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Thematic Issue

Amino Acid Transporters: Structure and Mechanism

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Foreword

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As with other areas of transport biology the study of amino acid transport in eukaryotes was revolutionized by the arrival (Kim et al., 1991; Wang et al. 1991) of molecular sequences of proteins that catalyze membrane transport of such solutes. And more recently the field has been reinvigorated by the appearance in the literature of three-dimensional structures, at the atomic level, for prokaryote members of a few of these transporters (e.g., Yernool et al., 2004; Yamashita et al., 2005; Boudker et al., 2007), albeit at this stage of transport proteins 'locked' in but a single conformation. These have been major exciting developments.

In this thematic issue we have asked the contributors to consider a topic that is directly related to these molecular developments, but which is also in danger of being side-lined, namely, how these recent developments shed light on the mechanism of transport. Specifically, topics covered here review: the secondary transport of amino acids in prokaryotypes, as an excellent example of the breadth of biology embraced by recent studies (Jung, Pirch & Hilger, 2006); the neurotransmitter serotonin transporter SERT, a member of the SLC6 family (Rudnick, 2006), with focus on the permeation pathway; the neurotransmitter transporter for glutamate, a member of the SLC1 family, with specific emphasis on comparative structure-function relationships revealed from structural work as well as, similarly, studies on another SLC6 family member, the GABA transporter (GAT-1) (Kanner, 2006); the SLC6 family members that encode the B^0 neutral amino acid transporters (O'Mara, Oakley and Broeer, 2006) and the impact on these studies of structural work; a transporter modelling approach for studies on the SLC15 family PepT1 transporter (Meredith & Price, 2006) that uses published structures of other bacterial transporters to model a mammalian transporter for alpha-amino nitrogen, important both for nutrition and for drug delivery; and a review of the cationic amino acid transporters, SLC7 family members, including very recent work on the mechanism of regulation (Closs et al., 2006).

Key words: Mechanism — Structure — Structure/function — Amino acid — Transporter — Peptide — Plants — Animals

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Amino acid transporters have an extraordinarily wide range of functions, being involved in processes as different as cellular nutrition in plants and synaptic physiology in the central nervous system. Not surprisingly, such transporters can be grouped in families that present differences in their substrate specificities, substrate affinities and the coupling to different energy sources (Hediger et al., 2004). In addition, evolution appears to have sculpted selection of a wide range of closely related amino acid transport proteins within individual transporter families that show subtle, but relevant, variations in their functional features.

In spite of all this knowledge, a major question remains unanswered, namely, how is function related to structure? An important theoretical underpinning of the transport field has come from analysis of the kinetics of the transport process, that is of the exploration of the mechanism, both regarding the way the substrate and the transporter interact to produce a complex, and the mechanism involved in the process of translocation of the substrate through the membrane. Predictions from models (such the 'simple' carrier model) of transport have proved exceptionally important, for example in explaining the different capacities of transporters to produce net transport or to act as exchangers, the mechanism of action of inhibitors, the binding asymmetries of substrates, the sidedness of inhibitor action and the coupling between different electrochemical gradients. However, to date there has been little systematic attempt to relate the kinetic approach (the fruit of over 50 years of analysis, e.g., Widdas, 1952) to the more recent structural work. The contributions that are found in this issue have been selected for their contribution to this process.

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