

# Drug Transporters in Toxicology



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## General Overview

While it has long been accepted that transporters and proteins must exist to move solutes such as drugs across lipid membranes, it is only fairly recently that the nature and properties of the drug transporter proteins involved have come to light [1]. The discovery that these transporter proteins are linked to multi-drug resistance in a range of cancer cells by increasing the removal of chemotherapeutics from out of a cancerous cell, and thereby protecting it, has led to wider research in interest and a rapid increase in the understanding of their form and function and over 400 drug transporter proteins are now known [2, 3]. In pharmacology transport proteins are crucial for moving drug molecules across physiological barriers (e.g. gut lumen, blood-brain-barrier) allowing both absorption and excretion to occur [4]. Changes in the expression and function of the drug transport proteins is known to alter the basic pharmacokinetic parameters of any given drug molecule and therefore possible inducers and inhibitors can lead to drug interactions [5]. However, their function in toxicology has not been as widely discussed.

## What are Transporters?

Transporter protein is widely classified into two main groups, Solute Carriers (SLC) and ATP-Binding Cassette (ABC) proteins [6]. The SLC are passive solute carriers transporting either anions (Organic Anion Transporters, OAT) or cations (Organic Cation Transporters, OCT) across a membrane generally as an influx mechanism [6]. The ABC transporters use energy from ATP to actively move molecules specifically and/or against their concentration gradient most often as an efflux mechanism. It is the ATP-transporter family that is particularly associated with the multi-drug resistant phenotype with the most widely cited being p-glycoprotein (P-gp, ABCB1) and the breast cancer resistance protein (BCRP, ABCG2) [7]. ABCB1 has been historically associated with the absorption of drugs and molecules across the intestinal lumen but it is now known to have a wide distribution across the body including functional expression in the blood-brain-barrier, kidney, liver, placenta and testes [8]. ABCG2 expression is linked with cancer cells where its up-regulation can result resistance to chemotherapeutics such as doxorubicin [2] however, similar to ABCB1, it is also located in the liver, intestine, brain, placenta and kidney [9]. While the

bulk of research to date has focused on transporter expression in humans (and model species such as rat and mouse), the gene sequences of most ABC transporters is conserved across vertebrates, some invertebrates and some plants [10,11]. Analogous genes have been identified in bacteria and fungi [12].

## Induction/Inhibition of Transporter Systems

It is now becoming clear that drug transporter proteins are critical in the movement of endogenous compounds as well as xenobiotics [13]. Similar to drug metabolising enzymes, the function of transporters is critical for normal homeostasis and alternation in transporter activity can have effects beyond drug resistance [14,15]. As well as being regulated through DNA transcription (detailed below) a variety of substrates have been shown to induce (e.g. rifampin, carbamazepine, St Johns' Wort) or inhibit (e.g. erythromycin, ketoconazole, verapamil) drug transporters and therefore affect the action of drugs using these transporters (e.g. digoxin) [16,17]. Similar to drug metabolizing enzymes each individual drug transporter seems to have both a wide substrate preference and also a range of possible inducers and inhibitors, our knowledge of these is really only starting to develop [6].

## Regulation (PXR/CAR/AhR)

Regulation of DNA transcription is transporter specific and can include regulation through the TATA or CCAAT/CT rich promoter sequences [18]. Regulation by p53, AP-1, the Ras/Raf pathway and APC have also been reported [18]. There is growing evidence of co-regulation of drug metabolism and transport with clear overlaps of transporter expression with the induction/inhibition of CYP3A in particular [19]. Drug metabolising enzymes are often up-regulated in response to environmental signals and there is increasing evidence of co-regulation of drug metabolizing enzymes with the efflux transporters (ABC transporters) [20]. Key to this interaction is nuclear receptors such as the pregnane-X receptor (PXR) and Constitutive Androstane Receptor (CAR). Both the CAR and the PXR receptors are involved in the regulation of enzymes such as CYP3A and also seem to form the basis of cross-talk between enzyme and transporter function [21]. For example, the PXR ligand (and CYP3A inducer) chloropyrifos caused

increased ABCB1 expression in killifish (*Fundulus heteroclitus*) hepatocytes [22,23]. For this reason, it has become common practice to presume that CYP3A inducers/inhibitors will affect drug transporter action but the actual relationship is likely to be more complex [24]. Additionally, regulation of the drug transporter proteins via the Aryl-Hydrocarbon Receptor (AhR) has been reported [25]. The AhR is most closely associated with dioxin toxicity and its associated effects on sex ratios [26]. The discovery that drug transporters, as well as the classical induction of CYP1A, may be affected by AhR ligands may open a new line of investigation into potential toxic pathways for these substances. Beyond these specific receptor-mediated effects, recent evidence suggests that drugs widely associated with clinical toxicology, such as acetaminophen, impact transporter function but the mechanisms and implications of this are not widely accepted or understood [27].

### Cisplatin

The most widely cited example of drug transporters in toxicology is their role in cisplatin toxicity in the kidney. Cisplatin is a widely-used platinum-based chemotherapeutic which is taken into cells by the OCT2 transporter [28]. The expression of this transporter specifically in the proximal tubule of the kidney and cochlea hair cells has been directly linked with toxicities in these tissues [29]. The uptake of cisplatin into the cell causes a toxic cascade through their targeting of DNA within the nucleus [28]. Interestingly, hepatic toxicity is not reported with cisplatin due to the preferential expression of OCT1 which does not transport the cisplatin drug [30]. This expression pattern mirroring toxic symptoms remains one of the clearest cases demonstrating the importance of drug transporters in toxicology.

### Environmental Toxicology

Discussion on the role of drug transporters in human health and drug uptake/excretion dominates the literature, however these transporters are vital protective mechanism that prevent absorption or remove toxins from animals, plants and micro-organisms. The accumulation of cisplatin into kidney cells highlights the role of transporters in the movement of heavy metals. Evidence from plants suggests that these systems have a wider role in the removal of heavy metal contamination from cells thereby protecting them from potentially toxic accumulation [31,32]. The identification of multiple ABC transporters in fish species suggests that these organisms may be susceptible to a range of chemical contaminants (e.g. oil) and that marine species may be more widely affected by the contamination of waterways with sewage containing waste human drugs than has been previously thought [8,33]. The toxicology of mixtures is complex but evidence is growing that compounds that inhibit transporter molecules can lead to sensitization to a wide range of other pollutants [34]. Recent studies have confirmed that in yellow fin tuna (*Thunnus albacares*) pollutants such as polybrominated diphenyl ether can bind directly to transporter proteins and inhibit their action [35]. A similar interaction,

through possible inhibition of the ABC transporters, is being investigated an underlying cause of honey bee colony collapse through increased sensitivity to ivermectin due to concomitant exposure to inhibitors such as quercetin or fungicides [36-41]. This role of the transporters in sensitisation to other chemical entities is likely to become more of an issue as we better understand transporter roles and functions.

### Summary

Overall, our knowledge of the drug transporters (SLC and ABC) are growing, however we still lack good understanding of their roles beyond drug metabolism. Furthermore, as safety toxicology moves into a more cell-based predictive model, developing a better understanding of the regulation and expression of these molecules is vital. Additionally, we need to develop a better understanding of the interactions that can lead to chemical sensitisation via alteration of transporter function.

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