The epidermal growth factor receptor at the crossroads of airway remodeling

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AIRWAY REMODELING during chronic inflammatory disease processes such as asthma and chronic obstructive pulmonary disease involves a variety of morphological changes, including mucous cell metaplasia and airway fibrosis. Over the past several years, an intense effort has been aimed at elucidating the cellular and molecular mechanisms that contribute to this complexity. Increasing evidence has revealed potentially important roles for the epidermal growth factor receptor (EGFR) in mediating several aspects of airway disease. In particular, the EGFR system has been postulated to play important roles in the growth and differentiation of epithelial and connective tissue cells types in the lung.

It is clear that EGFR and its ligands are elevated during the pathogenesis of asthma, and induction of this system correlates with goblet cell hyperplasia in the airways of asthmatics (1, 16). Therefore, understanding the mechanisms that regulate the EGFR and its ligands in mediating mucous hypersecretion by airway epithelial cells has become an active area of research in attempts to understand airway remodeling in asthma. The role of EGFR and its ligands in orchestrating epithelial growth, repair, and differentiation during airway remodeling is complex and involves 1) the cleavage and release of membrane-bound EGFR ligands [transforming growth factor-α (TGF-α), heparin-binding epidermal growth factor (HB-EGF)] from the cell membrane by a variety of endogenous mediators that activate metalloproteinases, 2) inflammatory cytokines [e.g., tumor necrosis factor (TNF)-α] produced by leukocytes that have the potential to induce EGFR expression, and 3) the ligand-independent activation of EGFR by reactive oxygen species (ROS) generated by leukocytes or by inhaled pollutants.

A seminal paper by Takeyama and coworkers (14) identified the EGFR system as a regulatory axis for mucin production in airways. Before this work, it had been reported that neutrophils mediate goblet cell degranulation, and this was associated with increased elastase activity (13). Moreover, Voynow and coworkers (18) demonstrated that neutrophil elastase increases the mRNA stability of MUC5AC (a major respiratory mucin) and increased production of MUC5AC glycoprotein. More recently, Fischer and Voynow (4) reported that neutrophil elastase induces MUC5AC gene expression in airway epithelium via the generation of ROS. Although neutrophil elastase and ROS generated by neutrophils had been shown to increase mucin production by airway epithelial cells, until now the connection to EGFR signaling had not been established.

The study by Kohri et al., one of the current articles in focus (Ref. 6, see page L531 in this issue), makes an important advance by connecting the concept of neutrophil elastase-induced mucin production to EGFR activation. Using NCI-H292 cells, they show that human neutrophil elastase-induced MUC5AC production was preceded by EGFR tyrosine phosphorylation and was inhibited by selective EGFR kinase inhibitors and by a neutralizing antibody raised against TGF-α. Moreover, they show that neutrophil elastase treatment depleted pro-TGF-α and increased TGF-α in cell culture supernatant. Thus their findings show that neutrophil elastase triggers cleavage of membrane-tethered TGF-α to bind and phosphorylate EGFR in an autocrine manner, resulting in downstream signaling pathways that culminate in the expression of MUC5AC. Although this is potentially an important mechanism for increasing mucin secretion in airways, it should be mentioned that the NCI-H292 cells are a human pulmonary mucoepidermoid carcinoma cell line. It would be important to know whether or not normal human bronchial epithelial cells, maintained in air-liquid interface cultures to promote mucociliary differentiation (5), would respond to neutrophil elastase via the same mechanism as described for NCI-
H292. It is also noteworthy that paracrine signaling involving TGF-α released from other cell types could also be important in driving MUC5AC expression and mucin production by airway epithelial cells. For example, eosinophils are a predominant inflammatory cell in asthma, and activated eosinophils release mature TGF-α (3).

Other cytokines that are upregulated during airway remodeling may also exert their biological effects via the EGFR system. It is increasingly recognized that interleukin-13 (IL-13), a Th2 cytokine, plays a critical role in the pathogenesis of asthma, and recent reports have linked IL-13-induced airway epithelial cell proliferation and mucin production to EGFR activation. Booth et al. (2) reported that IL-13 stimulates the release of TGF-α from the membranes of human bronchial epithelial cells, which then binds to the EGFR and initiates proliferation. Shim et al. (12) demonstrated that intratracheal instillation of IL-13 into the lungs of rats causes goblet cell metaplasia and increases mucin production via a complex mechanism wherein IL-13 induces the production of IL-8, thereby causing neutrophil recruitment. In that study, the authors proposed that TNF-α secreted by recruited neutrophils induces EGFR expression in the airway epithelium. Finally, they proposed that the release of oxygen free radicals by neutrophils contributes to EGFR phosphorylation via a ligand-independent receptor activation mechanism (12, 15).

