

Metabolism

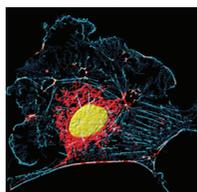
Major finding: PI3K induces cytoskeletal reorganization, leading to release and activation of actin-bound aldolase.

Mechanism: PI3K activates RAC to remodel the actin cytoskeleton and coordinate glycolysis, independent of AKT.

Impact: *PIK3CA* mutations may result in excess free cytoplasmic aldolase that can drive tumor glycolysis.

PI3K PROMOTES GLYCOLYSIS THROUGH RELEASE OF CYTOSKELETAL ALDOLASE

The PI3K pathway is involved in the regulation of glucose metabolism and remodeling of the actin cytoskeleton, and alterations in PI3K signaling occur frequently in epithelial cancers. However, the coordination of these two processes by PI3K is not fully understood. Hu and colleagues found that PI3K inhibitors resulted in decreased glycolytic capacity in mammary epithelial cells, whereas AKT and mTOR inhibitors did not have this effect. Quantification of steady-state metabolite levels indicated that inhibition of PI3K, but not AKT, reduced the levels of the products of the aldolase reaction, indicating that PI3K regulates flux through the aldolase step of glycolysis. Further, aldolase activity increased with insulin stimulation of PI3K signaling or in response to activating *PIK3CA* mutations, due to the release of aldolase from actin filaments in the cytoskeleton into the cytoplasm following PI3K activation. The mobilization of aldolase from F-actin into the cytoplasm activates the enzymatic activity of aldolase and was mediated by PI3K activation of RAC. A RAC1 inhibitor prevented insulin-induced aldolase activity and mobilization,



but not AKT phosphorylation. To test the effects of PI3K inhibition on glycolysis in cancer *in vivo*, a BRCA1-related breast cancer mouse model was used. In this model, PI3K inhibitors decreased the rate of conversion of ^{13}C -pyruvate to ^{13}C -lactate by 40%–50%, consistent with a reduction in mid- or lower glycolysis, independent of glucose uptake.

In vivo isotope tracing analyses confirmed that PI3K inhibitors target the aldolase step of glycolysis, with the sharpest drop in ^{13}C -glucose metabolites occurring in an aldolase product. Taken together, these data integrate the glycolytic and cytoskeletal roles of PI3K signaling, and show that PI3K-mediated activation of RAC leads to the release of active aldolase from the actin cytoskeleton independent of AKT, allowing for maximal glycolytic rate. These findings may be helpful in guiding the selection of PI3K versus AKT inhibitors for cancer treatment. ■

Hu H, Juvekar A, Lyssiotis CA, Lien EC, Albeck JG, Oh D, et al. Phosphoinositide 3-kinase regulates glycolysis through mobilization of aldolase from the actin cytoskeleton. *Cell* 2016;164:433–46.

Drug Resistance

Major finding: In TNBC c-MET increases PARP enzymatic activity and promotes resistance to PARP inhibitors.

Mechanism: c-MET binds to and phosphorylates PARP at Tyr907, blocking its interaction with PARP inhibitors.

Impact: Combined treatment with PARP and c-MET inhibitors may prevent resistance to PARP inhibition.

TUMOR SUPPRESSION BY PARP INHIBITORS IS POTENTIATED BY c-MET INHIBITION

PARP is recruited to reactive oxygen species (ROS)-induced DNA damage sites, where it is involved in the DNA-repair process. Thus, PARP inhibitors can prevent DNA repair and promote cell death, and have shown promise as cancer therapeutics. However, many tumors exhibit resistance to PARP inhibitors. Du and colleagues investigated the mechanism of resistance in triple-negative breast cancer (TNBC) cells. PARP1 activity was associated with ROS, which can activate receptor tyrosine kinases (RTK), and a screen identified three RTKs that associate with PARP in response to ROS, of which MET was the only RTK more highly expressed in TNBC than non-TNBC. Under oxidative stress, c-MET was transported to the nucleus where it interacted with PARP, and combined treatment with PARP and c-MET inhibitors increased the sensitivity of TNBC cells to PARP inhibition. TNBCs often harbor mutations in or downregulation of BRCA1/2, and reduction of BRCA1 or BRCA2 expression resulted in increased sensitivity to PARP inhibitors only in cells with low c-MET levels. The

kinase activity of c-MET was required to promote the DNA-repair function of PARP via phosphorylation at tyrosine 907 (Y907), and the phosphorylation reduced binding to PARP inhibitors. Combined treatment with PARP and c-MET inhibitors potentiated the effects of PARP inhibition, *in vitro* and in xenograft tumor models, resulting in reduced tumor growth accompanied by increased apoptosis and DNA damage. Additionally, this combination was well tolerated in mice. Similar results were observed in a lung cancer xenograft model. Taken together, these findings indicate that phosphorylation of PARP at Y907 may be a useful biomarker for PARP inhibition in patients, and that c-MET promotes resistance to PARP inhibitors, suggesting that combined inhibition with c-MET may be effective in reducing resistance to PARP inhibitors. ■

Du Y, Yamaguchi H, Wei Y, Hsu JL, Wang H-L, Hsu Y-H, et al. Blocking c-Met-mediated PARP1 phosphorylation enhances anti-tumor effects of PARP inhibitors. *Nat Med* 2016;22:194–201.

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CANCER DISCOVERY

PI3K Promotes Glycolysis through Release of Cytoskeletal Aldolase

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