Unraveling metabolic vulnerabilities to counteract sorafenib resistance in hepatocellular carcinoma

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Hepatocellular carcinoma (HCC) is the most common type of primary liver malignancy worldwide often diagnosed in late stages with a median survival of less than a year. Current treatments, including the oral kinase inhibitor sorafenib (SOR), for advanced-stage HCC are unsatisfactory due to the onset of resistance. However, the biochemical and molecular mechanisms of SOR resistance remain unclear.

Here, we show that murine hepatoblasts with myc oncogene overexpression and $p53^{-/-}$ are resistant to SOR. We defined that SOR negatively affects mitochondrial function by acting as an uncoupling agent, disrupting electron transport chain (ETC) complexes, and altering ETC super-complex assembly. This causes reactive oxygen species (ROS) production within mitochondria. To counteract ROS production and continue to proliferate, SOR-resistant cells rewire their metabolism by activating the glyoxalase system to promote glutathione (GSH) shuttling into the mitochondria and the production of D-lactate.

Integrated data from transcriptomic and metabolomic profiles, along with metabolic tracing experiments, demonstrate that SOR-resistant cells increase glucose uptake for serine production. This serine is used in mitochondria by the one-carbon metabolism to generate enough NADPH for GSH regeneration and to promote purine biosynthesis. Moreover, SOR-resistant hepatoblasts rely on cysteine for L-lactate generation, as the contribution of glucose, glutamine, and alanine was only marginal.

Chemical and genetic inhibition of these key metabolic pathways engaged by SOR-resistant cells identify metabolic vulnerabilities that enhance sorafenib efficacy. Furthermore, analysis of SOR-resistant human hepatocyte cells (Huh7) and SOR-resistant patient samples revealed superimposable metabolic gene expression profiles identified in our SOR-resistant hepatoblasts, highlighting the role of these metabolic pathways in drug resistance.