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## Elucidating the role of Hexokinase-2 in hepatocellular carcinoma and implications for cancer therapy

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Hepatocarcinogenesis (HCC) induces profound glucose metabolism reprogramming by repressing endogenous glucokinase (GCK) and expressing the high-affinity hexokinase-2 (HK2). This quality differentiates HCC from normal hepatocytes that can be exploited to selectively target HCC. Hepatic deletion of HK2 inhibits DEN-induced hepatocarcinogenesis. Silencing of HK2 in human HCC cell lines increases cell death and inhibits tumorigenicity *in vitro* and *in vivo*, that could not be restored by GCK nor a mitochondrial binding deficient mutant. Metabolically, HK2 loss reduces glycolytic flux to pyruvate and lactate, but TCA flux is maintained. Cells were vulnerable to serine depletion, consistent with their increase in serine uptake/glycine secretion, suggesting an increase in one-carbon metabolism. Decreased glycolysis was, however, coupled to increased respiration, that could be diminished by treatment with metformin, which increased cell death and inhibited tumor growth. Interestingly, neither HK2 silencing nor metformin treatment alone inhibits mTORC1, whereas the combination inhibits mTORC1 signaling that is dependent on REDD1 and not AMPK. Lastly, HK2 silencing synergizes with the FDA-approved therapeutic, sorafenib, to inhibit tumor growth.

### Biography

Dannielle DeWaal completed her graduate studies at the University of Illinois-Chicago in the Department of Biochemistry and Molecular Genetics in the laboratory of Dr Nissim Hay. As a cancer biologist, she examined and elucidated the role of Hexokinase-2 in hepatocellular carcinoma and its relevance as a novel therapeutic target. She continues her studies at UIC and is currently a Postdoctoral Research Associate. She enjoys working on various projects, including metabolic analyses using a GC-MS, which she has been learning and teaching the lab about. She currently serves on the Editorial Board of International Journal of analytical and bioanalytical methods.

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