The renal proximal tubule TXG-MAPr: safety assessment based on quantitative gene network analysis

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INTRODUCTION

Animal-based safety assessment of drug candidates is a tedious and expensive process which is obligatory for market authorisation. Intensive and low-throughput pathology evaluation does not assess mode-of-action but rather focusses on comparison to human pathophysiology. Scientific advances in -omics technologies and ever-increasing knowledge on human biology render pre-clinical in vivo testing unsustainable in the future. In the kidneys, proximal tubule epithelial cells are the primary target for drug-induced injury by cause of increased drug exposure, high oxygen consumption and bilateral transporter-mediated uptake.

METHODOLOGY

Identification of gene networks involved in nephrotoxicity using high throughput whole genome transcriptomics will provide mechanistic insight in the cellular stress response. Through targeted chemical exposure, i.e. affecting a single intracellular target using pharmaceuticals for which on-target pharmacology has been established, target specific transcriptome modulation can be achieved. This allows weighted correlation network analysis to deduce co-regulated gene networks. In addition, dose response relationships can reveal tipping points where on-target pharmacology switches to off-target toxicity.

RESULTS

We generated a collection of pharmacologically driven cellular responses in the human proximal tubular cell line RPTEC-TERT1, to identify and investigate kidney specific co-regulated gene networks resulting in adverse outcomes. On the other hand, preservation of co-regulated gene networks among different model cell systems for organ toxicity revealed the most common off-target cellular response.

DISCUSSION

Quantitative mode-of-action evaluation by targeted whole genome transcriptomics and co-expression analysis provides in depth knowledge of transcriptional modulation and supports the replacement of animal-based safety assessment with high-throughput in vitro chemical safety assessment.