Editorial
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The Emerging Role of TRPV1 in Airway Inflammation

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Bronchial asthma is one of the most common chronic inflammatory diseases of the respiratory tract, and is characterized by reversible episodes of wheezing, breathlessness, chest tightness, and cough. These symptoms have been attributed to a dysfunction in airway innervation, precipitated by exposure to relatively innocuous stimuli, such as aerosols and strong odors, or by changes in air temperature. Upon activation of the nervous system in the airway, the release of neuropeptides leads to vasodilation, plasma extravasation, bronchoconstriction, and mucus production.[1] This process has previously been referred to as "neurogenic inflammation," and recent studies have highlighted a role for neuro-immune interactions in asthma pathogenesis.[2]

The transient receptor potential (TRP) proteins, a family of Ca^{2+}-permeable, non-selective cation channels that sense a variety of chemical and physical stimuli, are believed to play an important role in the regulation of airway function in both healthy and disease states. The transient receptor potential vanilloid type 1 (TRPV1) channel is mainly activated by capsaicin; however, it also activated by other physical and chemical stimuli, including low extracellular PH and lipoxygenase products.[3] TRP proteins are expressed in dorsal root ganglia nociceptor neurons, as well as in non-sensory tissues such as the airway epithelium, smooth muscle cells, fibroblasts, and T cells in the upper and lower airways.[4]

Several studies suggest that TRPV1 activation stimulates the release of proinflammatory cytokines from bronchial epithelial cells. TRPV1 mRNA expression was increased in whole-lung homogenates from COPD patients compared with those of healthy nonsmokers.[5] Moreover, TRPV1 was overexpressed in the airway epithelium and submucosa of asthmatic patients compared with healthy controls, suggesting that increased expression of TRPV1 is associated with disease pathophysiology in non-neuronal cell types.[6]

Choi *et al.*[7] investigated the role of TRPV1 in airway inflammation using a murine model of chronic asthma. In their study, treatment with a TRPV1 antagonist or TRPV1 siRNA reduced airway hyperresponsiveness (AHR) and airway inflammation. In addition, levels of both type-2 cytokines (interleukin [IL]-4, IL-5, and IL-13) and epithelial cell-derived cytokines (thymic stromal lymphopoietin, IL-33, and IL-25) were reduced, a novel finding demonstrating the association between TRPV1 and epithelial cell inflammation.

TRPV1 is expressed in neuronal cells as well as structural and immune cells. Using immunocytochemistry, the authors showed that TRPV1 expression was increased in lung tissues, but that this expression was attenuated by treatment with an antagonist. However, the role of TRPV1 in airway tissue inflammation is not well understood, and the possible different effects of TRPV1 antagonists and siRNA on cell types remain to be examined. Kark *et al.*[8] compared neuronal and non-neuronal TRPV1 responses in vascular tissue and showed contrasting results: vascular dilation was observed in response to neuronal TRPV1 activation, but at higher concentrations non-neuronal TRPV1 induced vasoconstriction. Czikora *et al.*[9] showed that systemic capsaicin treatment in rats evoked anatomical and functional disappearance of TRPV1-expressing neuronal cells, but did not affect TRPV1-expressing cells in the arterioles, indicating that the effects of TRPV1 stimulation differ by cell type. Moreover, Devos *et al.*[10] demonstrated that both activation of TRPV1 and transient receptor potential ankyrin 1 and the presence of mast cells were essential to induce AHR in a TRP-knockout, chemically-induced asthma mouse model. Directly comparing TRPV1 func-

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tion among different tissues after antagonist stimulation is difficult; however, determining the similarities and differences between tissue and cell types will expand our understanding of the role of TRPV1 in airway inflammation.

In the chronic asthma model used by Choi *et al.*[7] TRPV1 expressed in neuronal and non-neuronal tissues resulted in the release of cytokines from Th2 and epithelial cells, which subsequently drove airway remodeling. This was significantly alleviated by using a TRPV1 antagonist or siRNA, suggesting that TRPV1 might be a novel target for anti-inflammatory therapy in patients with chronic asthma. However, it remains unknown whether the different functions of TRPV1 depend on the site of TRP expression, and whether the combined effect of TRPV1 expression and its interaction with immune cells is related to asthma pathogenesis.

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