CANCER METABOLISM

Suppressing insulin feedback to improve efficacy of cancer therapeutics

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Mutations in the genes encoding proteins involved in the phosphoinositide 3-kinase (PI3K) signalling pathway are very common in human cancers; however, efforts to target this pathway therapeutically have had mixed results. New research from Benjamin Hopkins, Lewis Cantley and colleagues sheds light on the mechanism underlying this phenomenon and puts forward a possible solution to the variable efficacy of PI3K inhibitors.

"Previous reports and clinical trials had demonstrated that chronic use of PI3K inhibitors resulted in hyperglycaemia and hyperinsulinaemia," explains Hopkins. "The goal of this study was to test if we could circumvent the acute hyperinsulinaemia, and if this would have an effect on the efficacy of these compounds in preclinical models."

To begin testing this theory, the researchers first treated wild-type mice with therapeutic doses of a range of inhibitors that target components of the PI3K signalling pathway and then monitored their blood levels of glucose. They found that many of the tested agents caused an increase in blood levels of glucose and serum levels of insulin. These glucose levels returned to normal over time without intervention, suggesting that the PI3K signalling pathway is eventually reactivated (as a result of insulin feedback) despite the presence of a PI3K inhibitor. Analyses of mice with tumour allografts also showed that glucose uptake into the tumour increased following treatment with a PI3K inhibitor. The authors suggest that this finding indicates that spikes in insulin levels as a result of treatment with a PI3K inhibitor could be causing a transient increase in glucose uptake in the tumour. As glucose is required for tumour growth, these inhibitors could be increasing tumour growth.

Next, the researchers treated Kras-Tp53-Pdx-Cre (KPC) cells with a PI3K inhibitor, either with or without the addition of insulin. In cells that also received insulin, PI3K signalling was partially restored, despite the presence of the inhibitor; cellular proliferation was also partially restored. Similar results were seen when a range of other cell lines and patient-derived organoids underwent the same treatment. Although the results were variable across the cell lines, the authors suggest that these findings indicate that insulin activates PI3K signalling in certain tumours. "The most significant finding of this study was that acute spikes in blood insulin can activate PI3K signalling even in the presence of PI3K inhibitors, which has broad implications for a number of drugs that target PI3K," explains Hopkins.

To determine whether the effectiveness of PI3K inhibitors could be improved by suppressing this insulin feedback, the researchers tested the effects of metformin and a sodium–glucose cotransporter 2 (SGLT2) inhibitor, which are known to reduce the levels of insulin, and of a ketogenic diet, which can increase insulin sensitivity. Mice with a KPC tumour allograft were treated with metformin or an SGLT2 inhibitor or put on a ketogenic diet for 10 days, at which point a PI3K inhibitor was administered. Pretreatment with metformin did not alter the effects of treatment with a PI3K inhibitor. However, the mice that were pretreated with the SGLT2 inhibitor or were on a ketogenic diet exhibited decreased hyperglycaemia and reduced levels of insulin release; growth signalling in the tumour was also reduced.

To further explore the effects of a ketogenic diet, Hopkins and colleagues treated mice bearing an allograft of a tumour that had a mutation in *Pik3ca* with a ketogenic diet and a PI3K inhibitor. The mice were administered with insulin 15 mins after each dose of PI3K inhibitor. They found that the administration of insulin reduced the beneficial effects of the ketogenic diet, including rescuing tumour growth. The authors conclude that a ketogenic diet, therefore, improves the response to PI3K inhibitors by reducing blood levels of insulin, which in turn limits the ability of insulin to activate insulin receptors in tumours.

"We are in the process of taking these findings into the clinic," says Hopkins. "We are actively planning a clinical trial combining PI3K inhibition with the ketogenic diet." Hopkins also notes that the team's finding of hyperinsulinaemia enhancing tumour survival has broad implications for a range of treatments. "We are actively developing models and precision medicine approaches to capture how the systemic metabolism affects therapeutic efficacy more broadly," concludes Hopkins.

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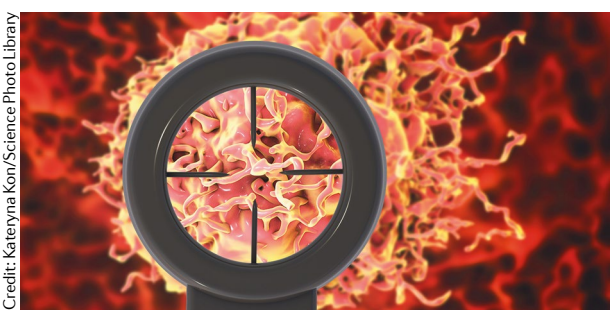

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