THE ABC TRANSPORTERS OF HUMAN PHYSIOLOGY AND DISEASE

Genetics and Biochemistry of ATP Binding Cassette Transporters

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THE ABC TRANSPORTERS OF HUMAN PHYSIOLOGY AND DISEASE

Genetics and Biochemistry of ATP Binding Cassette Transporters

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The front cover shows a cartoon based on the crystal structure of a related drug efflux ABC transporter (Sav1866) from *Staphylococcus aureus*. The relevance of this structure for our understanding of how human ABC transporters work is described in Chapter 1. The back cover shows an unrooted phylogenetic tree of the human ABC transporter family.

All 48 full length proteins were aligned in Clustal W and phylogenetic analysis was performed in Seaview.

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Preface

ATP binding cassette (ABC) proteins are versatile machines that convert chemical energy from the hydrolysis of ATP into mechanical energy. These domains can be used to drive diverse cellular processes such as chromatin organization, DNA repair and mRNA trafficking, but the vast majority power the flow of solutes across cellular membranes.

ATP binding cassette transport proteins are integral membrane proteins that catabolize ATP to drive the uptake (prokaryota only) or efflux (prokaryota and eukaryota) of solutes across membranes. Their ubiquity and abundance (many different forms are found in all species) is indicative of their importance to the maintenance of a healthy cell, organ and organism with an impact both directly and indirectly on human health. Chloroquine resistance in *Plasmodium* sp., antibiotic efflux from bacterial producers and some pathogenic bacteria, and fungal-pathogen resistance in wheat, remind us that you do not have to stray far from a human centric view of the biosphere to see the influence of this superfamily of transporters.

This volume focuses specifically on the direct influence imparted by the complement of more than 40 ABC transporters encoded by the human genome. Increasingly, studies from laboratory bench to clinical care reveal that human ABC transporters are crucial to both normal physiology and pathology. These include important roles, for example, in haem, lipid and fatty acid metabolism, bile flow, drug disposition and ion flux, which encompass nearly every organ, tissue and cell type in the body.

Their malfunction or dysregulation is linked to more than 30 diseases and conditions, and it seems likely that more will be discovered as disease aetiologies, or the precise function of some of the transporters, are clarified.

This is a particularly exciting time for those in the ABC transporter research field. The recent FEBS special meeting on ABC transporters in Innsbruck in 2010 attracted 300 delegates committed to the analysis of the structure, biochemistry and genetics of diverse ABC transporters from many species. The field is certainly broad but the seemingly highly conserved fundamentals of ABC transporter mode of action ensures that those of us who work in the realm of biomedical sciences can learn from the advances in distant disciplines; from the structure and function of bacterial transporters, to the role of plant transporters in lipid or wax metabolism. Although we now have a reasonable idea of the general principles driving the action of these transporters, we still lack details of crucial aspects of the mechanism, including the nature of endogenous allocrites (the transported “substrates”), how these proteins fold and how the expression of individual ABC transporter genes are regulated. With greater understanding of the basic science and knowledge of disease aetiology, this will afford the development of diagnostic and prognostic tools, and consequently more informed clinical intervention. Concerning the latter, several recent examples herald much promise: gene therapy for the neurodegenerative disease, X-linked adrenoleukodystrophy; the development and use of small molecules to switch on the chaperones needed to facilitate maturation and function of folding mutants of the cystic fibrosis transmembrane regulator. One of the most difficult challenges remains the design of specific drugs for clinical use that can successfully modulate the action of the multidrug efflux ABC transporters, without serious side effects. More distant objectives include drug therapy developed on personalized lines, and the targeting of new drugs to circumvent the action of the resident ABC transporters. This will allow penetration of specific barriers to treat, for example, brain tumors, epilepsy or psychotic

disease. If such aims are to be achieved, this is certainly not the time to restrict research activity in this field. On the contrary we would very much encourage young scientists to apply their skills to the study of these fascinating proteins not least in the clinical environment.

Kenneth Linton
Barry Holland