Opinion Article

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Enhancing Renal Proximal Tubular Cells with Physiological Oxygen and Fibroblast Co-Culture

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Description

The primary role of the kidneys is to regulate the extracellular fluid. The Proximal Tubule (PT) is the main site where amino acids, peptides, proteins, organic solutes, glucose, water, ions, urea and uric acid are reabsorbed from the primary urine into the blood. The PT epithelium is abundant in various transporters such as Organic Anion Transporters (OATs), Organic Cation Transporters (OCTs), glucose transporters and aquaporins that facilitate transcellular water transport and endocytosis *via* receptors like megalin/cubilin. These transporters use ATP, electrochemical gradients, or ion exchange to actively secrete Organic Anions (OA) and Cations (OC) into the primary urine. Organic anions are taken up from the vasculature at the basolateral side depending on the Na+ gradient maintained by Na^+/K^{+-}ATPase activity and then secreted into the tubular lumen *via* anion exchange or facilitated diffusion down the electrochemical gradient. Conversely, organic cation secretion is driven by OC/H^+ antiport, mediated by luminal Na^+/H^+ exchangers or actively secreted *via* transport proteins like Multi-Drug-Resistance protein 1 (MDR1)/P-glycoprotein (P-gp) into the tubular filtrate. The expression and levels of these transporters significantly impact the onset of drug-induced nephrotoxicity. The broad substrate specificity of these transport systems makes them susceptible to competitive transport reduction by alternative substrates. When multiple drugs compete for the same outward-directed transporter, renal clearance can be reduced, leading to increased intracellular drug concentrations and potential nephrotoxicity. Preclinical safety studies for drug candidates typically involve tiered approaches, including *in vitro* tests using human or animal-derived primary cells and immortalized cell lines from various species. Despite this, the routine and regulatory accepted approach involves *in vivo* testing in at least two species. However, there are concerns about the translatability of these safety tests, particularly *in vivo* tests, to reliably detect potential renal toxicity in humans and predict early drug attrition due to species-specific effects. The predictive value of rodent assays for urological toxicity in humans is limited due to substantial differences in renal transporter expression, metabolic capabilities and pharmacokinetic profiles compared to humans, with predictivity at best around 70%.

Various pharmaceuticals

On the other hand, adverse outcomes observed in rodents may be specific to their species and not applicable to humans, as exemplified by the renal toxicity and cancer-causing effects related to male rat-specific α2u-globulin from various pharmaceuticals, plant protection products and bulk chemicals. For instance, the development of renal tumors in male mice due to the metabolism of empagliflozin was not observed in female mice or any other species, including humans. Despite ongoing efforts to use *in vitro* methods to predict potential adverse effects in humans, such as employing Renal Proximal Tubular Epithelial (RPTEC) or other renal cells in semi-static or microfluidic systems, with or without biomarkers and supported by computational tools, the reported predictability rate of approximately 76%–85% still leaves considerable room for improvement. Beyond the challenge of standardizing protocols to enable data extrapolation, many *in vitro* systems struggle to replicate the true *in vivo* cell microenvironment, particularly the interactions with neighboring cells of diverse origins (e.g., endothelial and mesenchymal cells) and physiologically relevant oxygen levels. Efforts to emulate authentic physiological conditions in renal *in vitro* studies have yielded promising results in terms of cell behavior, as evidenced by the self-organization of RPTEC/TERT1 into tubular structures when cultured in a matrigel matrix and refined with the integration of fibroblasts into a more refined matrix. Moreover, these cells expressed transporter genes at higher levels compared to those grown in conventional culture conditions. One method of improvement involves providing a scaffold to support 3D structure development, although this often leads to increased workload and lower reproducibility due to setup variability. Another approach is co-culturing RPTECs with other renal cell types, such as interstitial or endothelial cells. In the renal cortex, peritubular capillaries are closely situated to Proximal Tubular (PT) epithelium, facilitating dynamic solute transport and reabsorption of water by PT cells through interactions with endothelial cells and vice versa.

Structural components

As part of the kidney's structural components essential for its anatomical and physiological function, connective tissue

fibroblasts play a crucial role in depositing extracellular matrix. Although in normal physiological conditions, communication between RPTEC and endothelial cells is considered more significant, fibroblasts and to a lesser extent RPTEC, become remodelers of the extracellular matrix under pathophysiological conditions, both *in vivo* and *in vitro*. However, the mechanisms of communication between fibroblasts and healthy RPTECs have not been thoroughly investigated. Existing research often focuses on how RPTECs influence fibroblasts to become myofibroblasts, while the impact of fibroblasts on RPTEC functionality is less explored. Therefore, RPTEC functionality should be evaluated alongside accompanying fibroblasts and/or endothelial cells, especially for prolonged exposure periods (weeks) to better understand potential renal toxicity. *In vitro* assessment of cell functionality, as mentioned above, is crucial for improving renal toxicity prediction systems. However, a critical parameter often overlooked is the oxygen concentration used in cell culture practices. Standard cell culture typically uses 5% CO_2 and atmospheric oxygen (approximately 18%–20% O_2 in the media), assuming that high oxygen tension does not affect cell growth, signaling, or functionality. In contrast, the renal cortex and medulla experience lower oxygen tension (approximately 5%–10% O_2) due to blood perfusion. Consequently, experimental results obtained from *in vitro* models under hyperoxic conditions may provide suboptimal or misleading insights for drug safety studies. Therefore, *in vitro* studies should not only aim to predict renal toxicity accurately in humans but also consider clinically relevant oxygen concentrations.