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Control of the airway smooth muscle cell cytoskeleton by gelsolin: a potential novel therapeutic target for bronchoconstrictive diseases

Abstract

Anesthesiologists frequently encounter patients with asthma since 9% of the US population has this disease. Perioperative bronchospasm can lead to devastating outcomes, and optimizing asthma therapy pre-operatively reduces the incidence of these events, but up to 40% of severe asthmatics are inadequately controlled on the current recommended regimen of inhaled steroids and long acting beta-agonists. Remarkably, when this chronic therapy fails and exacerbations occur, the recommended acute rescue medication is still beta-agonists. There is a serious unmet need for improved asthma therapies in the perioperative period and chronically. Recently, diverse classes of ligands have been discovered that relax airway smooth muscle (ASM) despite a transient increase in intracellular calcium [Ca2+]i. They are considered attractive novel therapeutics, however, the cellular mechanisms by which these agents induce relaxation is not understood. Gelsolin is a calcium-activated actin severing protein that depolymerizes the actin cytoskeleton leading to ASM relaxation. Thus, activation of gelsolin by [Ca2+]i increases may be the unifying mechanism that would account for ASM relaxation by these diverse ligands. We propose to:

1. Demonstrate that mice genetically lacking gelsolin exhibit impaired ASM relaxation ex vivo and in vivo.
2. Identify the cellular mechanisms of gelsolin-mediated ASM relaxation using measurements of actin polymerization, cell stiffness, [Ca2+]i, and inositol phosphate synthesis. We will further demonstrate that controlling gelsolin's expression and activation is a therapeutic strategy for ASM cell relaxation using lentiviral-mediated overexpression and intracellular introduction of a functional gelsolin peptide.