Interactions of Kidney Function Related Genes and Proteins With Anticancer Drugs and Strategies To Mitigate Their Adverse Effects

Nelluru, Mithun Reddy (School: Little Rock Central High School)

Sorafenib, a targeted anticancer therapy, is used in the treatment of advanced renal cell carcinoma by inhibiting vascular endothelial growth factor receptors (VEGFRs) and tyrosine kinases (TKs), both essential for tumor growth. However, the use of sorafenib leads to adverse effects such as renal damage, particularly focal segmental glomerulosclerosis (FSGS). Currently, there are no effective therapeutics to mitigate sorafenib-induced renal damage, posing a significant clinical challenge. Epoxyeicosatrienoic acids (EETs) are being investigated for their renoprotective effects and represent a potential protective agent. However, they quickly degrade to the less active 8,9-DHET. This study investigates a novel, more bioavailable mimic, the 8,9-EET analog, specifically designed to reduce sorafenib-induced toxicities by modulating key gene expression pathways. Gene expression profiles were obtained from the Nephroseq database, with key gene targets analyzed via ingenuity pathway analysis. Cultured mesangial and tubular cells were treated with various combinations of sorafenib and the 8,9-EET analog to identify drug-enriched pathways. Results indicated that sorafenib-induced FSGS was linked to the downregulation of genes involved in cellular metabolism (CYP27B1, PDK4), transcription (ANKRD7, ZNF189), cytoskeletal integrity (ACTA2), and stress regulation (DUSP1). Conversely, pro-inflammatory and immune markers (IL10RA, PYCARD, TNFRSF-a, CX3CR1, ZFP36, TRIM32) were significantly upregulated, suggesting metabolic dysfunction, inflammation, and structural injury in renal tissues. Treatment with the 8,9-EET analog effectively balanced the expression of key renal genes, preserving renal function and enhancing the efficiency of VEGF-TKI therapies like sorafenib.

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