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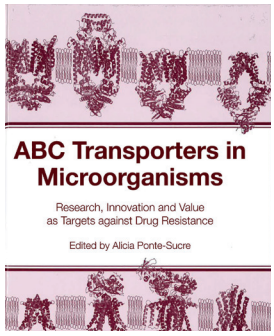

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"It is almost 25 years since the ATP-binding cassette (ABC) protein superfamily was identified ... This volume collectively reviews our knowledge of the ABC proteins found in microbes."

In total, 25 authors from a range of internationally reputable centers contributed to this comprehensive volume, which has been very capably edited by Alicia Ponte-Sucre from the Universidad Central de Venezuela (Caracas, Venezuela).

It is almost 25 years since the ATP-binding cassette (ABC) protein superfamily was identified, and in the intervening years there have been many significant advances in our understanding and appreciation of their role and impact. This volume collectively reviews our knowledge of the ABC proteins found in microbes. Broadly, the book is divided into three sections; the first covers the structure, function and evolution of the transporters. The second set of chapters discuss the role of ABC proteins in the physiology of microorganisms and the final set of chapters discuss the potential role of these proteins in the ongoing battle against antimicrobial resistance, which is burgeoning in many species of organisms.

Jumpertz *et al.* discuss one of the largest membrane protein families, ABC transporters. These transporters use energy from ATP to transport a large variety of substances across biological membranes. They are comprised of two nucleotide-binding domains (NBDs) and two transmembrane domains (TMDs), which can be arranged in a multitude of ways. Extended NBDs and TMDs interact with other proteins with functional or regulatory sequences. ABC proteins are classified into three classes: 1, 2 and 3. In class 1, the transmembrane components and ABC domains are fused by single polypeptide chains. Class 2 is made up of ABC proteins that lack intergral membrane component. Class 3 recognizes ABC transport systems where the ABC and membrane components are encoded on separate polypeptide chains and where essential additional components are inserted. These proteins are used to mediate the import of nutrients and export of toxins across membranes.

The major ABC transporter families are P-glycoprotein and cystic fibrosis transmembrane conductance regulator (CFTR). P-glycoprotein was first identified in drug-resistant cells that were showing resistance during cancer therapy. They are expressed in epithelial cells lining the colon and kidney proximal tubules, and protect cells from toxic compounds. Following recent descriptions of crystal structures of NBDs, we now have an improved understanding of the 3D structure of these proteins and their recognition of specific substrates.

ABC systems are significant to prokaryotic cellular physiology, facilitation of nutrient importing and toxin exportation, and DNA repair; these systems are described by Sauna and Ambudkar. They function primarily as efflux pumps and offer protection from xenobiotics, antigen presentation, and cholesterol and lipid transport in eukaryotes. ABC transporters extrude many chemically diverse compounds, as well as hindering treatment of microbial infections and human cancers, and are associated with multidrug resistance. In prokaryotes, there are 29 families of ABC proteins, which are part of three main classes, classified according to their function. There are importers, exporters and 'others'. However, in vertebrates, ABC proteins are not organized based on their function. This section covers the evolution and structure–function relationship of mammalian and microbial ABC transporters and their impact

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on multidrug resistance, as well as the current status of substrate specificity and mechanisms of mammalian ABC drug transporters.

Gutmann and van Ween review the evidence that ABC transporters are the basis of many inherited disorders and are linked to multidrug resistance in cancer cells and pathogenic microorganisms. ABC transporters are classified into four-domain 'core' organizations. ABC transporters are importers or exporters; importers use an accessory substrate-binding protein. Multidrug resistance of pathogenic bacteria and tumors can be related to increased expression of ABC transporters, which actively export multiple drugs from the interior of the cell. Mutations in ABC transporters cause many hereditary diseases, such as adrenoleukodystrophy, cystic fibrosis and intrahepatic cholestasis.

> "...ATP-binding cassette proteins play a major role in emerging resistance to anti-infective drugs; however, our improved understanding of these mechanisms may enable us to develop alternative approaches to treating currently problematic organisms."

