Proliferous Metabolics: Targeting Nucleotide Metabolism in Cancer Chemotherapy

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Chemotherapy is the primary form of treatment for the majority of cancer patients, using cytotoxic drugs to suppress tumor growth. However, cancer cells, by evolving through rapid generations, are able to adapt to the conditions and structures of chemodrugs, culminating in treatment failures. Urothelial carcinomas (UCs), a cancer of the kidney and ureter, are one such example, oftentimes developing these chemoresistances alongside metastasizing, ultimately leading to a grim 17.7% survival rate with metastasis. To understand how tumors reprogram cellular metabolism to counter chemotoxicity, metabolic alterations were characterized in UC patients and cell lines through metabolomics and [1,2-13C]glucose isotope tracing assays. Through LC-MS metabolomic analysis, distinct metabolic profiles were discovered in tumor samples compared to the normal tissues, with metabolites of nucleotide synthesis pathways, particularly in the pentose phosphate pathway (PPP), showing the most significant increase in abundance. These metabolic pathways provide cancer cells with nucleotides, essential building blocks for enhancing DNA-repair mechanisms and counteracting chemodrug-induced DNA damage and cell death. Glucose is the primary carbon resource for synthesizing nucleotide backbones through PPP, with the stable isotope tracing assay showing increased carbon production through the non-oxidative PPP branch, a response to the chemodrugs. Pharmacological inhibition of key PPP enzymes, TKT and G6PD improved the sensitivity of chemoresistant UC cells to chemotherapy. Taken together, these findings reveal the mechanistic basis for targeting nucleotide synthesis pathways as a therapeutic opportunity to conquer chemoresistance in cancer therapy.

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