to exogenous oxidants, such as CS, which summate with endogenous ROS production to elevate oxidative stress and further increase the inflammatory and destructive response in COPD.

Activation of MAPK and NF-κB pathways [68, 76] and increased cytokine release [77] has also been demonstrated in airway epithelial cells in response to oxidant stress *per se* and this may be linked, at least in part, to alterations in the histone acetylation/deacetylation balance [78, 79]. The increased expression and release of mediators, such as CXCL8/IL-8, GM-CSF, soluble ICAM-1 and TNF-α, may also

regulate the influx of inflammatory cells [80]. For instance, exposure of human airway epithelial cells to ozone results in the induction of adhesion molecules on BECs leading to increased neutrophil adhesion [81]. Therefore, oxidative stress in BECs may amplify the ongoing inflammatory responses in COPD. In addition, oxidative stress can increase both airway mucus obstruction *in vivo* and the expression of mucin genes (MUC5AC) *in vitro* by activating epidermal growth factor receptors (EGFRs) in BECs [82, 83]. The activation of EGFR also mediates oxidative stress induced-proliferation of BECs [84].

Oxidative stress causes direct injury of BECs. Ozone alters the distribution of β1 integrins in cultured primate BECs resulting in damage of cells and loss of cilia [85]. Exposure of BECs to oxidants increases their permeability and can result in apoptosis or necrosis [86, 87]. These effects may be attributed to DNA strand breaks in airway epithelial cells that induce changes in the expression of epithelial cell-specific genes [88]. These injuries to BECs impair their protective capacity against inhaled oxidants and other insults, enhancing local inflammation and cell death.

Numerous endogenous antioxidants are produced to maintain oxidant/antioxidant homeostasis in the airways. Glutathione (GSH) is a major antioxidant in airway epithelial cells and in epithelial lining fluid, but the concentration of GSH in the latter is much higher than that in the former [89, 90]. Extracellular glutathione peroxidase can be released by BECs and macrophages particularly in response to CS or oxidative stress [91]. GSH and its redox system can inactivate H_2O_2, $O_2\bullet^-$ and reactive nitrogen species [90] and are important for the detoxification of lipid peroxides or other toxic metabolites in lung tissue. Oxidative stress induced by hyperoxia, H_2O_2, menadione or ozone exposure *in vivo* in rats and monkeys, may initially deplete GSH although this is followed by a significant increase in GSH levels. Similar results are seen *in vitro* in human BECs which was associated with the tolerance of cells to further oxidative stress [92, 93]. However, Rusznak et al. [94] demonstrated that exposure to CS leads to a significant decrease in intracellular GSH levels without a rebound increase in levels within primary cultures of human BECs derived from healthy never-smokers, smokers with normal pulmonary function and those with COPD.

Furthermore, Van der Toorn M et al. [95] showed that CS irreversibly modifies GSH, thereby depleting the total available GSH pool in airway epithelial cells. These findings indicated a chronic lack of protection against oxidative stress, providing a mechanism by which BECs contribute to CS-induced oxidative damage found in patients with COPD **(Figure 2).**

Goblet cell hyperplasia and mucous metaplasia results in CB in COPD

Mucus is a liquid bilayer that lines the inner surface of the airways and exists as the first line of defence against various insults. Inhaled particles are trapped in viscous, adhesive liquid gel and removed from the airways by mucociliary clearance [96]. The efficiency of mucociliary transport depends on the viscoelasticity of mucus, which is conferred by mucous glycoproteins or mucins [97]. Mucins are produced and secreted by several cell types and seromucous glands in the submucosa. Among these cell types, goblet cells have the greatest potential for mucus composition [198, 99]. Chronic bronchitis (CB) is one of the two major diseases constituting COPD. CB is caused by excessive luminal mucus resulting from a combination of mucus hypersecretion by goblet cells and decreased mucus elimination. Smokers with CB have increased numbers of goblet cells, which are associated with elevated amounts of intracellular mucin, in which MUC5AC is predominant form, compared with non-smoking controls [100, 101]. The hypersecreted mucus with increased viscosity and decreased antibacterial products aggravates airflow limitation and leads to an increased risk of chest infection [98, 102].

