

## Metabolism

**Major finding:** *IDH1*-mutant cancers are addicted to  $\text{NAD}^+$  and grow independent of 2HG levels.

**Mechanism:** Mutant IDH-driven reduction of *NAPRT1* confers sensitivity to  $\text{NAD}^+$  depletion via *NAMPT* inhibition.

**Impact:** Metabolic targeting is a potential therapeutic strategy for *IDH1*-mutant tumors.

IDH1-MUTANT CANCERS ARE SUSCEPTIBLE TO  $\text{NAD}^+$  DEPLETION

Mutations in isocitrate dehydrogenase 1 (*IDH1*) and *IDH2*, which have been identified in multiple tumor types, result in the reduction of  $\alpha$ -ketoglutarate ( $\alpha$ -KG) to the  $\alpha$ -KG analog 2-hydroxyglutarate (2HG), which has been associated with the hypermethylator phenotype of *IDH*-mutant cancers. Given that mutant *IDH1* has also been shown to alter classical metabolic pathways, Tateishi and colleagues used a mutant *IDH1*-specific inhibitor (*IDH1i*), which inhibits 2HG formation, to perform an unbiased screen of *IDH1*-mutant glioma tumor-initiating cell (TIC) tumorsphere lines to identify targetable metabolic vulnerabilities. Treatment of TICs with *IDH1i* resulted in decreased 2HG but did not alter TIC growth or global methylation *in vitro* or *in vivo*. Short- and long-term inhibition of mutant *IDH1* resulted in a significant increase of metabolites related to the  $\text{NAD}^+$ / $\text{NADH}$  shuttle system, which suggested that  $\text{NAD}^+$  was a potential therapeutic target. Consistent with this finding, *IDH1*-mutant TIC lines exhibited significantly lower levels of  $\text{NAD}^+$ / $\text{NADH}$  and decreased expression of a rate-limiting enzyme in the  $\text{NAD}^+$  salvage pathway, nicotinate phosphoribosyltransferase (*NAPRT1*), compared with *IDH1*-wild-type TIC lines. Further-



more, rescue experiments showed that mutant *IDH1* downregulated *NAPRT1*, possibly by *NAPRT1* promoter hypermethylation, which resulted in reduced  $\text{NAD}^+$  levels and sensitization of *IDH1*-mutant cells to inhibition of nicotinamide phosphoribosyltransferase (*NAMPT*), another rate-limiting  $\text{NAD}^+$  salvage enzyme. Accordingly, treatment with *NAMPT* inhibitors resulted in a significant reduction of intracellular  $\text{NAD}^+$ / $\text{NADH}$  and cell death in *IDH1/2*-mutant cancer cell lines. *NAMPT* inhibitor-mediated  $\text{NAD}^+$  depletion resulted in the disruption of the tricarboxylic acid cycle and induction of AMP-activated protein kinase-mediated autophagy in *IDH1*-mutant cancer cells *in vitro*, and inhibited the growth of *IDH1*-mutant tumors *in vivo*. Together, these results show that *IDH1* mutations promote selective addiction of cancer cells to the metabolite  $\text{NAD}^+$ , resulting in a metabolic vulnerability that can be therapeutically targeted by inhibitors that are currently in clinical development. ■

Tateishi K, Wakimoto H, Iafrate AJ, Tanaka S, Loebel F, Lelic N, et al. Extreme vulnerability of *IDH1* mutant cancers to  $\text{NAD}^+$  depletion. *Cancer Cell* 2015;28:773–84.

## Lymphoma

**Major finding:** *RRAGC* mutations in follicular lymphoma activate *mTORC1*, even during amino acid depletion.

**Approach:** Exome sequencing together with *in vitro* experiments highlight the role of *RRAGC* mutants.

**Impact:** *RRAGC* mutations may be exploitable as therapeutic targets in patients with follicular lymphoma.

RRAGC MUTATIONS ACTIVATE *mTORC1* SIGNALING IN FOLLICULAR LYMPHOMA

Follicular lymphoma is a B-cell neoplasm with characteristic mutations in epigenetic regulators and the t(14;18) translocation. Genome-wide genetic profiling provides the opportunity to discover novel biomarkers. To address this, Okosun, Wolfson, and colleagues performed exome sequencing on successive tumor biopsies from five patients with follicular lymphoma. In the discovery cohort, 4 of 5 patients had somatic mutations in RAS-related GTP binding C (*RRAGC*) which were observed in the dominant clone and maintained during disease progression. Targeted sequencing of a larger cohort of patients with follicular lymphoma found *RRAGC* mutations in 17% of patients, which were primarily missense mutations in highly conserved residues in the nucleotide-binding domain. *RRAGC* mutations were rare in other hematologic malignancies and nonhematologic cancers, suggesting a functional importance of this mutation in follicular lymphoma. *RRAGC* encodes RagC, which forms heterodimers with other RAG proteins and complexes with the vacuolar ATPase (V-ATPase) to activate *mTOR* complex 1 (*mTORC1*).

The genes encoding two subunits of the V-ATPase complex, *ATP6V1B2* and *ATP6A1*, were also frequently and mutually exclusively mutated in follicular lymphoma, and strongly correlated with the presence of *RRAGC* mutations. RNA sequencing of *RRAGC*-mutant follicular lymphoma tumors showed upregulation of *mTOR* targets compared to wild-type. The binding of RAG GTPase heterodimers to *mTORC1* is essential for its amino acid-induced activation, and mutant RagC exhibited increased binding to the *mTORC1* subunit Raptor. Further, RagC mutants activated *mTORC1*, even under conditions of amino acid deprivation. Taken together, these findings indicate that mutations in *RRAGC* activate *mTORC1* signaling independent of amino acid availability and suggest that RagC may be an effective therapeutic target in follicular lymphoma. ■

Okosun J, Wolfson RL, Wang J, Araf S, Wilkins L, Castellano BM, et al. Recurrent *mTORC1*-activating *RRAGC* mutations in follicular lymphoma. *Nat Genet* 2015 Dec 21 [Epub ahead of print].