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Development of Novel TRPM6-Targeted Therapy for Hypomagnesemia

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Summary

Magnesium is an essential cofactor for over 300 enzymes involved in metabolism and energy production. The magnesium balance of whole body is regulated by the kidney which adapts magnesium excretion based on net magnesium absorption from the intestine. Mg^{2+} filtrated by glomeruli is reabsorbed by transcellular and paracellular pathways in renal tubular epithelial cells. Transient receptor potential melastatin 6 (TRPM6) channel is expressed in the apical membrane of distal convoluted tubules and transport Mg^{2+} from the lumen into cells. We recently reported that TRPM6 expression is up-regulated by epidermal growth factor (EGF) in renal epithelial NRK-52E cells. Anti-EGF receptor (EGFR) tyrosine kinase inhibitors (TKIs) such as erlotinib and gefitinib may be predicted to cause a side effect of hypomagnesemia mediated by the decrease in TRPM6 expression. In the present study, we searched for molecule that increases TRPM6 expression in the presence of EGFR TKIs.

Tumor necrosis factor-α (TNF-α) increased TRPM6 expression in the presence of erlotinib. EGF increased the levels of phosphorylated extracellular signal-regulated kinase 1 and 2 (p-ERK1/2), which were inhibited by erlotinib. In contrast, TNF-α did not change p-ERK1/2 levels, but it increased the phosphorylation and nuclear localization of nuclear factor-κB (NF-κB), which were blocked by the NF-κB inhibitors, BAY 11-7082 and pyrrolidinedithiocarbamate ammonium. Similarly, reporter activity of human *TRPM6* gene promoter was increased by TNF-α, which was blocked by NF-κB inhibitors and a mutation of κB-binding site in the promoter. A chromatin immunoprecipitation assay revealed that NF-κB binds to the κB-binding site of *TRPM6* gene promoter after treatment with TNF-α. In the presence of erlotinib, TNF-α increased Mg^{2+} influx, which was blocked by NF-κB inhibitors. These results suggest that TNF-α reverses the reduction in Mg^{2+} reabsorption caused by anti-EGFR TKIs mediated by the activation of NF-κB signaling pathway.