

Structure-function studies on PepT1, a multimeric transport protein with broad substrate specificity

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The majority of uptake of protein from the diet is widely accepted to be via the proton-coupled di- and tri-peptide transporter PepT1, cloned by Fei et al. in 1994 (1). PepT1 has a wide range of substrates, including di- and tri-peptides and a range of therapeutically important compounds including β -lactam antibiotics and angiotensin converting enzyme (ACE) inhibitors.

One of the challenges in the absence of a crystal structure is to understand how one protein can transport so many substrates with such diverse chemical structures. To address this, a number of approaches have been taken to identify the substrate binding site and the residues which form it, either from the view of the substrate or the transporter. First is the creation of a substrate template, onto which potential substrates can be overlaid and their binding affinity predicted (eg 2). Secondly, site-directed mutagenesis (SDM) has allowed the identification of a number of amino acid residues that are involved in PepT1 operation, including in substrate binding and mode of transport. A third approach, used in combination with SDM, has been compu-

ter modelling. To date this has largely been limited to predicting the arrangement of the twelve transmembrane domains in the membrane (eg 3), and has sought to identify the binding site and/or the 'pore' through which the substrate moves. Finally, evidence suggests PepT1 is a multimeric protein in the membrane, and the implications of this will be considered.

References

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