AN OVERVIEW OF CELL-BASED MODELS TO EVALUATE KIDNEY TOXICITY

Kidney toxicity or nephrotoxicity is defined as a dysfunction caused by drugs, chemical or environmental agents, and is typically a result of inflammation or obstruction of kidney function. While drug-induced nephrotoxicity can cause acute injuries or chronic diseases, recognizing acute kidney injury is the primary focus when evaluating new drugs. Drug-induced nephrotoxicity ranges from 14 to 26% and about 16% of pediatric patients are hospitalized due to drug-induced kidney injury[1]. As a part of PK/PD studies, it is critical to understand how drugs circulating in the vasculature are transported into the kidney for excretion. The FDA requires the testing of new drugs to determine drug-drug interactions that includes the principal routes of elimination, the roles that specific transporters play in drug elimination, and the effect of the drug on those transporters[2].

The kidneys clear drugs and drug metabolites via a combination of passive glomerular filtration and active tubular secretion. The process of tubular secretion has 2 components: the drug and/or metabolites are taken up from the blood via the basolateral membrane of proximal tubule cells and are then transported into the lumen through the apical membranes. Drug transporters typically fall in two categories: the solute carriers (SLC) that are expressed on the basolateral membrane and apical membranes and ATP binding cassettes (ABC) that are expressed on the apical membrane. Animal models are commonly used for ADME studies but there is increasing interest in *in vitro* models to study specific endpoints such as kidney toxicity. More complex cell-based models are being developed to study drug-transporter interactions. The models range from simple cell lines that overexpress a single transporter to bioprinted kidney models that recapitulate in vivo kidney function.

Cost-effective cell line-based models have been used to study drug-transporter interactions. The most popular cell lines are Caco-2 (human colorectal cancer) and MDCK (canine kidney) cells. Both cell lines partially recapitulate transporter expression profiles - MDCK cells are able to correctly sort transporters to the apical or basolateral cell membrane, and Caco-2 cells endogenously express several transporter proteins. However, these cell lines do not accurately recapitulate the structure and function of renal proximal tubule cells that are highly polarized columnar cells with specific transporters expressed on the apical and basolateral membranes. Proximal tubule epithelial cells isolated from normal kidney tissues are considered optimal for *in vitro* assessments of drug-transporter interactions and have been shown the highest accuracy in predicting toxicity of over 40 compounds[3]. Studies on the kidney chip showed improved expression of uptake and efflux transporters, resulting in accurate and reproducible responses to known transporter inhibitors such as cimetidine[4]. Currently, several commercially available organ-chip models are available to evaluate drug-transporter interactions in drug toxicity studies. The bioprinted kidney model has complex architecture with proximal tubule epithelial cells lining a lumen, and fluid shear stress is applied to the lumen to mimic glomerular filtration[5], and is being evaluated as a scalable model to evaluate kidney toxicity.

Based on the sustained activity in developing more physiologically relevant *in vitro* toxicity models, the drug development community is moving towards more complex cell models leaving the simple cell line approach in the dust.

References:

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