Differential Regulation of Airway Smooth Muscle Cell Functions by E-prostanoid Receptor Subtypes

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I. INTRODUCTION
Contraction of airway smooth muscle (ASM) induces large mechanical stress in the airways in patients with asthma. Moreover, increased thickness of the ASM layer due to cell proliferation and migration is the major cause of airway remodeling in asthma. Prostaglandin (PG)E2 mediates physiological functions by binding to four different E-prostanoid (EP) receptor subtypes (EP1-4) in target organs. We investigated the role of EP receptors subtypes in the regulation of ASM cell functions mediated by PGE2.

II. METHODS
Proliferation of human ASM cells was by WST-1 assay. Cell migration was assessed by a chemotaxis assay using a modified Boyden chamber. Intracellular Ca\(^{2+}\) concentrations ([Ca\(^{2+}\)]\(_i\)) were measured by fura-2 fluorescence.

III. RESULTS AND DISCUSSION
Human ASM cells expressed mRNAs for EP2, EP3, and EP4 receptors but not EP1 receptor. Cell migration induced by PDGF-BB was inhibited by PGE2, the specific EP2 agonist, the specific EP4 agonist, forskolin, and a β2-adrenergic receptor agonist procatanol. The inhibition of cell migration by PGE2 was significantly reversed by a blockade of EP2 and EP4 receptors using antagonists or transfection with siRNAs. Moreover, PGE2, the EP2 agonist, the EP4 agonist, and forskolin significantly inhibited serum-induced cell proliferation with increases in cytosolic cAMP. In contrast, the EP3 agonist significantly promoted baseline cell migration with elevation of [Ca\(^{2+}\)]. The EP3 agonist did not affect PDGF-BB-induced cell migration or serum-induced cell proliferation. In summary, activation of EP2 and EP4 receptors and subsequent cAMP mobilization are the main mechanisms of inhibition of ASM cell migration and proliferation by PGE2. Conversely, EP3 is potent in promoting cell migration. EP receptor subtypes may be novel therapeutic target molecules in airway remodeling and asthma.

References