

Regulation of Function and Expression of Organic Cation/Carnitine Transporter OCTN Family by PDZ Adaptor Proteins

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Urinary excretion of cationic xenobiotics is thought to be mediated by organic cation transporter (OCT and OCTN) families expressed on both basolateral and brush-border membranes of proximal renal tubules. The OCTN family members (OCTN1 and OCTN2) are also involved in reabsorption of carnitine from the tubular duct space in kidney. To obtain such vectorial transport of xenobiotics and nutrients, OCT/OCTN family members should be appropriately targeted to either basolateral or apical plasma membranes, although the molecular mechanisms for targeting of these transporters to each membrane are poorly understood. As a first step to clarify the regulatory mechanisms governing cell-surface expression and/or function of these transporters, we have recently performed protein-protein interaction analysis and found specific interaction of cytosolic domains of apically expressed solute carrier (SLC) superfamily transporters including OCTNs with PDZ (PSD-95/Discs-large/ZO-1) domain-containing proteins, suggesting possible roles of PDZ proteins as regulatory mechanisms for the apical transporters. The PDZ proteins can alter transport function and/or cell-surface expression of OCTNs, thereby affecting membrane transport of their substrates at least in vitro. Especially, PDZK1, which has four PDZ domains in its structure, is colocalized with OCTN2 on apical membranes of epithelial cells in kidney and small intestine, and stimulates transport capacity for carnitine by OCTN2 with minimal change in its cell-surface expression, suggesting that PDZK1 could be involved in the regulation of reabsorption of carnitine via OCTN2 in kidney. Considering the multiple interactions between PDZ domains and various xenobiotic transporters, PDZ proteins have the potential to influence membrane transport of many substrates, possibly affecting disposition of these substrates in the body.