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RESEARCH HIGHLIGHT

# Uridine: as sweet as sugar for some cells?

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**Nucleosides fuel mammalian cell energy needs and biosynthetic pathways such as ribosylation, glycosylation, redox metabolite generation, and nucleotide biosynthesis. Two recent studies published in *Nature Metabolism* and *Nature* follow distinct screening approaches to reveal that uridine, a pyrimidine nucleoside, maintains metabolic homeostasis during growth and cellular stress**.

Glucose oxidation ordinarily drives cellular bioenergetics and some biosynthesis. When glucose is scarce, some cells can switch to alternative fuel sources. For example, in ischemic cortical astrocytes, glucose deprivation-induced cellular stress was reversed with externally-sourced uridine.[1]

The maintenance of blood-mobilized uridine is orchestrated at the organism level. Synthesis is mediated by adipocytes,[2] the liver,[3] and potentially erythrocytes,[4] while the liver canonically orchestrates breakdown. Tight control is crucial, as uridine nucleotides have signaling roles and uridine itself is connected to the physiological hunger response and body temperature changes.[3,5]

Facilitating the cellular-level adaptive catabolism in astrocytes was Uridine Phosphorylase 1 (UPP1), which catalyzes the reversible cleavage of uridine to ribose-1-phosphate and uracil (Fig. 1). UPP1 transcription responded to growth factors and TNF-α via MAPK and NFκB signaling in cancer cells in the context of chemotherapy efficacy; p53 and p65 are the known transcription factors.[6–8] Additionally, studies in astrocytes discovered that low glucose increased UPP1 expression through an unknown signaling mechanism.[1] Thus, while some aspects of the physiological relevance of uridine catabolism and regulation have been pursued, the cellular-level dynamics and biochemistry of this pathway in cancer was largely unclear.

In *Nature Metabolism*, Skinner and Blanco-Fernández et al. reported that UPP1 facilitates proliferation in glucose-deprived, uridine-supplemented K562 cells, and that RNA is a viable uridine source in vitro.[9] A genome-wide CRISPR-Cas9 screen determined that genes of the non-oxidative pentose phosphate pathway and glycolysis were also required, alongside PGM2. PGM2 connects uridine to central carbon metabolism via ribose phosphate isomerization. This mechanism was validated in vitro and in vivo with isotope tracing metabolomics (Fig. 1).

Screening of the PRISM Project cancer cell line collection showed that several cancer cell types (notably melanoma and glioma) used uridine to fuel proliferation. Mouse and human macrophages were also able to catabolize uridine in vitro. Finally, the authors established UPP1 transcriptional upregulation by MITF and NFκB in their melanoma and macrophage cell lines, respectively, and that neither glucose deprivation nor OXPHOS inhibition increased uridine catabolism in UPP1-overexpressing K562 cells. Since uridine-derived carbon enters at late glycolysis, the authors infer that its regulation could be independent of the signals that govern carbohydrate metabolism in early glycolysis reactions.

The complementary study published in *Nature* by Nwosu, Ward, Sajjakulnukit, and Poudel et al. identified uridine and UPP1 from a glucose-deprivation nutrient screen and gene transcription correlation analysis.[10] Uridine was an alternative energy source for both pancreatic cancer and non-transformed pancreatic cell lines, catabolized by UPP1.

As expected, KRAS-MAPK-ERK activity (and specifically a Kras-activating, disease-driving mutation common to pancreatic cancer) upregulated UPP1 transcription and uridine catabolism in pancreatic ductal adenocarcinoma cells. Uridine catabolism activity was also tuned via UPP1 transcription in response to glucose and uridine supplementation. We propose that an unknown signaling axis — sensing nutrient availability or metabolism — integrates with MAPK-ERK and NFκB to control UPP1 transcription adaptively, thereby maintaining energetic and biosynthetic homeostasis despite a range of stressors. Underlining the relevance of uridine catabolism in cancer biology, high UPP1 expression in patient tumors predicted poorer survival outcome in several cancers, and UPP1 knockout severely blunted tumor growth in pancreatic cancer mouse models. Thus, the mechanism of integration of combinations of signals deserves investigation, and it is important to test whether there are cell type-agnostic pathways controlling uridine catabolism.

The findings above should also be understood in the context of fluoropyrimidine chemotherapies. UPP1 is required for the efficacy of the 5-fluorouracil prodrug and front-line pancreatic cancer therapy Capecitabine.[7] Because of this, it would be worthwhile to be cautious about — and further investigate — directly targeting UPP1 or KRAS-MAPK for drug development and clinical practice, as either could decrease fluoropyrimidine activation by repressing UPP1.

