

Uridine as a novel fuel for cancer cells



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Cancer cells are known to have an enormous appetite for calories.¹ This is something they are addicted to sustain their unrestricted growth and rapid proliferation.² To accomplish this feat, cancer cells have evolved multiple mechanisms, rewiring their metabolic circuitry such that metabolic fuels are preferentially diverted to meet their energy demands.³ A classic example (Warburg effect) of this is aerobic glycolysis and preferential production of lactate to produce ATP (without relying on mitochondrial oxidative phosphorylation).^{4,5} Further, the rapid proliferation of cancer cells exhausts the nutrient and oxygen supply derived from the existing vasculature, making them hypoxic. In turn, triggers the upregulation of pro-angiogenic factors from the hypoxic tumor sites (HIF), which in turn revascularizes the tumor mass, bringing in metabolic cargo.⁶

When it comes to cancer metabolism, cancer cells are highly innovative to devise novel mechanisms to bypass metabolic regulations. In a recent article published in nature metabolism,⁷ Skinner et al. identified an unusual source of glucose in cancer cells. The ribose moiety of uridine can be repurposed to replenish the energy requirements in cancer cells through the uridine phosphorylase UPP1/UPP2-mediated cleavage of uridine into its constituents, uracil and ribose-1-phosphate (R1P). R1P is then utilized to convert into fructose-6-P and glyceraldehyde-3-P by the non-oxidative branch of the HMP shunt back to glycolysis and ATP production.

These findings are novel and intuitive. It means that the cancer cells have the ability to salvage glucose from uridine when needed. This also indicates that cutting off the uridine supply to cancer cells may be a mechanism to target cancer cells.

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