Inflammation, oxidative stress and proteases involved in COPD pathogenesis have been linked to goblet cell hyperplasia accompanied with hypersecretion of mucins. Various inflammatory mediators and signalling pathways regulate the transcription of MUC genes. IL-1β, IL-17A and TNF-α induce mucus production via the activation and nuclear translocation of NF-κB [103, 104]. IL-1β-induced MUC5AC expression also depends on cyclooxygenase (COX)-2-generated PGE_2 and triggering of a cyclic AMP-protein kinase A-dependent pathway through PGE receptors (EPs), specifically EP2 and EP4 receptors [105]. Up-regulation of chloride channels expressed in BECs

increases Cl^- secretion and regulates mucus volume [106]. IL-13 can also induce mucin gene expression in human BEC cultures through the MAPK and phosphatidylinositol 3-kinase pathways [107]. IL-13 also induces disordered mucus cell metaplasia via EGFR activation in COPD [108]. Oxidative stress, both exogenously from CS and endogenously from neutrophils, can activate EGFR and induce mucin synthesis [109]. Furthermore, a recent study reported that human BECs express the arylhydrocarbon receptor (AhR) whose activation causes excess mucin production in a ROS-dependent manner [110]. Furthermore, human neutrophil elastase [111], MMP-9 [112] and MMP-14 [113] also increase mucin production via an EGFR-mediated mechanism.

Failure to clear mucus from the airway surface is another critical event in the pathogenesis of CB. Excess mucin production leads to an imbalance of mucin, salt and water on the airway surface, resulting in mucus stasis and reduced clearance, which may be attributed to two mechanisms. One is the reduced ciliary beat efficiency due to the increased viscosity of the periciliary liquid layer (PCL) which underlies the mucus layer and acts as a lubricant. The other is that the depleted PCL, flattened cilia and adhesion of the thickened mucus to the apical cell surface contribute to the failure of cough-dependent clearance [114].

Disordered repair, regeneration and consequent remodelling of airways actively contribute to airflow limitation in COPD

In addition to mucus accumulation in airway lumen, airflow obstruction is also associated with small airway remodelling in COPD [115]. Thickening of airway wall tissue associated with BEC repair, squamous metaplasia and increased amounts of extracellular matrix (ECM) deposition are characteristic features of airway remodelling in COPD. Acute exposure to inhaled toxic insults, such as CS or microorganisms, induces the loss of epithelial integrity and increased epithelial injury. Under normal conditions this injury is repaired or the epithelium regenerated as exemplified in several animal models by the proliferation and migration of the basal epithelial cells neighbouring the wound over the provisional ECM secreted by

epithelial cells, squamous metaplasia, progressive redifferentiation and finally ciliogenesis and complete regeneration of a pseudostratified secretory or ciliated epithelium [116, 117]. This repair and regeneration “ad integrum” leaves no residual trace of the previous injury. However, any delay or interruption in the epithelial repair and redifferential process caused by interactions with other cells or the presence of inflammatory mediators may disturb the normal repair and regeneration process leading to ECM deposition and airway fibrosis.

Peripheral airway wall fibrosis is more prevalent in COPD compared with asthma and represents an important cause of airway narrowing in COPD [118, 119]. Chronic exposure to CS or environmental pollution induces the loss of epithelial integrity, leading to epithelial abnormalities which can affect airway tissue fibrosis. The loss of epithelial integrity impairs the innate immune functions of the airway epithelium [120, 121] and extensive molecular reprogramming allows mesenchymal transdifferentiation into fibroblasts by a process called epithelial-mesenchymal transition (EMT) [122]. Zhang et al. [123] demonstrated that EMT occurs in human BECs stimulated by TGF-β1. Furthermore, Sohal et al. [124] reported that EMT may be an active process in COPD airways. This process is accompanied with progressive loss of epithelial markers, gain in migratory and invasive potential and elevated ability to produce ECM components [125, 126] which all contribute to airway wall fibrosis and thickening. In addition, BECs can produce and release various inflammatory mediators and growth factors including TGF-β [50] which is the main stimulus causing fibroblasts to produce ECM constituents. MMPs, expressed by migrating epithelial cells, have key functions in the migration of BECs (MMP-9), the shift from an epithelial to a mesenchymal phenotype (MMP-3 and MMP-11) and degradation of ECM components during the tissue remodelling process (MMP-12) [127, 128]. Thus, COPD epithelial cells produce abnormal levels of active MMPs. Dysregulated production and activation of MMPs will result in an imbalance of ECM turnover and induce degradation in lung parenchyma and deposition in bronchi and bronchioles in COPD [128–130].