While both studies performed in vivo isotope tracing of labeled uridine, the *Nature* study confirmed that uridine from outside the tumor microenvironment — as if from plasma and other tissues — fueled tumor metabolism by partly contributing to the tumor uridine supply. Importantly, whole-mouse depletion of phagocytes (including macrophages) decreased plasma uridine and increased plasma uracil, as though phagocytes have a major role in uridine biosynthesis, but left tumor uridine levels

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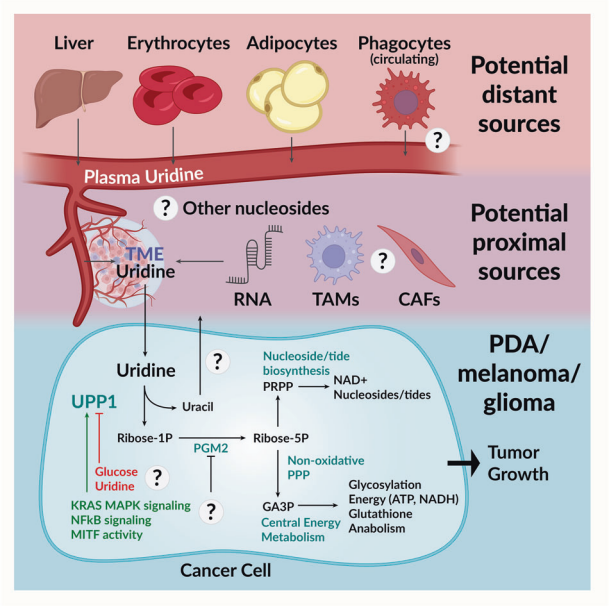


**Fig. 1 Uridine fuels dynamically-regulated cancer cell metabolism.** Uridine from several potential sources enters cancer cells, enabling continued tumor growth. Uridine sources include diverse cell types and RNA (based on published evidence), and could include other tumor cells (represented by "CAFs"). Other nucleosides (e.g., inosine, adenosine) may fuel tumors similarly, if available. Exogenous $^{13}C_5$(ribose)-uridine labeled carbon was traced using liquid chromatography mass spectrometry into the pentose phosphate pathway, central carbon metabolism, amino acid anabolism, glycosylation precursors, redox metabolites, and nucleotides; however, the fate and role of uracil after release by UPP1 is uncertain. UPP1 was regulated transcriptionally by major signaling mechanisms, but the integration of these signals with the unknown nutrient sensing axis remains unstudied. Finally, PGM2 (immediately downstream of UPP1) may also be important for tumor growth. Gray-highlighted question marks indicate areas needing further study. Red crossed lines indicate inhibition; green arrows indicate activation (transcriptionally). CAF cancer-associated fibroblast, GA3P glyceraldehyde 3-phosphate, PDA pancreatic ductal adenocarcinoma, PGM2 phosphoglucomutase-2, PRPP phosphoribosyl pyrophosphate, TAM tumor-associated macrophage, TME tumor microenvironment.

unaffected. Thus, an intratumoral source (e.g., cancer-associated fibroblasts (CAFs), or cellular decay leading to RNA release) may account for the non-plasma-derived uridine supply, especially since de novo synthesis by cancer cells would seem to require some level of futile cycling. More work is needed to determine whether macrophages are a key uridine source or consumer, given the uridine catabolism in cultured macrophages presented in the *Nature Metabolism* study.

One of the key findings from both studies was the path of uridine catabolism. Isotope tracing showed the contribution of uridine-derived ribose carbon to glycosylation, redox, and nucleotide metabolism, alongside central carbon metabolism and amino acid anabolism (Fig. 1). However, since both studies used $^{13}C_5$-uridine labeled only in the ribose ring, the fate of uracil after cleavage by UPP1 in cancer cells is unknown. We suspect, given the consistently strong net efflux of uracil, that much of this byproduct is discarded, but additional studies could investigate salvage or further catabolism. Further, in the *Nature* study only uridine was pursued, but other nucleosides were hits on the nutrient screen and follow a similar catabolic pathway.[11,12] The tumor-blunting effect of UPP1 knockout suggests that additional nucleoside catabolism is non-redundant, but targeted studies on catabolic activity in vivo and potential co-regulation (for efficient scavenging under stress conditions) are still warranted.

This research suggests that blocking uridine production, cancer cell uridine uptake, or nucleoside catabolism (e.g., at PGM2) could starve some cancers and be promising directions for therapy. However, the impact on organism-level uridine homeostasis and the potential for uridine catabolism blockade to sensitize/protect cancers to/against other treatments are important considerations. Finally, optimal targeting of uridine catabolism will likely require a stratified approach based on diabetic status and uridine transporter expression.

Overall, these two articles provide a detailed mechanistic framework on uridine as a stand-in metabolite for glucose in cancer, highlighting opportunities for therapeutic development.

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## ADDITIONAL INFORMATION

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