Although the work by Kohri and colleagues (6) demonstrates a role for TGF-α in neutrophil elastase-mediated mucin production, a novel mechanism for increasing MUC2 expression and mucin production by human airway epithelial cell lines was reported by Lemjabbar and Basbaum (7) that involves cleavage of HB-EGF in response to lipoteichoic acid (LTA), a bacterial cell wall component of the gram-positive bacteria Staphylococcus aureus. LTA was shown to bind the platelet-activating factor receptor (PAFR), and PAFR transduced the signal to EGFR via a metalloproteinase (ADAM10)-dependent proteolysis of transmembrane HB-EGF. This research emphasized clear differences between EGFR-dependent gram-positive bacterial responses and EGFR-independent gram-negative bacterial responses. Lipopolysaccharide (LPS) from gram-negative bacteria has been reported to bind and activate the Toll-like receptor (TLR) 4 via a mechanism that does not involve the EGFR (7). However, signaling by EGFR activation in response to LTA and TLR4 activation driven by LPS converge at the level of Ras to mediate downstream activation of nuclear factor-κB, which then turns on the transcription of MUC2. This work provided an important step for future treatment strategies of antibiotic-resistant strains of S. aureus and suggested that the PAFR-ADAM10-EGFR axis should be targeted to block S. aureus infections.

Inhaled pollutants that cause airway inflammation and remodeling also have the capacity to trigger EGFR phosphorylation through ligand-independent mechanisms. Ligand-independent receptor activation is a mechanism wherein exogenous stressors (e.g., ROS, metals) enter the cells and bypass the extracellular, ligand-binding domain of the EGFR to activate the intracellular domain of the receptor (19, 23). A variety of environmental agents that generate oxidative stress can activate EGFR via ligand-independent activation, and this is most likely achieved through inhibition of phosphatase activity associated with the kinase domain of the EGFR. For example, metals associated with air pollution particulates such as a vanadium are potent EGFR activators in bronchial epithelial cells and pulmonary myofibroblasts (19, 20, 22). Asbestos fibers stimulate apoptosis of pleural mesothelial cells via EGFR activation (21), and cigarette smoke induces mucin synthesis by airway epithelial cells via activation of EGFR (17). Collectively, these studies identify the EGFR as a common target of pollutant-induced oxidative stress.

Fibrosis is another component of airway remodeling that involves activation of the EGFR. In particular, the paracrine signaling between epithelial cells and peribronchiolar myofibroblasts appears to be important in mediating myofibroblast proliferation and subsequent collagen deposition. Zhang et al. (22) showed that human bronchial epithelial cells exposed to metal-induced oxidative stress release HB-EGF, and this EGFR ligand was found to be a major mitogen for human lung myofibroblasts in culture. They also showed that HB-EGF induction by metal-induced oxidative stress is dependent on the phosphorylation of EGFR and downstream mitogen-activated protein kinases, indicating that EGFR activation plays a role in growth factor expression. Animal models of fibrosis also support a role for the EGFR. Rice et al. (11) reported that a tyrphostin inhibitor of EGFR tyrosine kinase reduces metal-induced pulmonary fibrosis in rats. Madtes and coworkers (8) reported that TGF-α null mice are resistant to bleomycin-induced pulmonary fibrosis. Collectively, these studies indicate that both HB-EGF and TGF-α contribute to pulmonary fibrosis by serving as mitogens for myofibroblasts.

In summary, the EGFR system appears to play a central role in mediating airway remodeling during diseases such as asthma and fibrosis. Some of the recent studies summarized in this editorial focus underscore the complex mechanisms wherein the EGFR is a central convergence point or crossroad in cellular signaling that mediates mucous cell hypersecretion by airway epithelial cells and the enhanced growth of epithelial cells and myofibroblasts. It should be noted that, while many studies implicate the EGFR in the pathobiology of airway disease, it is also recognized that the EGFR may play an important role in bronchial epithelial repair in diseases such as asthma (10). New discoveries in other organ systems, such as the discovery that prostaglandin E2 promotes colon cancer growth through EGFR (9), should be investigated as possible mechanisms of EGFR-mediated airway disease. Future research in this exciting area should identify the balance between EGFR activation in mediating airway repair versus aberrant EGFR activation that leads to chronic airway inflammation and remodeling.
REFERENCES


