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Effects of Magnesium Channel TRPM7 on Zinc Homeostasis

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Summary

Recent studies on mineral transporters and channels have revealed a number of novel physiological significances for many minerals. They have also shown unexpected phenomena that transporters/channels, which had been thought to be specifically functional for one mineral, can operate to mobilize other minerals and be involved in their metabolism. Elucidating of the molecular basis of these events is important for our better understanding of mineral functions and for applying its information for human health. Thus, we tried to clarify how each mineral transporter or channel can be associated with transporting its second mineral substrate, in addition to its primary substrate, and can be involved in its cellular metabolism in more detail.

Just like calcium ion as a second messenger, zinc ion is released into the cytosol, in which zinc transporters localized to Golgi apparatus play a pivotal role. We found the Golgi-resident ZIP9 and ZIP13 are necessary for sustaining the ERK phosphorylation level in the cells: the ratio of the phosphorylation ERK to total ERK was significantly decreased in chicken DT40 deficient in ZIP9 and ZIP13 (*ZIP9*$^{-/-}$*ZIP13*$^{-/-}$ cells) compared with wild type DT40 cells. To evaluate magnesium channel TRPM6 on the regulation of this zinc signaling function, we overexpressed TRPM6 in *ZIP9*$^{-/-}$*ZIP13*$^{-/-}$ cells and examined its contribution. However, we found no restoration of the reduced ERK phosphorylation ratio by TRPM6 expression. Moreover, we added magnesium in the culture medium of *ZIP9*$^{-/-}$*ZIP13*$^{-/-}$ cells stably expressing TRPM6 and examined its effects, but addition of magnesium caused no significant effects on the reduced ERK signaling. We have not yet found directs evidences that TRPM6 plays a role in zinc signaling originated from the Golgi-resident ZIP9 and ZIP13.

Furthermore, we evaluated the molecular mechanism how mineral transporter determine its substrate metal. We found ZnT10 plays a role manganese specific transporter, while ZnT1 plays a zinc specific transporter. A domain swapping and substitution analysis between hZnT10 and hZnT1 showed that residue N43 of hZnT10, which corresponds to H43 in the intramembranous zinc coordination site of hZnT1, is necessary to impart hZnT10's unique manganese mobilization activity. Interestingly, the H->N reversion mutant in hZnT1 conferred manganese transport activity and loss of zinc transport activity. These results provide important information about metal substrate discrimination mechanis in mineral transporter/channels and crosstalk among minerals.