Published OnlineFirst October 25, 2012; DOI: 10.1158/2159-8290.CD-RW2012-188

Lymphoma

Major finding: Diffuse large B-cell lymphoma (DLBCL) subgroups have distinct metabolic signatures.

Concept: Heterogeneity in fuel utilization programs can exist among tumors of the same type.

Impact: Inhibition of mitochondrial fuel oxidation may be toxic to DLBCLs that do not depend on BCR signaling.

DIFFUSE LARGE B-CELL LYMPHOMAS ARE METABOLICALLY HETEROGENEOUS

Diffuse large B-cell lymphomas (DLBCL) are aggressive tumors with genetic and clinical variability. DLBCL has been classified into several molecular subgroups based on transcriptional profiling, suggesting that different pathogenic mechanisms and therapeutic targets may exist within this disease. For example, B-cell receptor (BCR) signaling is critical to the survival of a subset of DLBCLs, and inhibitors of BCR signaling show activity in these tumors. Another DLBCL subgroup shows upregulation of genes involved in mitochondrial oxidative phosphorylation (OxPhos), but the functional implications of this transcriptional signature are unclear. OxPhos DLBCLs do not have functional BCR signaling and are insensitive to BCR inhibition, suggesting that they are dependent on alternative survival mechanisms. Caro and colleagues hypothesized that the OxPhos subgroup is metabolically distinct from other DLBCLs and showed that the mitochondrial proteome of OxPhos DLBCL cells was significantly enriched for enzymes involved in mitochondrial β-oxidation, the tricarboxylic acid cycle (TCA cycle), oxidative phosphorylation, and detoxification of reactive oxygen species compared with non-OxPhos DLBCL cells. Furthermore, OxPhos DLBCL cells utilized nutrients differently than non-OxPhos DLBCL cells, as OxPhos cells diverted glucose into the TCA cycle and generated ATP and biosynthetic intermediates from fatty acid oxidation. Most of the total cellular energy of OxPhos cells was derived from mitochondrial oxidative metabolism as opposed to BCR DLBCL, which primarily depended on aerobic glycolysis. Notably, OxPhos DLBCL cells were selectively sensitive to pharmacologic or genetic inhibition of fatty acid oxidation, suggesting that the metabolic features of this subtype could be exploited therapeutically. These findings indicate that a unique metabolic program is activated in a subset of DLBCLs that confers growth and survival advantages and highlight the metabolic heterogeneity that can exist even within a single tumor type. ■

Caro P, Kishan AU, Norberg E, Stanley IA, Chapuy B, Ficarro SB, et al. Metabolic signatures uncover distinct targets in molecular subsets of diffuse large B cell lymphomas. Cancer Cell 2012;22:547–60.

Autophagy

Major finding: AKT-mediated phosphorylation of Beclin 1 inhibits autophagy and promotes tumorigenesis.

Mechanism: Phosphorylation enhances Beclin 1 interaction with 14-3-3 and intermediate filament proteins.

Impact: Inhibition of AKT-driven Beclin 1 modification enhances autophagy and impairs tumor formation.

AKT PROMOTES TUMORIGENESIS VIA REGULATION OF A CORE AUTOPHAGY PROTEIN

Autophagy is a catabolic process in which damaged cellular proteins and organelles are degraded via the lysosome and can be induced by nutrient starvation. Increasing evidence suggests that autophagy has a role in tumor suppression and can be inhibited by aberrant AKT activation in human cancer, in part through its downstream target mTOR. Because AKT also inhibited autophagy in the presence of an mTOR inhibitor, Wang and colleagues examined whether AKT negatively regulates this process by directly modulating components of the core autophagy machinery, in particular the tumor suppressor Beclin 1, which contains 2 potential AKT phosphorylation motifs. AKT interacted with endogenous Beclin 1 and promoted its phosphorylation at 2 serine residues within these motifs; this Beclin 1 modification was associated with increased AKT activation in multiple human tumor cell lines and resulted in reduced Beclin 1–associated class III phosphoinositide 3-kinase VPS34 activity. Mutation of these serines to alanine impaired AKT-mediated autophagy suppression and decreased AKT-driven fibroblast transformation, suggesting that the protumorigenic effects of AKT are partially mediated via Beclin 1 phosphorylation. Indeed, tumors expressing active AKT and the nonphosphorylatable Beclin 1 mutant exhibited reduced proliferation, increased apoptosis and autophagy, and a less invasive phenotype compared with tumors expressing wild-type Beclin 1. Mechanistically, AKT-mediated phosphorylation stimulated binding of Beclin 1 to 14-3-3 and intermediate filament proteins, including keratin 18 and vimentin, whereas this interaction was blocked by starvation or by expression of dominant negative AKT or mutant Beclin 1. Importantly, this interaction of Beclin 1 with vimentin was necessary for autophagy inhibition and AKT-dependent transformation. Taken together, these results define a mechanism by which oncogenic kinase signaling promotes tumorigenesis via regulation of autophagy effectors and cytoskeletal proteins. ■

Wang RC, Wei Y, An Z, Zou Z, Xiao G, Bhagat G, et al. Akt-mediated regulation of autophagy and tumorigenesis through Beclin 1 phosphorylation. Science 2012 Oct 25 [Epub ahead of print].