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EDITORIAL

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A multi-faceted world of transporters

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This issue of *Naunyn-Schmiedeberg's Archives of Pharmacology* contains seven reviews on transporters of endo- and xenobiotics, with the objective of providing the reader with short surveys covering such topics as the structures, physiological functions and biological importance of these transporters. The reviews are based upon a selection of presentations given at the *5th Transport Colloquium at Castle Rauischholzhausen*, which took place in May 2005 nearby Marburg, Germany. Each review covers a specific transport system, such as the ABC-transporters in bacteria (Oswald et al. 2006), sodium-coupled transporters in bacteria and in tissues with hormonal activities, respectively (Alexeej and Müller 2006; Geyer et al. 2006), organic anion transporters in the liver, kidney, intestine, and brain (König et al. 2006) and peptide transporters associated with putative roles in antigen processing in dendritic cells (Zhao et al. 2006). One review deals with solid-state NMR techniques targeting the identification of dynamic transporter structures during the transport cycles (Blasting et al. 2006), and another review describes how drug transporters are embedded in the pharmacokinetic process of drug elimination by the liver (Petzinger and Geyer 2006).

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Carrier protein structures may be understood by applying physico-chemical approaches, which will lead to a better knowledge of ligand binding pockets and their handling of the ligands during a transport cycle. Blasting et al. (2006) describe one of these approaches for small multidrug resistance proteins of bacterial origin. They also depict the requirements for long-range structure analysis based on the labelling of disulfide-linked cysteines of the carrier protein by 19F-trifluoroacetone. The 19F–19F dipolar couplings are a useful strategy for obtaining long-range information at a suitable sensitivity. Alexeej and Müller (2006) discuss a second approach using single-molecule imaging and time-lapsed force spectroscopy to observe the folding pathway and folding kinetics of native, membrane-embedded Na^+/H^+ antiporters from *Escherichia coli*. The interaction of sodium ions being triggered by – or triggering – the dynamic protein folding can be followed by this technique at high-time resolution. A third method is presented by Oswald et al. (2006) and combines information obtained from crystal structures of haemolysin B from *gram*-negative bacteria with the translocation of haemolysin A, a pore-forming bacterial toxin, through the bacterial inner and outer membrane. The motor domain of haemolysin B, which is an ABC-transporter, generates the energy for this process. Using a mutational approach, the authors describe how the chemical energy of ATP-binding and its hydrolysis is linked to certain essential amino acids and how these residues contribute to the conformational plasticity during haemolyxin A translocation.

A biological treatise is to identify natural mutations (carrier polymorphisms) in hot-spot regions and to relate them to ligand recognition and functional pharmacokinetics. König et al. (2006) describe the functional consequences of single nucleotide polymorphisms in the genes of members of the OATP (organic anion transporting polypeptide) family on the uptake of drugs across the membrane of polarized cells from various organs. Such polymorphisms have an impact on the elimination kinetics, extraction ratios and residence times of drugs in man, resulting in marked changes of systemic exposure. Drug-transport and

its implications for the field of pharmacokinetics is discussed by Petzinger and Geyer (2006). A so-called extended phase concept is presented which combines biotransformation pathways of phase 1 and phase 2 metabolism with carrier-mediated drug uptake (phase 0), intracellular traffic of drugs (phase 3), and carrier-mediated drug excretion (phase 4) on the liver. The representative carriers enabling such vectorial transport under normal and diseased conditions are indicated.

Geyer et al. (2006) report on new carriers of the SLC10-family, formerly believed to comprise only the liver and intestinal sodium-dependent bile acid-transporters. They identified four new members with no bile acid-transporting activity and relate them phylogenetically to new SLC10-family subgroups on the basis of their genomic and protein structures. One member is a sodium-dependent steroid sulfate transporter whose functional importance for intracrine oestrogen supply is discussed.

The function of ABCB9 (TAPLike), a newly identified ABC-transporter, is reported by Zhao et al. (2006). By means of heterologous expression, TAPLike was identified as a peptide transporter with a broad peptide specificity, ranging from 6-mer up to 59-mer peptides. This transporter is localized in lysosomes and forms a homodimer. TAPLike is not involved in classical major histocompatibility complex (MHC) I-mediated antigen processing. However, TAPLike expression is strongly induced during the maturation of dendritic cells. Based on these observations, the authors discuss the involvement of TAPLike in the cross-presentation of endogenous antigens.

We hope that this collection of papers on transporters will stimulate further discovery in the area, thus contributing to even more fruitful discussions at the next Transporter Colloquium to be held in May 2007.

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