A systems biology approach to understanding the role of peptide transporters in biology

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Cell membrane transporters for di- and tripeptides are found in bacteria, yeast, plants, invertebrates and vertebrates including mammals. They mediate the cellular uptake of essentially all possible di- and tripeptides and numerous pharmacologically active peptidomimetics by a proton-dependent electrogenic symport mechanism.

In mammals, the two di-tripeptide transporters that have been characterized in detail are PEPT1 and PEPT2. PEPT1 mediates as a low affinity but high capacity system the influx of peptides from dietary protein digestion in the gut into intestinal epithelial cells whereas PEPT2 as the high affinity subtype transporter is found in a variety of epithelial cells (i.e. lung, mammary gland, choroid plexus) and prominent expression in renal cells with a role in the reabsorption of filtered peptides. For understanding the biological importance of peptide transporters we follow two lines of research; a gene guided approach by comparing the structure and functions of the same proteins in various organisms (*E. coli, C. elegans*, zebrafish, mice, rabbit, humans) and a technology-driven approach by applying transcriptomics, proteomics and metabolomics for phenotype analysis in animals (*C. elegans* and mice) lacking either one of the peptide transporters.

The cloning and functional characterization of *E. coli* peptide transporters with only a low sequence homology (YGDR) but high functional similarity to mammalian PEPT1 provides new insights into structure-function relationship. Carriers from the various species when studied by electrophysiology after expression in *Xenopus* oocytes show very similar features despite marked sequence differences. Gene deletions followed by analysis of phenotypical consequences have been carried out in *C. elegans* and mice. In the nematode, a deletion of the PEPT1 homologous gene provides clues for the role of the intestinal peptide transporter in delivery of bulk qualities of amino acids for growth and development and for a critical crosstalk with the insulin/IGF receptor pathway. There is also a significant effect on stress-resistance of the animals when lacking PEPT1 (Meissner *et al.*, 2004).

A mouse line lacking a functional PEPT2 protein did not show any obvious phenotypical changes despite impaired transport of model peptides in kidney and choroids plexus (Rubio-Aliaga *et al.*, 2003). However, when kidney tissue samples of KO and WT mice were submitted to gene expression analysis by cDNA microarray, proteome analysis by 2D-SDS-PAGE and peptide mass fingerprinting *via* MALDI-TOF-MS and metabolite fingerprinting *via* GC-MS a variety of metabolic alterations were identified. Pathways of amino acid handling showed impairments and also pathways that process keto acids and carbohydrates. Metabolism of cysteine and moreover of cysteinyl-glycine (Cys-Gly), the break-down product of GSH by γ-GT was identified as altered as well. Analysis of urine samples suggests that PEPT2 in renal cells is primarily responsible for uptake of Cys-Gly from the tubular fluids.

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