Role of GPR40 in Airway Smooth Muscle Function and Bronchconstriction

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Background & Hypothesis: Asthma is characterized by airway hyperresponsiveness (AHR), remodeling and inflammation. Airway smooth muscle (ASM) primarily mediates AHR, therefore remains an attractive target in asthma therapy. G Protein-Coupled Receptor 40 (GPR40) is a deorphanized free fatty acid binding receptor (FFAR) expressed in a variety of cell types. Previous studies reported thet GPR40 ligands increase intra cellular Ca2+ mobilization. We hypothesized that GPR40 enhances contractile signaling in ASM cells. Methods: To determine whether GPR40 activation enhances ASM cell shortening, human ASM (HASM) cells were exposed to selective GPR40 agonist GW9508 or vehicle, acutely for 10 min) or for 24 h and carbachol-induced myosin light chain (MLC) phosphorylation was determined as a surrogate measure of ASM cell shortening. To confirm GPR40 activation by GW9508, Akt phosphorylation was determined in the cell lysates. Results: Acute or prolonged treatment with GW9508 attenuated carbachol-induced MLC phosphorylation in HASM cells. Upon acute exposure, GW9508 induced Akt phosphorylation, suggesting that GW9508 binds to and activates GPR40. Conclusions: Phosphorylation of MLC is a surrogate measure of ASM cell shortening, which leads to bronchoconstriction. Acutely attenuated MLC phosphorylation by GPR40 agonist GW9508 suggests that GPR40 agonists can broncho-protect from contractile agonists. The inhibitory effect of GW9508 on MLC phosphorylation upon 24 h exposure indicate that GPR40 agonists can modulate contractile signaling in HASM cells, potentially through genomic mechanisms. Future Directions: The future studies will focus on a) determining whether GW9508 effect on MLC phosphorylation is mediated selectively through GPR40. GPR40 silencing by siRNA or overexpression with viral vectors will be used in these studies; and b) determining whether GPR40 agonists broncho-protect human airways from carbachol-induced bronchoconstriction. Human Precision-cut lung slices (hPCLS) will be used in these studies. Supported by NIH R25ES020721.