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New Therapy of Hypertension by the Regulation of Ion Channel Scaffolding

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Summary

【Back ground and objectives】Being the most common disorder in the industrialized societies and an independent risk factor for end-organ damage, hypertension is one of the chief burdens of the healthcare system. The treatment of hypertension based on its pathophysiology can arrest the progression of end-organ damage, and will relieve the burden on the healthcare system. Recent genetic analysis has revealed that the Na^+ reabsorption in the distal convoluted tubules (DCT) participates in the pathogenesis of hypertension. In the previous studies, we identified the components of K^+ recycling pathways, which is indispensable for the Na^+ reabsorption in DCT. A member of the Membrane Associated Guanylate Kinase (MAGUK) family, Membrane Associate Guanylate kinase with Inverted domain structure 1 (MAGI-1a), functions as a scaffolding protein for the basolateral K^+ channels, one of the K^+ recycling pathways in DCT. In this study, we aimed to identify the regulatory mechanism for the interaction of MAGI-1a and the K^+ channels.

【Methods and Results】By raising antibodies that specifically recognize isoforms of MAGI-1a, we clarified different intracellular distribution of two variants of MAGI-1a in DCT: one variant (MAGI-1a-long) on the basolateral side, and the other variant (MAGI-1a-short) on the apical side. MAGI-1a-long colocalized with the basolateral K^+ channels, and its intra-renal interaction with the channels was increased under a sodium-loading condition. The interaction between MAGI-1a-long and the channels was regulated by the phosphorylation of the carboxyl-terminal portion of the channel subunit, Kir4.1. The phosphorylation disrupted the interaction and changed the intracellular distribution of the channels, but did not affect the channel activity at least for short duration.

【Conclusions】MAGI-1a seem to participate in the intracellular distribution of membrane proteins in DCT, and different variants function as scaffolding protein for different part: MAGI-1a-long and MAGI-1a-short for basolateral and apical part, respectively. The phosphorylation-dependent regulation of the K^+ channels' scaffolding by MAGI-1a-long is thought to regulate the long-term but not short-term basolateral K^+ recycling. It is possible that MAGI-1a-short functions as a scaffolding protein for the apical channels and transporters, and the scaffolding is phosphorylation-dependently regulated. The *in vivo* mechanism for the phosphorylation could be a new target for the treatment of hypertension and hyperkalemia.