

Spotlight

Leveraging valine-restriction-induced DNA damage for targeted cancer therapy

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Metabolite microenvironment shapes cancer treatment strategies. In a recent paper in *Nature*, Jin et al.¹ demonstrate that valine deprivation triggers HDAC6 entry into the nucleus, leading to accumulation of DNA damage that could be harnessed for targeted cancer therapy.

Metabolite homeostasis is essential for sustaining cellular functions and facilitating metabolic pathways necessary for life. Cells have evolved various mechanisms to sense and respond to fluctuations in metabolite concentrations, thereby preserving metabolic balance. Consequently, disruptions in metabolite homeostasis are intricately associated with the development and progression of metabolic disorders and cancer. Indeed, it is well established that metabolic dysregulation is a hallmark of cancer, highlighting the potential of targeting metabolic vulnerabilities as a strategy for cancer treatment.² In this regard, it was shown that the essential branched-chain amino acid valine plays a multifaceted role in neurological disorders and cancer progression beyond its contribution to protein synthesis.³ However, the mechanisms by which cells directly sense and respond to valine abundance, independent of tRNA and mammalian target of rapamycin complex 1 (mTORC1) pathways, remain elusive. A groundbreaking study published in *Nature* identified an unexpected role for human histone deacetylase 6 (HDAC6) as a sensor of cellular valine levels.¹ This discovery unravels a novel signaling pathway linking nutrient availability to DNA damage and opens exciting avenues for cancer therapy.

HDAC6 is a ubiquitously expressed deacetylase primarily known for its role in regulating microtubule dynamics and the clearance of misfolded proteins through aggresome formation. Jin et al. revealed a novel function of HDAC6 in sensing valine concentration, mediated by its primate-specific SE14 repeat domain. The authors elegantly demonstrated that

valine directly interacts with SE14 domain, with a dissociation constant (K_d) of around 1.95 μ M. Crucially, this interaction is specific to valine, and structural analysis suggests that specific amino acid residues within the SE14 domain form a binding pocket for valine, establishing a direct link between SE14 domain and valine-sensing capability of HDAC6. The authors also demonstrated that the intracellular valine concentration dictates the subcellular localization of HDAC6. Under normal valine conditions, HDAC6 is predominantly cytosolic. However, valine deprivation causes HDAC6 to migrate into the nucleus, a process dependent on valine binding by the SE14 domain of HDAC6. Once in the nucleus, HDAC6 interacts with and deacetylates ten-eleven translocation 2 (TET2), a key enzyme involved in active DNA demethylation. Deacetylation of TET2 enhances its enzymatic activity, leading to an increase in DNA hydroxymethylation (5hmC), a crucial intermediate in the demethylation process. This increased active DNA demethylation, mediated by the HDAC6-TET2 axis, subsequently promotes DNA damage through the action of thymine DNA glycosylase (TDG). TDG excises the oxidized DNA bases formed by TET2 activity, resulting in the formation of single-strand breaks (SSBs) and elevated levels of the double-strand break (DSB) marker γ H2AX. The consequences of this newly discovered valine-sensing pathway are profound, particularly in the context of cancer. Indeed, the authors provided compelling evidence showing that dietary valine restriction significantly inhibits tumor growth in xenograft models, especially when combined with poly (ADP-ribose) polymerase (PARP) inhibi-

tors (PARPis) (Figure 1A). This synergistic effect underscores the potential of targeting the HDAC6-TET2-TDG axis as a promising therapeutic strategy for cancer treatment.

While valine is an essential amino acid in mammals, the mechanism of its sensing by HDAC6 is primate specific, highlighting evolutionary diversity in response to valine deprivation. Similar species-specific variability in metabolite sensing has been reported previously; for instance, different sensors for arginine and methionine levels have been found in mammals, flies, and *C. elegans*, indicating species-specific nutrient-sensing mechanisms.⁴ These observations suggest that the sensing mechanisms of other amino acids may also exhibit species-specific characteristics.

Interestingly, two of the top valine interactors identified by Jin et al. are the peroxisomal proteins VWA8 and PEX14, yet the functional relevance of these interactions remains unknown. We propose that the peroxisome, which plays a central role in various metabolic processes including lipid and amino acid breakdown, may interact with valine as part of a signaling mechanism to regulate its catabolism. Under conditions of valine deficiency, it is plausible that peroxisomal valine catabolism is suppressed to fine-tune intracellular valine levels. Additionally, another high-scoring valine interactor is the DBT protein, a critical component of the mitochondrial branched-chain alpha-keto acid dehydrogenase (BCKD) complex involved in valine breakdown. Therefore, DBT may function as a metabolic switch, which senses valine deficiency and

