HEPATOCELLULAR CARCINOMA A TEASPOON OF SUGAR?

One of the many hallmarks of cancer is enhanced aerobic glycolysis, which produces glucose and other metabolites to maintain cellular division and tumour growth. New preclinical research published in *Nature Communications* suggests that reversing this process by promoting the opposing metabolic process—gluconeogenesis—might be effective in treating hepatocellular carcinoma (HCC).

In their study, Bo Huang and colleagues showed that glucose metabolism was altered in both mouse and human HCC. Specifically, they discovered decreased expression of phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase), two enzymes central to gluconeogenesis in cells. They also showed that two other enzymes—11 β -hydroxysteroid dehydrogenase type 1 (11 β -HSD1) and type 2 (11 β -HSD2)—had altered expression, with the former being downregulated and the latter upregulated. These enzymes are crucial for maintaining homeostasis of glucocorticoids, which activate hepatic gluconeogenesis.

In human tumour samples, Huang and colleagues also revealed that the 11 β -HSD1 to 11 β -HSD2 ratio was associated with prognosis and survival; those with high ratios had better clinical outcomes than those with low ratios. Whether this finding can be translated into a useful clinical biomarker remains to be seen.

Overall, these findings of altered glucose metabolism suggest that treatment with an active glucocorticoid—such as dexamethasone, a widely used anti-inflammatory—might reverse glycolysis in these cells and promote gluconeogenesis. Indeed, administration of dexamethasone to a murine xenograft model of HCC resulted in upregulation of PEPCK and G6Pase, and decreased tumour growth. The effect was reversed on dexamethasone cessation, and no effect was apparent using the inactive glucocorticoid prednisone. Accordingly, active glucocorticoids might be a worthy avenue for further exploration as a treatment for HCC.

As Huang notes, this is just the “tip of the iceberg in liver cancer metabolism. We aim to develop diagnostic strategies for HCC using metabolics.”

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Original article Ma, R. *et al.* Switch to glycolysis to gluconeogenesis by dexamethasone for treatment of hepatocarcinoma. *Nat. Commun.* 4, 2508 (2013)