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Elucidation of Novel Regulatory Mechanisms of Intestinal Na Metabolism by a Tricellular Tight Junction Protein

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Summary

The intestinal epithelium needs selective absorption mechanisms to take up nutrients from the luminal environment, technically a space outside the body, as well as a barrier function to prevent the entry of noxious luminal contents. The barrier function of the epithelia is responsible for tight junctions, and claudins connect two cell membranes like zippers and close the intercellular space. However, at the tricellular junctions, where three cells are in contact, a special tricellular tight junction mechanism is required. Recently, Angulin-1 has been identified as a protein that localizes only to tricellular tight junctions. Knockdown of Angulin-1 in epithelial cell lines resulted in reduction of transepithelial electrical resistance, suggesting that Angulin-1 is involved in epithelial barrier function. Since mice lacking Angulin-1 exhibits an embryonic lethal phenotype, the physiological function of Angulin-1 in the intestine has not been studied. We therefore aimed to elucidate the role of Angulin-1 in the small intestine using intestine-specific Angulin-1 deficient (Ang-1 cKO) mice. Transepithelial ion and mannitol permeability in the small intestine were measured using the Ussing chamber method. Unexpectedly, transepithelial mannitol and Na^+ fluxes were decreased in Ang-1 cKO mice. In addition, a decrease in Na^+ selectivity in the tight junctions was observed. Furthermore, Na^+-dependent nutrient absorption activity was decreased in Ang-1 cKO mice. These results suggest that Angulin-1 which is expressed at the tricellular junctions may indirectly regulate the Na^+ permeability of the bicellular tight junctions and transcellular Na^+-dependent nutrient transport.