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The Role of a Novel Subunit of Large-Conductance Ca^{2+}-Activated K^+ Channels in Normal and Pathological Airway Smooth Muscle Cells

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Summary

Excess contraction and remodeling of airway smooth muscle (ASM) are associated with airway diseases such as asthma and chronic obstructive pulmonary disease. Bronchodilators (BD) including muscarinic receptor antagonists and β_2 adrenergic receptor agonists are used in the treatment of these diseases. Relaxing ASM using BD is also effective for prevention of sever and chronic airway diseases, because repetitive excess contraction causes irreversible bronchial remodeling. However, pre-existing BD cannot be used for patients in some cases due to side effects. Therefore BD more specific to ASM needs to be developed. Large-conductance Ca^{2+}-activated K^+ (BK) channel is an attractive target for bronchodilator (BD), because BK channel hyperpolarizes membrane potentials and inhibit contraction in bronchial smooth muscle cells (BSMCs). Recently leucine-rich-repeat-containing (LRRC) proteins are identified as novel auxiliary (γ) subunits. However, the roles of BKγ subunits in SMCs are unclear. We found that LRRC26 (BKγ1) is highly and specifically expressed in mouse BSMCs (mBSMCs). Co-immunoprecipitation and single molecule imaging analyses showed direct interaction between BKα and BKγ1 in mBSMCs. Whole-cell patch-clamp analyses revealed that significant BK channel currents were evoked under the conditions where $[Ca^{2+}]_i$ was fixed at 10 nM (pCa8.0) in mBSMCs, but not in mouse aortic SMCs (mASMCs). Mallotoxin, which activates BK channels that do not contain BKγ1, dose-dependently activated BK channel currents in mASMCs, but not in mBSMCs. Knock-down of BKγ1 in mBSMCs significantly reduced BK channel currents at pCa8.0 and recovered sensitivity to Mallotoxin. These results suggest that BKγ1 in mBSMCs increases BK channel activity and inhibits bronchial contraction in physiological conditions by keeping membrane potential negative range. BKγ1 may be a potential target for BSM-specific BD.