Mutational study of receptor-activated cation channels (TRPC6) and a possible linkage to pulmonary hypertension

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Pulmonary vasodilators and its downstream ion channels have been considered in therapeutic targets for either clinical or experimental pulmonary hypertension. Transient Receptor Potential Canonical 6 (TRPC6) channel is non-selective cation channel activated by phosphatidylinositol- 4,5-bisphosphate ($PI(4,5)P_2$) signaling, and is also known to involve in pulmonary hypertension (Weissmann, 2006, PNAS). However, it is largely unknown what is the primary mechanism of TRPC6 leading to the hypertension. Signals from vasodilators and regulatory mechanism on TRPC6 channel could be a key for therapeutic targets. Here, we found out that $PI(4,5)P_2$-association sites on TRPC6 through a kinetics based analysis with voltage-sensing phosphatases (VSP). This study identified several critical residues for $PI(4,5)P_2$ regulation on TRPC6 which were broadly located in TRP box, S4-S5 linker, and the pre-S1 segment. Among in effective segments, pre-S1 segment is the most severely affects for the on-set and off-set kinetics. The receptor-activated current of pre-S1 segment mutants exhibited a reduced slow-activation phase and current amplitude. Moreover, mutation in pre-S1 segment reported in PPHN (persistent pulmonary hypertension of the newborn) is functionally evaluated. Those will be valuable for understanding $PI(4,5)P_2$ regulatory mechanism on TRPC6 channels as well as give a hint for a possible linkage between inositol signaling and pulmonary hypertension.