Molecular physiological exploration beyond the transcriptome. Focus on “Molecular mechanisms underlying active desalination and low water permeability in the esophagus of eels acclimated to seawater”

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Overcoming the imbalance in body fluid water is one of the most critical issues in a euryhaline fish upon seawater (SW) challenge. Euryhaline teleosts have to drink SW and absorb water in the digestive tract and simultaneously secrete excess salt in the gills in order to maintain body fluid ionic and osmotic homeostasis during acclimation to a SW environment (5, 8, 11). After SW is ingested, the first step is desalination (absorbing NaCl with minimal water transport) in the esophagus, and the resultant osmotic fluid is moved toward the intestine for water absorption following active NaCl uptake (6, 9, 12). As such, desalination in the esophagus is the first critical process in adaptation of euryhaline teleosts to salinity. This important process, as a traditional issue in fish physiology, had been investigated, and the basic outline was described earlier (6, 9, 12); however, the exact molecular mechanism of esophageal desalination has not been as well characterized as that of intestinal salt uptake/water absorption (5). In Takei’s elegant and comprehensive study (14), they first characterized the basic transport function of NaCl in eels acclimated to fresh water (FW, control) and SW by using an esophageal sac preparation and demonstrated that the Na⁺-Cl⁻-coupled desalination is enhanced over 10-fold after SW acclimation. Further pharmacological experiments with various transporter inhibitors showed possible involvement of several transporters, including the Na⁺-Cl⁻-cotransporter (NCC), Na⁺/H⁺ exchanger (NHE), anion exchanger (AE), Na⁺-K⁺-ATPase (NKA), and chloride channel (CLC), in this NaCl uptake mechanism. To identify the exact transporters (and the specific isoforms), Takei et al. (14) took advantage of RNA sequencing to compare esophageal transcriptomes between of FW- and SW-acclimated eels and narrowed the candidate genes on the basis of criteria, such as the targets of transporter blockers, substantial expression of transporters, and/or SW-affected transporters. The selected genes were further analyzed by quantitative PCR and in situ hybridization, and the results reinforced those of the physiological and pharmacological experiments. Integrating all of these data, therefore, Takei et al. (14) proposed a model of desalination by absorbing NaCl accompanied with reduced water permeability in the SW eel esophagus. Apical NHE3, SLC26A3 and SLC26A6, NCC, basolateral NKA1 and NKA3α, CLCN2, and Na⁺-HCO₃⁻-cotransporter are responsible for NaCl uptake, while downregulated aquaporin (AQP1α and AQP3) and upregulated claudin (CLDN15A) suppress water transport.

Further studies are necessary to see whether the proposed model of desalination in the eel esophagus is applicable to...
other species. The esophagus and intestine collaborate in tandem to achieve the mechanism of NaCl uptake and water absorption in teleosts in a manner that maintains body fluid ionic and osmotic homeostasis. Interestingly, the esophagus and intestine adopt NCC and NKCC/NCC, respectively, for NaCl uptake, and this subtle difference reflects the distinct patterns of Na\(^+\) and Cl\(^-\) transport in the two regions of the digestive tract. That is, the esophagus transports equal amounts of the two ions, while the intestine transports much more Cl\(^-\) than Na\(^+\) (5). Other differences, like acid and base transport among the two organs, are also important components in terms of body fluid homeostasis during acclimation to salinity. In the intestine, there is a substantial base loss for the formation of CaCO\(_3\), and this is mainly achieved by apical SLC26A6 and membrane and cytosolic carbonate anhydrases (5). It is still unclear whether a net secretion of acid or base occurs in the esophagus, where apical NHE3 and SLC26A3 and SLC26A6 are supplied with H\(^+\) and HCO\(_3\)\(^-\), respectively, by cytosolic CA2a, according to Takei’s model. This remains to be clarified in the future.

The findings of Takei et al. (14) are important because they depict a comprehensive and clear picture of the mechanism mediating esophageal desalination, which enables us to further study the transport functions and their regulations by precisely targeting the specific ions or water and the specific transporters or enzymes. Their discovery also provides important materials to compare with the transport mechanisms in mammalian renal or enzymes. Their discovery also provides important materials to study the transport functions and their regulations by precisely mediating esophageal desalination, which enables us to further depict a comprehensive and clear picture of the mechanism in the future.

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REFERENCES

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AUTHOR CONTRIBUTIONS
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