MRP2 and the defence against drugs and toxins

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Chapter VII

Conclusions and perspectives
The human body is exposed to numerous exogenous compounds daily. A substantial part of these compounds is harmful to the organism and can cause toxic or genotoxic, i.e. carcinogenic effects. Those compounds are subjected to metabolism and elimination in order to detoxify them. For this purpose the organism displays a subset of more or less specific enzymes which, in a coordinated fashion, modify the exogenous compounds and excrete these modified molecules via bile or urine (summarized in chapter 1). The influence of individual genetic differences (either as mutations or polymorphisms) or acquired differences in activity has been highlighted for several enzymes including transporters (e.g. CYP, UGT, MDR1). However, as shown in chapter 2 of this book, sometimes and for certain compounds (as in this case the food-derived carcinogen PhIP), deficiency in one group of enzymes is not always a disadvantage in metabolism and elimination of reactive metabolites. From the data shown it is obvious that other enzyme systems (in this case sulfotransferases) can compensate for the absence of a whole enzyme group if the compound is substrate for both. This means that the effects of enzyme deficiencies have to be investigated for each xenobiotic separately.

In chapters 3, 4 and 5 of this book, using different model compounds, the contribution of Mrp2 to the defence system of the organism is studied. It is shown that biliary and intestinal Mrp2 in the rat provides protection against PhIP, a heterocyclic amine which is abundant in several forms of prepared meat. It has been shown to be a colon and breast carcinogen in the rat and is also implicated in human carcinogenesis. With PhIP the concept of transporters as “phase 0” and “phase III” enzymes could be studied very extensively. Intestinal Mrp2 (“phase 0”) pumps PhIP back into the gut lumen, reduces the initial uptake of this compound and thereby relieves the metabolizing enzyme systems (phase I and II) in the body. However, a certain amount will enter the body and must be detoxified. Afterwards, Mrp2, mainly in the liver (“phase III”), helps to eliminate these metabolites via bile. It is again intestinal Mrp2 which will reduce reuptake of these metabolites via the enterophepatic cycle in the gut.

Mrp2 also plays an important role in excretion of arsenite which is toxic and carcinogenic. PhIP and arsenite only represent two of numerous compounds human beings are exposed to. According to data from in vivo studies in the rat, the effect of one compound alone (at least not in doses commonly taken up) is much smaller than the combined effect of carcinogens as we take them up in our daily food. It is the
sum of all (geno)toxic effects from several compounds which destroys the cellular integrity or cause cancer after alterations in the DNA. Thus, Mrp2 is only one detoxifying enzyme in the cell where metabolism and excretion is influenced by several groups of enzymes. Again, the sum of all enzyme activities (the overall phenotype) leads to interindividual differences which may possibly cause cancer in one, but not in the other individual. One has to keep that in mind when interpreting data from studies dealing with the effects of single proteins on single xenobiotics. The issue is even more complex: In the case of ANIT, Mrp2 is required for the compound to exert its toxic effects in the bile duct (as shown in chapter 5). Additionally, there are clear hints that compounds which are beneficial for the body are metabolized and excreted by the same enzymes and transporters as the harmful compounds. This holds for example for metabolites of the flavonoid chrysin, which are substrates for Mrp2 as well. Decreases in activity of Mrp2 therefore may result in higher bioavailability not only of harmful compounds like PhIP but also of beneficial compounds which may counteract the first effect. In conclusion, when determining the overall cancer risk of one person, many endogenous (genetic/acquired differences in enzyme activity) and exogenous (diet/surroundings/physical and psychological habits) factors have to be taken into account. This complicates the issue and it seems unlikely that from isolated studies conclusions on the susceptibility to neoplastic diseases can be drawn. However, in order to obtain a full picture and to determine common risk factors, studies such as presented here are necessary. In vivo studies using biological endpoints as well as epidemiological studies in connection with genotyping will either support or weaken the conclusions drawn from the presented data. Several polymorphisms have already been described for MRP2, but their influence on protein expression or activity, hence the clinical relevance of these polymorphisms, is not defined yet. Furthermore, clinical entities, leading to reduced expression of MRP2 either in the liver or the intestine, have to be studied with regard to the influence on bioavailability of xenobiotics. This comprises also entities not yet commonly associated with changes in transporter expression such as hepatitis C.

In chapter 6 of this book one such disease which may lead to acquired reduction in MRP2 expression is investigated. The animal model of Primary Sclerosing Cholangitis (PSC) used here resembles closely the human disease entity, although it is unclear whether the animal data can be transferred to the human situation. On the one hand, the only published human study, though small, confirms results from the animal
model. On the other hand, expression levels of MRP2 may vary greatly between studies, stages of PSC and sometimes even within equally classified disease activities as shown for example for PBC. Additionally, systemic inflammation, caused by delivery of lipopolysaccharides via the portal vein, might be more important than the fact that inflammation occurs in the bile ducts, since TNBS colitis also causes downregulation of Mrp2 in the liver. Certainly further studies of different diseases, and their different stages in humans will be necessary to define influences on the expression of transporters involved in the defence system of the body.

References