Airway Tone and RGS Proteins: Intracellular Modulators of G-protein Coupled Receptors

Yan Xie¹, Haihong Jiang¹, Hoai Nguyen², Shuping Jia², Abdo Berro², Peter W. Abel¹, Reynolds A. Panettieri³, Thomas B. Casale², Yaping Tu¹

¹ Department of Pharmacology and ² Department of Internal Medicine, Creighton University School of Medicine, Omaha, NE, USA. ³ Pulmonary, Allergy and Critical Care Division, Airways Biology Initiative, University of Pennsylvania, Philadelphia, PA, USA.

Many factors, including airway inflammation and remodeling, contribute to airway hyperresponsiveness (AHR), the pathophysiologic hallmark of asthma, but it is airway smooth muscle (ASM) contraction that is directly responsible for AHR (1,2). Agonists for contractile Gq-protein coupled receptors (GPCRs) expressed on ASM are present or upregulated in the airway during allergic inflammation, and are mediators of bronchoconstriction and AHR (3). Drugs targeting individual GPCRs are used as asthma therapies, but this strategy is limited because airway constriction can be induced by different GPCRs simultaneously, thereby having constrictor signal redundancy. Regulator of G-protein Signaling (RGS) proteins act just downstream from the points of GPCR signaling convergence in cells so one RGS protein can potentially inhibit responses from multiple types of bronchoconstrictor GPCRs acting through the same signaling cascade (4), thus is attracting considerable interest (5-7). We recently found that RGS2, a member of the RGS family that selectively regulates Gq-coupled bronchoconstrictor receptors, was highly expressed in bronchial epithelium and ASM, and was markedly down-regulated in lungs of ovalbumin-sensitized challenged mice. Lung tissues from asthma patients expressed significantly lower RGS2 protein compared to nonasthmatics. Interestingly, both hetero-and homozygous RGS2 knockout (KO) mice exhibit spontaneous AHR, confirming the pathological significance of RGS2 partial repression in asthma. RGS2 was also repressed in primary human asthmatic ASM cells. Among six RGS proteins we tested, RGS2 is the most potent modulator of excessive asthmatic ASM cell contraction and RGS2 knock-down augments Ca²⁺ oscillations, causing enhanced human normal ASM cell contraction. Thus, we speculate that RGS2 is an important gene regulating AHR, and RGS2 repression allows uncontrolled Ca²⁺ oscillations and sensitization in response to bronchoconstrictor GPCRs, which in turn causes sustained ASM contraction, leading to exaggerated airway narrowing and AHR. Although there is heterogeneity in human asthma, targeting RGS2 protein could be a novel strategy for broad-based suppression of excessive airway constriction intrinsic to asthma. American Asthma Foundation (to Y.T.), Nebraska LB595 and 692 (to Y.T. and T.B.C.), NIH R01 HL097796 and P30 ES013508 (to R.A.P.).