Conclusions and future directions

CODP is characterised by airflow limitation that is not fully reversible because of remodelling of the small airway compartment and emphysematous destruction of the parenchyma [131]. Several mechanisms have been implicated in the pathogenesis of the disease, including immune dysregulation, exaggerated chronic inflammation and oxidant and antioxidant imbalance in response to inhaled insults. As the first line of defence against noxious insults, the human bronchial epithelium lining the respiratory airways exerts a negative regulatory function in the preventing the onset of COPD. Upon repeated environmental challenge, BECs serve as a switchboard to initiate and orchestrate immune responses through the release of chemokines and cytokines, which recruit and activate inflammatory cells. Epithelial cells damaged by inhaled agents, such as CS, produce a disorganised immune response and heightened inflammatory processes. Exposure of BECs to CS, inhaled airborne pollutants or other oxidants not only generates excess ROS but also impairs antioxidant gene expression in BECs [75, 94, 95] leading to an oxidant/antioxidant imbalance and lung inflammation. In addition, goblet cell hyperplasia, mucus accumulation, squamous epithelial metaplasia, airway wall fibrosis and thickening caused by ECM deposition underlying the epithelium are major characteristics of COPD and can cause small airway obstruction and airflow limitation.

Even after smoking cessation in COPD patients, oxidative stress and pulmonary inflammation persist, which may hamper or prevent tissue repair [35]. Therefore, an effective treatment regime for COPD requires stopping exposure to toxic substrates, such as CS, as well as inhibition of excessive inflammation, oxidative stress and ideally reversal of structural changes within the small airways and parenchyma [132].

Considering the ability of BECs to orchestrate the myriad of downstream responses to cigarette smoke, drugs that modify the ability of activated COPD BECs to modulate these oxidative stress, immune responses and inflammatory processes should be effective in COPD. A consequence of preferentially targeting BECs is that downstream effects on inflammatory cell recruitment and on airway remodelling should also be improved without the need for separate therapies.

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Table 1. Mediators produced by BECs in COPD.

Lipid mediators	PGE_2, LTs B4 and C4, PAF
Reactive oxygen species (and products)	H_2O_2, superoxide anion radicals, hydroxyl radicals, nitric oxide, peroxynitrite, 8-isoprostanes, 3-nitrotyrosine
Cytokines Proinflammatory	IL-1β, TNF-α, IL-6, IL-8, GM-CSF
T-helper	IL-4, IL-9, IL-10, IL-13 (T-helper-2); IFN-γ (T-helper-1)
Chemokines CXC	IL-8 (CXCL8), GRO-α (CXCL1), ENA-78 (CXCL5), IP-10 (CXCL10)
CC	MCP-1 (CCL2), RANTES (CCL5), eotaxin (CCL11)
Growth factors	TGFβ, Endothelin-1, PDGF, VEGF, EGF
Proteases	MMP-1, -2, -7, -9, -12, Cathepsins, Cysteine proteinases

PDGF: Platelet-derived growth factor; VEGF: Vascular endothelial growth factor; EGF: Epidermal growth factor

Figure legends.

