Metabolism

Major finding: Low glucose-sensitive cancer cells have impaired OXPHOS up-regulation and respond to phenformin.

Concept: Complex I mtDNA mutations or defective glucose utilization confer sensitivity to glucose limitation.

Impact: Glucose utilization defects or mtDNA mutations may identify tumors more likely to respond to biguanides.

METABOLIC STATUS DETERMINES CANCER CELL SENSITIVITY TO LOW GLUCOSE

Rapidly proliferating tumors must satisfy energetic demands for cell growth and replication and adapt to diminished nutrient concentrations within the tumor microenvironment. In an effort to identify cancer cell metabolic dependencies under chronic low-glucose conditions, Birsoy and colleagues used a continuous-flow culture system that maintains cells at a steady low-glucose concentration to perform a long-term competitive proliferation assay of 28 pooled patient-derived cancer cell lines in culture. The proliferative response to glucose limitation was diverse, as most cell lines were unaffected, but others showed impaired or enhanced growth. An RNAi screen of human metabolic genes identified the nuclear-encoded components of mitochondrial oxidative phosphorylation (OXPHOS) as necessary for optimal proliferation of cancer cells under low-glucose conditions. Consistent with this finding, low glucose-sensitive cell lines had a significantly reduced ability to increase their oxygen consumption rates under glucose limitation that correlated with either reduced expression of *GLUT3* and *GLUT1* glucose transporters or heteroplasmic mutations in the mitochondrial genome-encoded (mtDNA) respiratory chain complex I subunits, suggesting that impaired glucose utilization and mitochondrial dysfunction are two distinct mechanisms that confer low-glucose sensitivity. Interestingly, cancer cell lines with these metabolic features were 5- to 20-fold more sensitive to OXPHOS inhibition with phenformin, a potent biguanide compound used as an antidiabetic agent, under glucose limitation *in vitro* and in a murine tumor xenograft model. Overexpression of GLUT3 in cells with glucose utilization defects or ectopic expression of the yeast ubiquinone oxidoreductase NDI1 to allow bypass of complex I in cells with mtDNA complex I mutations rescued the defects in oxygen consumption rate and proliferation caused by glucose limitation as well as phenformin sensitivity *in vitro* and in mouse tumor xenografts. Together, these findings suggest that impaired glucose utilization and mtDNA complex I mutations may be used to predict sensitivity of tumors to OXPHOS inhibition with biguanides. ■

Birsoy K, Possemato R, Lorbeer FK, Bayraktar EC, Thiru P, Yucel B, et al. Metabolic determinants of cancer cell sensitivity to glucose limitation and biguanides. Nature 2014;508:108–12.

Immunotherapy

Major finding: Localized Newcastle disease virus (NDV) therapy induces a systemic antitumor inflammatory response.

Clinical relevance: Local NDV therapy and systemic CTLA-4 blockade led to distant tumor rejection and antitumor immunity.

Impact: Oncolytic virotherapy may improve the clinical efficacy of immune checkpoint inhibitors.

LOCALIZED ONCOLYTIC VIROTHERAPY HAS DISTANT ANTITUMOR EFFECTS

Localized administration of oncolytic viruses that preferentially infect and kill cancer cells has shown antitumor activity, but the effects on distant or metastatic tumors are unknown. To recapitulate the effects of localized oncolytic virotherapy on metastatic disease, Zamarin and colleagues used a bilateral flank tumor model in which only one tumor was injected with Newcastle disease virus (NDV), a nonpathogenic oncolytic virus that has been safely used in clinical trials. Although viral replication was limited to the injection site, NDV treatment stimulated a potent inflammatory response that delayed growth and induced infiltration by innate and effector T cells of both local and distant tumors. This NDV-driven response was tumor antigen specific and required $CD8^+$ T cells, natural killer cells, and type I IFN. However, NDV therapy only induced complete contralateral tumor regression in approximately 10% of treated mice, suggesting that immunosuppressive tumor microenvironments limited the effect of the NDV-induced inflammatory response. Consistent with this possibility, the T-cell inhibitory receptor cytotoxic T-lymphocyte antigen 4 (CTLA-4) was upregulated on tumor-infiltrating T cells, prompting the authors to hypothesize that NDV therapy might sensitize tumors to CTLA-4 blockade. Indeed, combining localized NDV therapy with systemic anti-CTLA-4 antibody therapy led to greater bilateral tumor rejection, long-term survival, and protection against tumor rechallenge than either agent alone. The efficacy of this combination therapy was successfully extended to cancer cell types that are known to be strongly resistant to virus-mediated lysis, further demonstrating that NDV mediates its antitumor effects by stimulating the innate and adaptive immune system rather than by direct lysis. In addition to showing that localized oncolytic therapy activates a tumor-specific systemic antitumor inflammatory response that enhances lymphocyte infiltration of distant tumors, these findings provide a rationale for combination immunotherapy with oncolytic viruses and immune checkpoint inhibitors. ■

Zamarin D, Holmgaard RB, Subudhi SK, Park JS, Mansour M, Palese P, et al. Localized oncolytic virotherapy overcomes systemic tumor resistance to immune checkpoint blockade immunotherapy. Sci Transl Med 2014;6:226ra32.