Dorrian and Kerr discuss the role of ABC proteins and their ability to confer resistance without being export pumps. The inhibition of bacterial protein translation is important in antimicrobial intervention therapy; they inhibit protein synthesis by binding to the 50S ribosomal subunit. Resistance to these types of antibiotics is mediated by multiple mechanisms, one of which involves an unusual class of ABC proteins. These ABC proteins are called antibiotic-resistant element (ARE)-type proteins and they do not include membrane-spanning segments within the polypeptide. Furthermore, they are not linked in operons to membrane-spanning regions. ARE proteins produce antibiotic-resistant isolates.

Multidrug transporters actively catalyze the extrusion of a wide range of structurally and functionally unrelated drugs from the cell and as such are major contributors to multidrug resistance in bacterial cells. In this chapter, Bakkes *et al.* describe the recent advances in ABC types involved in bacterial multidrug resistance.

The impact of resistance to standard drugs used in malaria has contributed to the huge mortality and morbidity caused by *Plasmodium falciparum*. The role of ABC transporter proteins in this parasite is discussed by Pradines, Parquet and Orlandi-Pradines in this chapter. The emergence of quinoline resistance is associated with a reduced drug uptake in intracellular vacuoles or is due to increased efflux of the drug from the cell or, in some cases, a combination of both processes. There are several ABC transporters that cause antimalarial resistance. Targeting these specific proteins may allow reversal of this resistance mechanism. Compounds have demonstrated this capability in *in vitro* studies as well as animal and human studies. The authors review these recent advances and describe how the biochemical and genetic basis of antimalarial resistance may be reversed by modifying these proteins.

Other infectious diseases of the developing world that have been implicated with the ABC transporter proteins include Leishmaniasis and Trypanosomiasis (e.g., caused by *Trypanosoma cruzi* and *Trypanosoma brucei*). Lephron, Legare and Oulelette review the recent survey of the genome sequences of the three trypanosomatid parasites that showed the presence of a complete set of ABC genes. The functions of these proteins are described from a physiological and drug-resistance perspective.

Another eukaryotic group of organisms, the yeasts, including several significant human pathogens such as *Candida albicans,* have been the subject of intensive studies. Consequently, our understanding of the ABC proteins in these increasingly significant pathogens has improved. Sanwal, Panwar and Prasad describe how the ABC proteins enable yeasts to secrete toxic compounds in the competitive environment to provide a defense mechanism. Among this set of proteins are subfamilies that code for multidrug resistance and pleiotropic drug resistance. *Saccharomyces cerevisiae* is the most studied of the yeast group, although recent reports of similar resistance mechanisms have also been observed in pathogenic yeasts. The presence of large numbers of ABC members in yeast genomes suggests that they are critical to yeast physiology as well as their defense mechanisms.

From the eight chapters reviewed so far, it is evident that ABC proteins play a major role in emerging resistance to anti-infective drugs; however, our improved understanding of these mechanisms may enable us to develop alternative approaches to treating currently problematic organisms. The editor of this collection, along with Padron-Nieves and Diaz, reviews the recent progress made in the identification, design, availability and utility of compounds that may work as ABC transporter blockers. Such agents may have applicability in parasitic infections as well as other emerging infectious diseases.

In the final chapter of this excellent collation of contemporary insightful perspectives, Lage reviews the role of ABC transporters in many drug resistance situations including in prokaryotes, parasites and, increasingly, in cancer cells. Use of the novel strategy RNA interference (RNAi) may be a major step forward as we are losing many battles against various pathogens.

Various RNAi technologies have been applied to tumor models *in vitro* and *in vivo* with encouraging results following reversal of ABC transporter-mediated multidrug resistance in cancer. The RNAi pathway can only be used in eukaryotes, but it may have utility in parasitic infections currently resisting our conventional approaches.

The final section of the book contains a comprehensive collection of color illustrations and relevant tables, which augment the overall thorough and easy-to-read series of informative chapters written by experts in this emerging and exciting sector of molecular biology, which are relevant to the daunting issue of anti-infective or cancer therapy.

The detail and insight provided as well as thorough referencing in each chapter suggest that this collection will be an excellent addition to most libraries in medical schools and research laboratories, especially at the price of US$310. Ponte-Sucre is to be complimented on her efforts, as are her coauthors and contributors.

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The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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