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Proliferation of the Airway Epithelium in Asthma*

Are Inflammatory Cells Required?

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Abbreviations: EGF = epidermal growth factor; EGFR = epidermal growth factor receptor; IL = interleukin; NHBE = human bronchial epithelial; TGF = transforming growth factor

Asthma is associated with a T helper type 2 phenotype in which interleukin (IL)-4, IL-5, and IL-13 predominate. In addition, the long-term presence of these inflammatory mediators is thought to lead to airway structural changes that are collectively referred to as airway remodeling. Data from our laboratory, and those of others, have suggested a role for IL-13 in the development of mucous cell hyperplasia that is associated with this remodeling. Others have suggested a role for inflammatory cells such as neutrophils in mediating this process. Using normal human bronchial epithelial (NHBE) cells differentiated in vitro, we have shown recently that IL-13 (10 ng/mL for 24 h) induces the proliferation of NHBE cells via a mechanism that is dependent on the IL-13-induced release of transforming growth factor (TGF)-α by the epithelial cells. This epithelium-derived TGF-α then acts in an autocrine/paracrine manner to bind the epidermal growth factor receptor (EGFR) on these NHBE cells, enhancing proliferation. Specifically, soluble TGF-α is

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Histamine Decreases E-Cadherin-Based Adhesion To Increase Permeability of Human Airway Epithelium*

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Abbreviation: TER = transepithelial resistance

During the immediate airway response following aerosol antigen challenge of sensitized guinea pigs, there is an increase in airway epithelial permeability to large molecules.1,2 This increase in epithelial permeability is reproduced by aerosol challenge with histamine.3 We hypothesized that these effects were mediated by alterations in E-cadherin-based epithelial cell adhesion. When histamine (10^{-4} to 10^{-6} mol/L) was applied to the basolateral surface of primary differentiated human airways epithelial cells, it caused an immediate mean (± SD) fall (18.8 ± 6.25%) in transepithelial resistance (TER) that persisted for 3 to 5 min. The H1 receptor antagonist promethazine blocked the change in TER following histamine application. Interestingly, promethazine itself caused a gradual mean increase in TER of 14.9 ± 1.87%.

EVC304 cells are a transformed bladder epithelium cell line that form tight junctions and express N-cadherin but not E-cadherin. Histamine decreased the TER of EVC304 cells that were transfected with and expressed E-cadherin by 30 ± 5%, but histamine did not change the TER of EVC304 cells expressing lac-Z in the same vector. To more precisely localize the effects of histamine to E-cadherin-based adhesion, and to eliminate the potential response of tight junction structures, we examined the adhesion of L cells transfected with the H1 receptor and E-cadherin to a lawn of an E-cadherin-human Fc fusion protein. The extracellular domain of E-cadherin was fused to the Fc domain of human IgG. The fusion molecule bound to protein G-coated plates, orienting the E-cadherin domain away from the surface of the plate. We cloned the human histamine receptor from ECV304 cells and stably transfected L cells (which have no cadherins or claudins) with both the human H1 receptor and E-cadherin. The adhesion of L cells, expressing the histamine receptor and E-cadherin, to the E-cadherin lawn fell by 50% after exposure to histamine. The adhesion of L cells expressing the histamine receptor alone did not change. We conclude that histamine increases airway epithelial cell permeability by decreasing E-cadherin-based epithelial cell adhesion. These changes in permeability may expose subepithelial tissues to agents that alter their proliferation and physiologic state.

References

Is Asthma an Infectious Disease?*

Thomas A. Neff Lecture

Robert F. Lemanske, Jr, MD

Respiratory tract infections caused by viruses, Chlamydia, and Mycoplasma have been implicated in the pathogenesis of asthma. Of these respiratory pathogens, viruses have been demonstrated to be associated with asthma epidemiologically in at least two ways. First, during infancy, certain viruses have been