Airway epithelial cells and mediators of inflammation

There is increasing evidence to suggest that the airway epithelium, which has traditionally been regarded as a physical barrier preventing the entry of inhaled noxious particles into the submucosa, may play a more important role in its capacity as a metabolically active physico-chemical barrier, capable of expressing and/or generating increased amounts of (a) inflammatory eicosanoids, which are potent cell activators and chemo-attractants, (b) pro-inflammatory cytokines which have profound effects on growth, differentiation, migration and activation of inflammatory cells, (c) specific cell adhesion molecules, which play a vital role in inter-tissue trafficking of the inflammatory cells and (d) MHC class II antigens, which play an important role in antigen presentation to and subsequent activation of the T cells.

Studies of animal (1-3) and human (4,5) airway epithelial cells have demonstrated that these are capable of metabolizing arachidonic acid to compounds such as leukotrienes B₄ and C₄ (LTB₄ and LTC₄) and prostaglandins E₂ and F₂α (PGE₂ and PGF₂α), which have potent smooth muscle constrictor and leucocyte chemoattractant effects. Studies of exposure of airway epithelial cells to commonly occurring air pollutants such as ozone (O₃) and nitrogen dioxide (NO₂) and bacterial endotoxin, have further demonstrated that these agents can augment eicosanoid metabolism, with significant increases in PGE₂, PGF₂α, 6-keto-F₁₂, LTB₄, LTC₄ and 12-hydroxyeicosatetraenoic acids (12-HETEs) (3,6,7).

Similarly, studies of airway epithelial cells and cell lines have demonstrated that these are also capable of expressing and synthesizing a large variety of cytokines, including interleukins-1, -3, -6 and -8 (IL-1, -3, -6 and -8), granulocyte macrophage-colony stimulating factor (GM-CSF), granulocyte-colony stimulating factor (G-CSF) and tumour necrosis factor-α (TNF-α) which, either directly or in conjunction with one another, can influence the growth, differentiation, migration and activation of eosinophils, neutrophils, mast cells, macrophages and lymphocytes (8-14). Recent evidence, however, suggests that there may be differences in the ability of epithelial cells of individuals with or without respiratory disease, and likely between cells of atopic and non-atopic subjects, to synthesize different amounts and profiles of cytokines. Studies of cultured nasal (15,16) and bronchial (17,18) epithelial cells, from allergic rhinitis and asthma patients, respectively, have suggested that these are 'activated' to produce larger amounts of cytokines, such as IL-1β and GM-CSF, compared to cells from non-atopic non-allergic subjects.

More recent studies of exposure of airway epithelial cells to non-allergic stimuli have suggested that these may also induce increased synthesis of the inflammatory cytokines. Studies, in our laboratory, of cultured human bronchial epithelial cells exposed to NO₂ (19,20) and Haemophilus influenzae (21), have demonstrated that these agents significantly increase the synthesis of GM-CSF, IL-8 and TNF-α, by these cells in vitro. The possible mechanisms of virus-induced respiratory illnesses have also recently been reviewed, and although it has been postulated that several viral-induced effects, including fever and inflammation, may be occurring through release of pro-inflammatory cytokines, there is no firm evidence to support this hypothesis (22). It is likely, however, that factors which regulate the expression of TNF-α will be of particular significance in airway inflammation, since TNF-α is a multi-functional cytokine having significant influence on epithelial cell permeability (23), expression of IL-8, a major neutrophil chemotactic factor (24), and expression of intercellular adhesion molecule-1 (ICAM-1), a member of the immunoglobulin supergene family (25,26).

ICAM-1 has been shown to act as both the ligand and the counter receptor for leucocyte function antigen-1 (LFA-1) expressed on leucocytes (27), and consequently plays a vital role in the recruitment and migration of inflammatory cells to sites of inflammation in the airways (28,29). Furthermore, studies of nasal and bronchial tissue of patients with nasal polyps, perennial/seasonal allergic rhinitis and asthma, have suggested that the expression of ICAM-1 may be upregulated in the airway epithelium, in vivo (30-33). Other studies have suggested that ICAM-1 is the main surface receptor for the majority of Rhinovirus serotypes (34) and that viruses themselves may up-regulate the expression of this surface protein in human airway epithelial cells, as demonstrated by increased synthesis of ICAM-1, in virus transformed-human tracheal (25) and bronchial (35) epithelial cells.

© 1993 Baillière Tindall
in vitro. More recently, our studies with *Haemophilus influenzae* endotoxin have suggested that this agent may also up-regulate the expression of ICAM-1 in cultured human bronchial epithelial cells, in vitro (36).

Studies investigating the expression of the MHC class II antigens have demonstrated that in accordance with the findings for other cell types, human airway epithelial cells also have the ability to express the HLA-DR antigens and the genes encoding these antigens (37,38). Indeed, comparative studies have demonstrated that epithelial expression of HLA-DR is significantly up-regulated in bronchial and nasal epithelial cells of patients with asthma and nasal polyps, respectively, compared with expression in cells from normal subjects (33,39). The ability of airway epithelial cells to express HLA-DR antigens, however, suggests that these cells may play a potentially important role in antigen processing and/or presentation and possibly be involved in immunoregulation via recognition-, activation- and proliferation- of specific T-lymphocyte types (Th1 or Th2), which are thought to produce specific cytokines (14,40,41). It has been suggested that the Th1-like lymphocytes produce predominantly interleukin-2 (IL-2), IFN, and TNF-α and are involved in delayed-type hypersensitivity reactions and in the synthesis of IgM and some IgG subclasses. The Th2-like lymphocytes synthesize interleukins 3, 4, 5, 6, 8 and 10 and also TNF-α, and are thought to be important in allergic-type inflammatory reactions and defence against parasites.

In conclusion, it is tempting to hypothesize that in airway diseases, activation or dysfunction of epithelial cells themselves, results in attraction, maintenance and activation of the various inflammatory cells in the epithelium (Fig. 1). It is conceivable that in allergic airway disease, allergens presented by epithelial cells trigger the ‘Th2 cell-associated pathway’, to increase the transcriptional expression and synthesis of GM-CSF, IL-3, IL-4 and IL-5, which affect predominantly eosinophil, mast cell and macrophage cell function. On the other hand, non-allergic stimuli such as air pollutants, bacteria (endotoxin) and viruses, directly affect epithelial cells to increase the synthesis of GM-CSF, IL-8 and TNF-α, and in addition promote the ‘Th1 cell-associated pathway’, resulting in decreased synthesis of IL-3, IL-4 and IL-5. The overall effect would be to enhance migration and activation of neutrophils in

![Diagram of airway inflammation mechanisms](image-url)
particular, and to attenuate migration and activation of other inflammatory cell types.

J. L. Devalia and R. J. Davies
Department of Respiratory Medicine
St Bartholomew's Hospital
London EC1A 7BE, U.K.

References


