No. 1737

Blood Pressure Regulation Coupled with Magnesium Reabsorption

Yosuke Funato, Hiroaki Miki

Department of Cellular Regulation, Research Institute for Microbial Diseases, Osaka University

Summary

In this study, we aimed to clarify the relationship between Mg^{2+} exporting protein CNNM2 and blood pressure regulation. For this purpose, we focused on Mg^{2+}-permeable cation channel TRPM6, since microarray analyses revealed that the expression level of TRPM6 was significantly downregulated in CNNM2-knockout kidneys.

First, to confirm the result of microarray analyses, we quantified the TRPM6 expression level in CNNM2 knockout mouse kidneys via qRT-PCR, and confirmed that TRPM6 expression is indeed downregulated. The result was also confirmed by immunoblotting and immunofluorescence studies. To explore the mechanism of this TRPM6 downregulation, we next performed a series of analyses with distal convoluted tubule cell-derived cell line, MDCT. CNNM2 and/or CNNM4 knockdown raised the intracellular Mg^{2+} level, and the expression level of TRPM6 downregulated concomitantly. Also, when we reduced the extracellular (or medium) Mg^{2+} level, the downregulation of TRPM6 by CNNM2/4 knockdown was not observed. These results suggest that TRPM6 expression level is regulated through Mg^{2+} availability.

Furthermore, to clarify the relationship between TRPM6 and blood pressure regulation, we generated TRPM6 knockout mice. As reported, systemic knockout of TRPM6 revealed to be embryonic lethal, and when we generated kidney-specific TRPM6 knockout mice, the blood pressure was downregulated, as CNNM2 knockout mice are. Therefore, these results point out the importance of renal magnesium reabsorption in blood pressure regulation. Further detailed analyses will clarify the molecular mechanism of this blood pressure regulatory machinery.