Growing evidence suggests that changes in airway smooth muscle function play a role in the pathogenesis of asthma. Recently, great attention has been paid to the links between airway inflammation and airway smooth muscle function in order to better understand the development of airway hyperresponsiveness, a defining feature of asthma. Studies, using cultured airway smooth muscle cells or isolated human and animal airway preparations, presently suggest that modulation of G-protein-coupled receptor signaling in airway smooth muscle may represent one potential mechanism by which cytokines regulate the development of bronchial hyperresponsiveness. In this context, it has been suggested that tumor necrosis factor-α (TNF-α) potentially causes airway hyperresponsiveness via engagement of TNFR1, TNFR2, and CD38/cADP ribose pathways.

In the first Highlighted Topics article featured in this issue of the Journal of Applied Physiology, “TNF-α modulates murine tracheal rings responsiveness to G-protein-coupled receptor agonists and KCl,” Chen et al. examined the involvement of structural or functional alterations of airway smooth muscle induced by TNF-α in isolated murine tracheal rings. These investigators found that TNF-α acting via TNFR1 and a PTX-sensitive G-protein-coupled receptor pathway enhanced force generation in response to both cholinergic stimulation and KCl stimulation while impairing the relaxation induced by a β-adrenoceptor agonist. These results support the concept that modulation of airway smooth muscle contractility may play an important role in TNF-α (TNFR1)-induced airway hyperresponsiveness in chronic lung diseases by altering G-protein-coupled receptor responsiveness. Understanding the critical pathways associated with TNF-α and TNFR1 activation in murine tracheal preparations may represent a useful model to investigate the molecular mechanisms leading to airway hyperresponsiveness and may offer new therapeutic approaches to treatment of chronic lung diseases characterized by high levels of TNF-α in the airways.

In the second article featured in this issue, “How does airway inflammation modulate asthmatic airway constriction? An antigen challenge study,” Henderson et al. examined how the extent of airway inflammation may, or may not, dictate the phenotypic expression of asthma in a given patient. Motivating this study were the recent findings of these investigators, which revealed that asthmatic lungs constrict heterogeneously and that asthmatic airways cannot dilate to the same degree as those from normal lungs during a deep inspiration. Indeed, the latter finding implies that airway smooth muscle resides in a distinctly stiff and reactive state in the asthmatic but not the normal lung. The question posed was “How does this apparent smooth muscle defect interact with inflammation to produce the clinical features of asthma?” In nine asthmatic patients, these investigators performed an allergen study to measure mechanical phenotype before and after enhanced airway inflammation. The early-phase response to inhaled allergen reflects the impact of acute release of bronchoconstrictor mediators (e.g., histamine), whereas, during the late phase, mediators from neutrophils and eosinophils are released within the airways, resembling what occurs during an asthma attack. These results show that, after allergen exposure, heterogeneity and reduced capacity to maximally dilate airways are key features of the physiological response, regardless of whether provoked acutely (early phase) or with conditions akin to chronic inflammation (late phase). The implication of these results is that the endogenous constrictor milieu of chronic inflammation may serve to sustain smooth muscle tone and conditions that permit hyperreactivity and the resulting heterogeneity. In particular, heterogeneity motivates concern. Local marked constriction affecting only a small percentage of airways not only can greatly amplify dynamic lung resistance and elastance at typical breathing rates but can cause hypoxemia by altering ventilation-perfusion matching. It can also diminish dilator response to a deep inspiration and can produce refractoriness to inhaled medications by preventing their distribution to the most severely affected regions of the lung. Defining the biological basis for this pronounced and consistent heterogeneity and the diminished airway dilatory response may provide insight into key features of the asthmatic phenotype.

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