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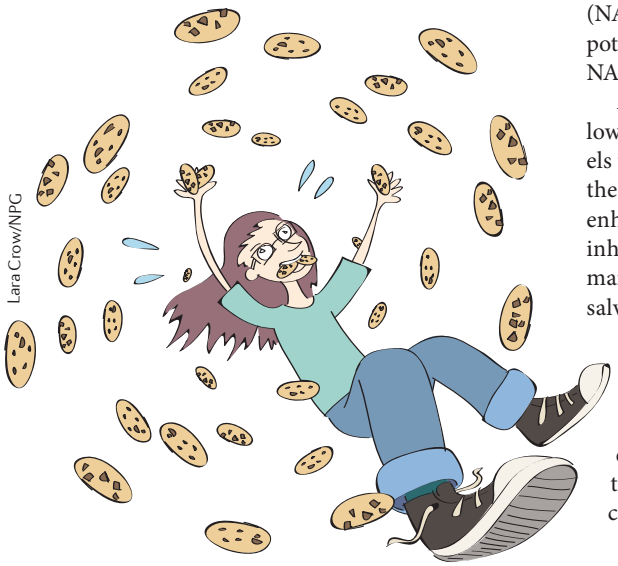
METABOLISM

Totally addicted to NAD$^+$

> the preclinical efficacy of making addicted cells 'go cold turkey'

Mutations in isocitrate dehydrogenase 1 (*IDH1*) and *IDH2* have been identified in several cancer types and result in increased levels of the oncometabolite 2-hydroxyglutarate (2-HG), which has been implicated in tumorigenesis and thus represents a therapeutic target. However, mutant IDH1 is also known to dysregulate other metabolic pathways. A study in *Cancer Cell* reports that the growth of some *IDH1*-mutant cancers is insensitive to 2-HG loss and instead depends on the addiction of these cells to NAD$^+$, a metabolic vulnerability that can be targeted by drugs that are already in clinical trials.

Despite potently reducing 2-HG levels in tumour cells, exposure to a specific inhibitor of mutant IDH1 (IDH1i) did not inhibit the *in vitro* growth of eight *IDH1*-mutant cell lines derived from three different cancer types or the *in vivo* growth of an orthotopically transplanted *IDH1*-mutant glioblastoma (MGG152) cell line. Using an unbiased systematic approach, the authors screened the metabolic profiles of MGG152 cells after both short-term and long-term IDH1i treatment *in vitro* and identified metabolites for which levels were significantly altered by IDH1i. These data highlighted the NAD$^+$/NADH cycling pathway, and further experiments demonstrated that IDH1i treatment significantly increased NAD$^+$ levels in MGG152 cells and other *IDH1*-mutant cell lines. In addition, inhibiting the rate-limiting enzyme of the NAD$^+$ salvage pathway, nicotinamide phosphoribosyltransferase (NAMPT), in *IDH1*-mutant cell lines potently reduced cell viability in an NAD$^+$-dependent manner.



Lara Crow/NPG

IDH1-mutant cell lines showed lower basal intracellular NAD$^+$ levels than *IDH1* wild-type cells, which the authors hypothesized could enhance sensitivity to NAMPT inhibition. Cellular NAD$^+$ pools are maintained by both the NAMPT salvage pathway and an alternative pathway that is rate-limited by nicotinate phosphoribosyltransferase 1 (NAPRT1). The authors found that expression of NAPRT1, but not that of NAMPT, correlated with cellular sensitivity to NAMPT inhibition, and they showed, using a tetracycline-inducible system, that mutant IDH1 expression significantly decreased levels of NAD$^+$ and NAPRT1. This suggested that suppression of the NAPRT1-mediated alternative salvage pathway in *IDH1*-mutant cells renders them vulnerable to further NAD$^+$ depletion through NAMPT inhibition. Indeed, NAPRT1 overexpression rescued *IDH1*-mutant cells from the effects of NAMPT inhibition.

Having identified a metabolic vulnerability in *IDH1*-mutant cells, the authors went on to demonstrate the *in vivo* efficacy of NAD$^+$ depletion in immunocompromised mice bearing *IDH1*-mutant xenograft tumours; NAMPT inhibitor treatment significantly reduced tumour growth in a heterotopic model and significantly prolonged survival in an orthotopic model.

In summary, this study reveals NAD$^+$ addiction as a previously unknown metabolic vulnerability in a proportion of *IDH1*-mutant cancers and demonstrates the preclinical efficacy of making addicted cells 'go cold turkey'. Notably, NAD$^+$-depleting NAMPT inhibitors are already in clinical trials for other cancer types and so could be readily repurposed for use in *IDH1*-mutant cancers.

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ORIGINAL ARTICLE Tateishi, K. *et al.* Extreme vulnerability of *IDH1* mutant cancers to NAD+ depletion. *Cancer Cell* **28**, 773–784 (2015)