Metabolism

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

Mechanism: Mutant IDH–driven reduction of NAPRT1 confers sensitivity to NAD^+ depletion via NAMPT inhibition.

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

IDH1-MUTANT CANCERS ARE SUSCEPTIBLE TO NAD^+ DEPLETION

Mutations in isocitrate dehydrogenase 1 (*IDH1*) and *IDH2*, which have been identified in multiple tumor types, result in the reduction of α-ketoglutarate (α-KG) to the α-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 NAD^+/NADH shuttle system, which suggested that NAD^+ was a potential therapeutic target. Consistent with this finding, *IDH1*-mutant TIC lines exhibited significantly lower levels of NAD^+/NADH and decreased expression of a rate-limiting enzyme in the NAD^+ salvage pathway, nicotinate phosphoribosyltransferase (NAPRT1), compared with *IDH1*–wild-type TIC lines. Furthermore, rescue experiments showed that mutant IDH1 downregulated *NAPRT1*, possibly by *NAPRT1* promoter hypermethylation, which resulted in reduced NAD^+ levels and sensitization of *IDH1*-mutant cells to inhibition of nicotinamide phosphoribosyltransferase (NAMPT), another rate-limiting NAD^+ salvage enzyme. Accordingly, treatment with NAMPT inhibitors resulted in a significant reduction of intracellular NAD^+/NADH and cell death in *IDH1/2*-mutant cancer cell lines. NAMPT inhibitor–mediated 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 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 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 *ATP6AP1*, 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].*