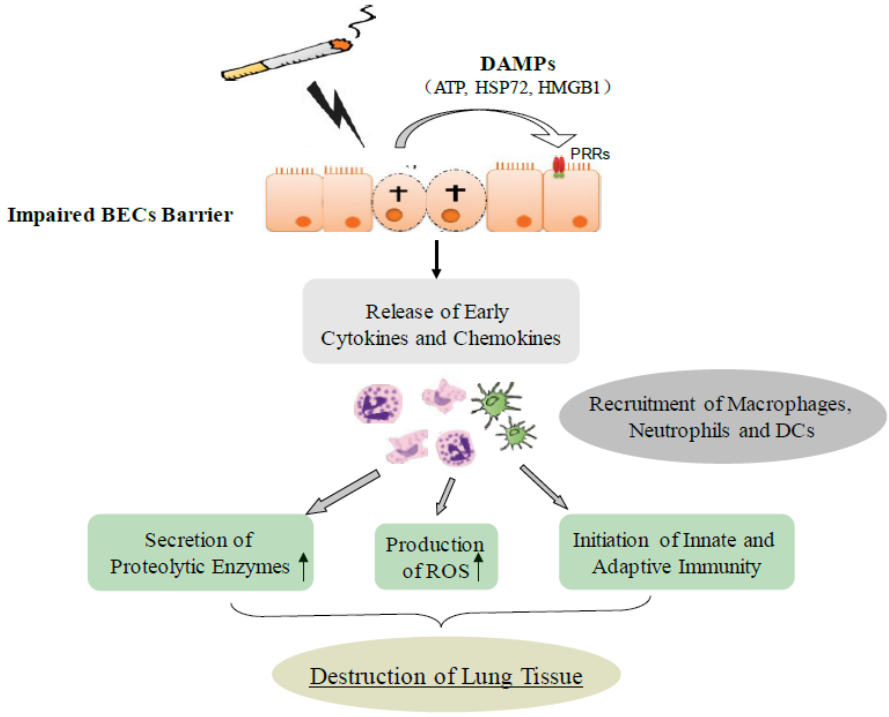

Figure 1

Figure 1. Bronchial epithelial cells (BECs) initiate and control immune and inflammatory responses in COPD pathogenesis

Cigarette smoke activates BECs by triggering pattern recognition receptors (PRR) such as Toll-like receptors (TLRs) either directly by cigarette components or indirectly via the release of damage-associated molecular patterns (DAMPs). On activation, BECs release pro-inflammatory cytokines and chemokines, which recruit infiltrating inflammatory cells including macrophages, neutrophils and dendritic cells (DCs). Activated immune cells, in turn, secrete additional inflammatory mediators, reactive oxygen species (ROS) and proteolytic enzymes (neutrophil elastase [NE] and matrix metalloproteinases [MMPs]). These mediators contribute to the airway remodelling and destruction of lung tissue that is involved in the pathogenesis of COPD. HSP=heat shock protein. HMGB1=high-mobility group box 1

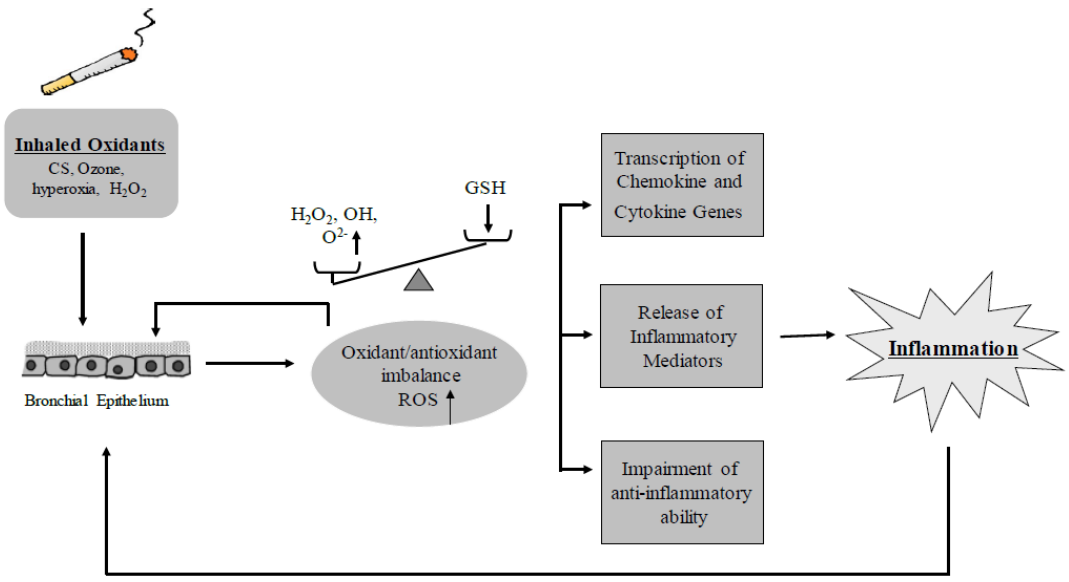

Figure 2

Figure 2. Bronchial epithelial cells (BECs) contribute to oxidative stress-mediated lung inflammation.

BECs are exposed to exogenous oxidants, such as CS, which induces production of ROS and depletion of some antioxidants. Excessive ROS production overwhelms the antioxidant defense mechanisms in the airways resulting in elevated expression of inflammatory mediators. This, in turn, induces an influx of inflammatory cells into the airway and lung. In addition, excess oxidative stress impairs the structural integrity of BECs and the protective capacity of the bronchial epithelium against inhaled oxidants, further enhancing the inflammation.