Common Pathways in Human Proximal Tubular Cells Altered by Exposures to Diverse Environmental Agents and Nephrotoxic Therapeutic Drugs

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Primary cultures of human proximal tubular (hPT) cells were used as the model system to test the hypothesis that exposure to low, physiologically relevant concentrations of diverse chemical agents causes release of proteins, lipids and metabolites into the extracellular space that correlate with specific exposures and cytotoxicity. hPT cells were incubated with two environmental contaminants [S-(1,2-dichlorovinyl)-L-cysteine (DCVC) and HgCl2] or three clinically used drugs whose efficacy is dose-limited by nephrotoxicity [cisplatin (CDDP), polymyxin B (PmxB), and tenofovir disoproxil fumarate (TDF)]. Using quantitative mass spectrometry and isobaric tags, several proteins were found to be increased in the extracellular media of hPT cells incubated with these chemicals. Both time- and concentration-dependent effects on protein abundance were noted, including several cytoskeletal proteins and multiple mitochondrial proteins. Using high resolution mass spectrometry coupled with ultrahigh performance liquid chromatography, effects of the diverse exposures on low-molecular-weight metabolites were studied showing time- and concentration-dependent perturbations in several common pathways, including amino acid metabolism, fatty acid metabolism, and carnitine shuttle pathways. Importantly, most of the changes in proteome or metabolome were caused by exposure concentrations that produce modest or no detectable cytotoxicity, as determined by release of Kidney Injury Molecule-1 (KIM-1) or neutrophil gelatinase-associated lipocalin (NGAL) from exposed hPT cells. These findings further support the overall hypothesis and identify multiple candidate biomarkers and altered biochemical pathways associated with early exposure to diverse nephrotoxicants.

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