Editorial

ABC Transporters: Role in Modulation of Drug Pharmacokinetics and in Physiopathology and Therapeutic Perspectives

The superfamily of ABC transporters comprises 49 proteins in humans. They all use ATP hydrolysis as an energy source and share common structural features. In particular, the presence of 2 membrane-spanning domains made of 6 transmembrane segments and of 2 ATP binding cassettes is required to make them functional. Yet, the function of many of these proteins still needs to be elucidated and their substrates remain unknown, but for those that are best characterized, it is clear that they play a critical role in the maintenance of cell homeostasis, by modulating the cell concentration in xenobiotics or in physiological substrates.

In the present issue, we will examine the role of selected transporters in this superfamily, to illustrate their importance in drug disposition or in physiopathology. We will also discuss therapeutic perspectives related to modulation of their activity. The figure illustrates the transporters we will focus on, together with the indication of their function and of the pathology associated to their dysfunction.

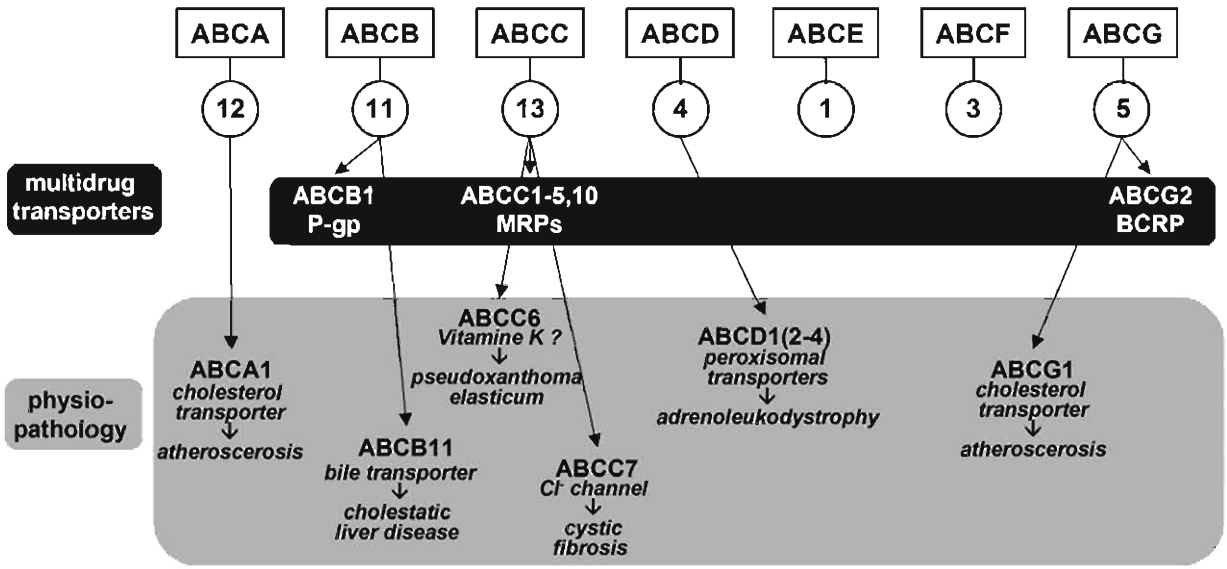

Figure: Families of ABC transporters (squared) with indication of the number of transporters in the family (circled).

Xenobiotic transporters catalyse the efflux of drugs, or metabolites thereof, out of the cells. In contrast to many other transporters, they all display very broad substrate specificity, recognizing their substrates based on physico-chemical properties rather than on specific molecular determinants, hence their appellation of 'Multidrug Transporters'. These transporters belong to 3 families, namely ABCB for P-glycoprotein, ABCC for MRPs (Multidrug-resistance Related Proteins), and ABCG for the half transporter BCRP (Breast Cancer Resistance Protein).

In this issue, we will review their specific role in modulating drug pharmacokinetics [1] or in conferring resistance to anticancer chemotherapy [2], and the interest of inhibitors to reverse their effect. We will also discuss for 2 of them (ABCB1 and ABCC2) how genetic polymorphisms can lead to variations in their transport capacity among individuals and therefore justify therapeutic monitoring of blood levels, or patient's genotyping for drugs with narrow therapeutic index [3].

Other ABC transporters rather transport physiological substrates that can be highly variable in their chemical nature (Chlorure ions for ABCC7 or cholesterol for ABCA1, for example). The physiological role of these transporters has been generally identified when discovering the molecular mechanism of the disease their defect can cause, which may explain why for most of them, it remains largely unknown.

In this issue, we will describe how the dysfunction in ABCA1 or ABCG1, ABCB11, ABCC6, ABCC7, or ABCD transporters can lead to atherosclerosis [4], cholestatic liver disease [5], Pseudoxanthoma elasticum [6], Cystic Fibrosis [7], or adrenoleukodystrophy [8], respectively. We will also examine the strategies that are developed to correct these defects in a therapeutic perspective.

Françoise Van Bambeke
(*Guest Editor*)

Pharmacologie cellulaire et moléculaire
Louvain Drug Research Institute
Université catholique de Louvain
Brussels, Belgium
E-mail: francoise.vanbambeke@uclouvain.be

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