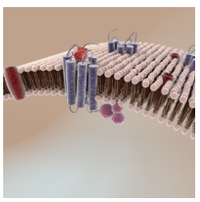
Signal Transduction

Major finding: Lipids modulate SH2 domain–mediated binding to pY-containing signal transducers.

Mechanism: Lipids bind to variable sites in SH2 domains to control SH2-mediated protein–protein interactions.

Impact: Targeting lipid-binding sites on SH2 domains may abrogate pY-mediated signaling pathways.

LIPIDS REGULATE SH2-MEDIATED PROTEIN–PROTEIN INTERACTIONS AND SIGNALING



The Src homology 2 (SH2) domain is a protein interaction domain (PID) contained within SRC and other intracellular signal-transducing proteins, many of which drive tumorigenesis, which mediates protein–protein interactions via the docking of SH2 domain–containing proteins to phosphotyrosine (pY) residues on other proteins. Membrane lipids have recently been shown to regulate protein–protein interactions mediated by a different PID and to bind to several SH2 domains. To elucidate the role of lipids in SH2 domain–mediated protein–protein interactions and signal transduction, Park, Sheng, Silkov, Jung, and colleagues performed surface plasmon resonance analysis to systematically characterize the binding affinities of 76 of the 121 known SH2 domains for plasma membrane (PM)–mimetic vesicles which recapitulate the lipid profile of cytofacial PM. Sixty-eight out of the 76 SH2 domains analyzed exhibited moderately high to high levels of affinity for PM-mimetic vesicles. Twelve of 18 SH2 domains exhibited high selectivity for phosphoinositides (PtdIns*P*), which play important roles in cellular signaling, and PtdIns*P*s were shown to control the recruitment of SH2 domains to the PM. SH2 domains were shown to contain both pY binding pockets and alternate cationic patches, the latter of which were shown to be the primary PtdIns*P*-binding sites in SH2 domains. Binding of PtdIns*P* to the SYK family member zeta-chain T-cell receptor (TCR) associated protein kinase 70 kDa (ZAP70), which contains SH2 domains that bind to TCR, was crucial for ZAP70-mediated downstream T-cell signaling. Similarly, nonspecific lipid binding was required for autophosphorylation of the nonreceptor tyrosine kinase PTK6, an intracellular signal transducer which is upregulated in several types of cancer, including breast cancer. Together, these results show that lipids spatiotemporally modulate protein–protein interactions mediated by SH2 domains in intracellular pY-containing signal transducers to control signaling pathways, and that this pathway represents a potential therapeutic target for patients with cancers driven by SH2 domain–containing proteins. ■

Park M-J, Sheng R, Silkov A, Jung D-J, Wang Z-G, Xin Y, et al. SH2 domains serve as lipid-binding modules for pTyr-signaling proteins. Mol Cell 2016;62:7–20.

Metabolism

Major finding: mTORC1 reprograms metabolism to promote cell survival following glycolytic block.

Mechanism: mTORC1 enhances glucose-derived metabolite entry into the TCA cycle via the pentose phosphate pathway.

Impact: Inhibition of mTORC1 signaling may potentiate the antitumor effects of inhibiting glycolysis.

mTORC1 SIGNALING ALLOWS CANCER CELLS TO ESCAPE GLYCOLYTIC DEPENDENCY

Glycolysis is elevated in many tumors despite the presence of oxygen; however, glycolysis inhibitors, including the glucose analog 2-deoxy-D-glucose (2DG), have not been successful in clinical trials. Pusapati and colleagues hypothesized that tumors might escape glycolytic dependence via utilization of other metabolites or metabolic pathways. To begin to model the escape from glycolysis dependency, a panel of cancer cell lines were treated with 2DG and classified as glycolysis-dependent or glycolysis-independent based on the response. The glycolysis-independent cells exhibited increased oxidative phosphorylation, which was promoted by glutamine. Consistent with these findings, glutamine could rescue the growth of glycolysis-independent cells, but not glycolysis-dependent cells, under glycolytic stress. In glycolysis-independent cells, treatment with 2DG drove glucose carbons through the pentose phosphate pathway and back into glycolysis, allowing glucose to continue to contribute metabolic precursors to the TCA cycle when glycolysis is disrupted. Treatment with 2DG reduced mTORC1 signaling in glycolysis-dependent but not glycolysis-independent cells, suggesting that sustained mTORC1 signaling contributes to glycolytic independence. Indeed, activation of mTORC1 in glycolysis-dependent cells rescued them from 2DG toxicity, and treatment of glycolysis-independent cell xenografts with 2DG and everolimus, a clinical mTORC1 inhibitor, reduced tumor burden. In an orthogonal approach to inhibit glycolysis *in vivo*, glucose-6-phosphate isomerase (GPI), the enzyme inhibited by 2DG, was inducibly knocked down to mimic 2DG treatment. GPI silencing initially inhibited tumor growth, but tumors eventually became glycolysis-independent. However, everolimus inhibited glycolysis-independent tumor growth, further supporting the importance of mTORC1 in promoting glycolysis independence *in vivo*. Altogether, these findings indicate that mTORC1 signaling drives metabolic rewiring to allow tumor cells to become glycolysis independent, suggesting that mTORC1 pathway inhibition may enhance the efficacy of glycolysis inhibitors. ■

Pusapati RV, Daemen A, Wilson C, Sandoval W, Gao M, Haley B, et al. mTORC1-dependent metabolic reprogramming underlies escape from glycolysis addiction in cancer cells. Cancer Cell 2016 Mar 24 [Epub ahead of print].