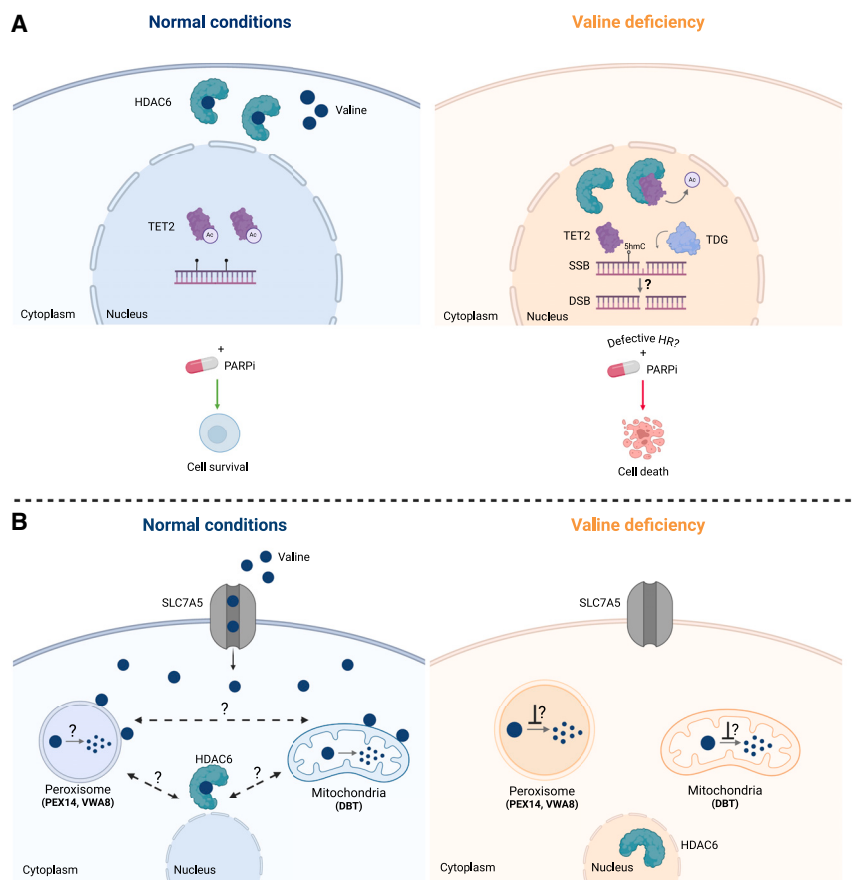


Figure 1. Linking valine homeostasis to genomic stability and precision cancer therapy

(A) Valine deficiency activates the HDAC6-TET2-TDG axis to induce DNA damage. Under normal conditions (left), valine retains HDAC6 in the cytoplasm. When valine is deprived (right), HDAC6 translocates to the nucleus, where it deacetylates TET2, enhancing its DNA demethylase activity and forming 5hmC. Next, TDG recognizes these modified bases and excises them, generating SSBs. These SSBs are likely converted into DSBs that sensitize cells to PARPis, possibly due to defective HR repair.

(B) Valine homeostasis in normal and deprived conditions. Under normal conditions (left), valine is transported into cells via the valine transporter SLC7A5, where it interacts with various proteins, including HDAC6, the peroxisomal proteins VWA8 and PEX14, and the mitochondrial protein DBT. Upon valine deprivation (right), the peroxisomal and mitochondrial valine-binding proteins likely detect the absence of valine and inhibit its catabolism, thereby contributing to the maintenance of residual cellular valine levels. This adaptive mechanism may help cells regulate valine availability during periods of scarcity. Figure was created using BioRender.

downregulates its catabolism to preserve its availability. Collectively, we propose that these identified valine interactors are part of an adaptive response that helps to maintain cellular homeostasis during valine deficiency (Figure 1B). Future research is needed to determine the functional relevance of these valine-interacting proteins and to investigate potential crosstalk between them.

The authors demonstrated that valine-deprived cells display heightened sensitivity to PARPis, both *in vitro* and *in vivo*. It is well established that PARPis hypersen-

sitize homologous-recombination (HR)-deficient tumors, due to their inability to repair DNA DSBs that arise from transcription-replication conflicts and the accumulation of replication-associated single-stranded DNA gaps.⁵ Therefore, future studies will be required to assess whether similar mechanisms underlie the sensitivity of valine-deprived cells to PARPis. If so, it would provide a rationale for assessing the therapeutic efficacy of other agents that target HR deficiency, such as Polθ inhibitors and ataxia telangiectasia and Rad3-related (ATR) inhibitors. In this regard,

accumulating evidence has established a direct link between metabolite homeostasis and the integrity of DSB repair. For example, the deprivation of specific metabolites, such as lactate, crotonyl-CoA, and acetyl-CoA, as well as the elevated levels of oncometabolites including 2-hydroxyglutarate, succinate, and fumarate modulate HR repair of DSBs.^{6–10} These findings underscore the clinical significance of utilizing DNA damage resulting from changes in metabolite homeostasis for personalized cancer therapy.

Jin et al. showed that specific conditions of valine deprivation can be harnessed for cancer therapy in mouse models, without impacting whole-organism characteristics such as body weight. However, a significant gap remains before this approach can be applied on humans, as the effect of valine deficiency in humans may differ substantially from those observed in experimental models. Moreover, understanding the effect of valine deprivation on the metabolic microenvironment across different types of human cancer is crucial, as it may reveal tumor heterogeneity that can profoundly affect treatment responses and outcomes.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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