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BOOK REVIEW

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Ian T. Paulsen, Kim Lewis (eds): Microbial multidrug efflux

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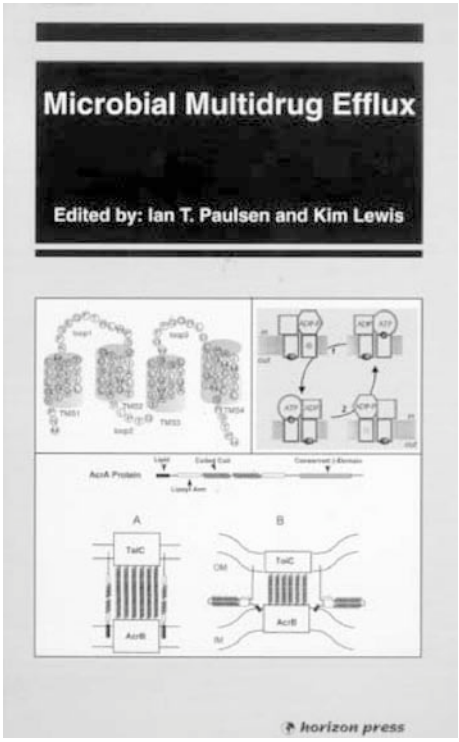
In the early 1970s, the discovery of the human P-glycoprotein and its involvement in the efflux of multiple antitumoral agents marked the beginning of a new era in cell biology. It was fascinating that one single transporter could selectively promote the transport of multiple drugs with no structural or chemical similarities among them. Soon after this discovery, multidrug efflux transporters were also found in microorganisms. These transporters were related to resistance to multiple antibiotics, toxic compounds, and many other sorts of molecules. Since then, the number of identified microbial multidrug efflux systems has increased, especially since the recent advances in sequencing of microbial genomes. These transporters not only contribute to the development of low-level resistance to multiple drugs, they are also in part responsible for the appearance of chromosomal mutations that lead to higher resistance levels. Thus, a better understanding of microbial multidrug transporters will play a key role in the discovery and development of new antimicrobial agents.

Microbial Multidrug Efflux, edited by Ian T. Paulsen and Kim Lewis, is a compendium of sixteen reviews on cutting-edge aspects of multidrug transporters, written by leaders of research groups from around the world. Most of the chapters are excellent and many also outline trends for future research on this topic. However, the book as a whole is somewhat heterogeneous; while some chapters provide a wide perspective, others focus very closely on one kind of transporter from a specific type of microorganism. Although general and basic information about multidrug transporters can be picked up in bits and pieces from most of the chapters, a general introduction giving an overview of microbial multidrug transporters would had been very useful for those readers not familiar with this aspect of microbial physiology. Nonetheless, the book contains a wealth of useful information and is essential reading for anyone interested or working on microbial multidrug efflux systems.



Among the reviews on general aspects of multidrug transporters, Chap. 2, by Paulsen et al., offers an interesting comparison of the number and types of membrane transport systems encoded in a selection of 27 completely sequenced microbial genomes. It is remarkable how the number, types, and apparent predicted specificity of transporters in each individual microorganism correlates with its lifestyle. Obviously, as the number of sequenced microbial genomes increases, these

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kind of studies will acquire more importance, especially if they are complemented with data from functional genomic analysis. Of particular interest is Chap. 14, in which Lomovskaya and Watkins discuss the potential benefits of combination therapies using efflux pump inhibitors. The inhibition of efflux pumps would result in an improvement of both the activity and the efficacy of antibiotics against resistant strains. Several molecules with such activities are described in this chapter.

Some chapters discuss the mechanistic aspects of efflux pumps. In Chap. 3, A.A. Neyfakh deals with the intriguing issue of how microbial transporters recognize and transport dissimilar compounds; BmrR, a regulator of the multidrug transporter Bmr from *Bacillus subtilis*, is used as an example. The author includes a crystallographic analysis of BmrR, which has demonstrated that the protein may bind different molecules due to the flexibility of its binding site. Models for the coupling of the energy provided by the hydrolysis of ATP and the transport of substrates in the ABC family of transporters are discussed in Chap. 8 by van Veen et al.

The characterization of multidrug efflux proteins has lagged because membrane proteins are usually difficult to overexpress and purify. In their review (Chap. 9), Ward et al. provide a new strategy to characterize proteins of the MFS family of transporters. Their approach offers a promising way to increase our knowledge about membrane transporters.

Several chapters focus on specific transporters or microorganisms. ''Precious things come in little packages'' is the title of Chap. 4, in which Schuldiner et al. focus on the study of EmrE, a small drug transporter from *Escherichia coli* that is capable of transporting a wide range of drugs by means of forming oligomers. In Chaps. 5 and 6, two transporters of the major facilitator superfamily are described. These are the QacA transporter from *Staphylococcus aureus* (in the review by M.H. Brown and R.A. Skurray), which has served as a model for studying the kinetics of transport of antimicrobial agents and inhibition, and MdfA (in the review by Bibi et al.), which is proposed as a model for studying transport.

Moving on to a different family of transporters, Nikaido and Zgurskaya (Chap. 12) describe the *E. coli* AcrB multidrug efflux pump, a member of the resistance-nodulation-cell division family of transporters (RND), and its associated periplasmic protein AcrA. This system seems to interact with the outer membrane protein TolC in order to export toxic compounds directly to the external medium. In Chap. 17, K. Poole reviews the RND proteins of *Pseudomonas aeruginosa* and related organisms.

Concerning bacterial pathogens, Davis et al. (Chap. 7) present in an interesting report on the multidrug resistance transporters encoded in the genome of the clinically important pathogen *Enterococcus faecalis*. The authors have identified up to 34 transporters and they have also carried out a systematic inactivation of all these genes. In four of the mutants, a change in the phenotype was observed. Antimicrobial efflux systems are presented from a different point of view in Chap. 13, in which Rouquette-Loughlin et al. discuss their implication as virulence factors in *Neisseria gonorrhoeae* and *Neisseria meningitidis*. In these two species, efflux pumps of the RND family of transporters are needed to escape from the antimicrobial compounds produced by host tissues.

One of the most controversial subjects regarding efflux pumps is their involvement in other cellular functions apart from antibiotic resistance. Krulwich et al. (Chap. 15) describe the implication of tetracycline transporters in sodium resistance and potassium acquisition. Following up on this issue, K. Lewis (chap. 16) discusses how our current knowledge of efflux pump substrates can be used to search for the natural substrates (not human-made antibiotics) of all families of multidrug efflux pumps.

Although most of the book deals with bacterial multidrug efflux proteins, in Chap. 10, Ouellette et al. focus on the importance of ABC transporters in parasitic protozoa, mainly *Plasmodium falciparum* and *Leishmania*, in which drug resistance is an important problem. Also, in Chap. 11, Decottignies et al. review the ABC-transporters encoded by *Saccharomyces cerevisiae* and describe the phenotypes of single and multiple mutants with deletions in these genes. For these analyses, the authors had to screen 349 toxic compounds, which illustrates the fact that, most of the time, finding a phenotype associated with a particular multidrug transporter is like searching for a needle in a haystack!