Abundant nutrients are essential for the growth of highly proliferative cancer cells to support biosynthetic reactions. Otto Warburg first observed that cancer cells take up glucose at a surprisingly high rate and convert a large majority into lactate to prevent its entry into the TCA cycle.1 Although at first glance this seems quite wasteful, new paradigms have hypothesized that the “Warburg effect” gives a selective advantage to cells, because glucose diverted from the TCA cycle can contribute to producing the large amounts of cellular biomass required for growth and division.1 Renewed interest in the “Warburg effect” has led to the conclusion that glutamine is also essential for fast-growing cells.2 As with glucose, glutamine uptake is under the control of oncogenic signaling pathways. When glutamine enters the cell, it is converted to glutamate by glutaminase enzymes, which can be catabolized into α-ketoglutarate and enter a truncated TCA cycle to produce energy and other biomass precursors, or converted into glutathione in order to dampen oxidative stress.

Enhanced utilization of nutrient metabolism often depletes its local supply, resulting in tumor cells encountering nutrient-deprived conditions. For example, it has been shown that glucose levels are significantly lower in bulk tumor specimens than those in normal tissues of the same tissue origins.3 Recent studies have advanced the field’s understanding of how cells sense and adapt to glucose levels. For example, it was demonstrated that AMPK is activated in response to glucose deprivation in order to promote survival, and abrogation of this association leads to cell death.4 Thus, adaptation to metabolic stress is a dynamic process, and investigating its intricacies is essential for understanding cancer progression and therapeutic potentials. Interestingly, it was reported many years ago that glutamine levels are almost undetectable in solid tumors when compared with surrounding healthy tissues.6 These findings present a paradox: if glutamine is critical for cancer cell survival and progression, then how can cells survive when glutamine levels are so low?

With this question in mind, we recently sought mechanisms used by cells in order to adapt to glutamine deprivation. Previously, we demonstrated that the protein phosphatase 2A (PP2A) binding protein α4 is an essential regulator of PP2A activity and can protect cells from various stress conditions.7 PP2A is a major serine/threonine phosphatase found in two distinct states: (1) the inactive state, where α4 is bound to the catalytic (C) subunit to prevent its degradation, and (2) the active state consisting of the C subunit in a complex with a scaffold (A) subunit and regulatory (B) subunit. It is the B subunit that conveys subcellular localization and substrate specificity. When PP2A activity is required, α4 releases the C subunit to promote formation of an adaptive PP2A A/B/C complex that dephosphorylates numerous substrates depending on the regulatory subunit contained in the complex.

Upon different nutrient stresses, ectopic expression of α4 significantly protected mouse embryonic fibroblasts (MEFs) from glutamine deprivation, but not other nutrient depletions.8 Because α4 maintains PP2A in an inactive state until stress conditions arise, we examined which B subunit was responsive to glutamine deprivation in order to determine the specific PP2A complex important for low-glutamine cell survival. Various experiments confirmed that only one regulatory subunit, B55α, was induced at the transcriptional level and incorporated into an active PP2A complex upon glutamine deprivation, and this activity was greatly enhanced in cells with ectopic α4 expression.9 Indeed, B55α-deficient cells showed reduced ability to survive low glutamine levels. Further experiments identified that the PP2A-B55α target responsible for glutamine survival was EDD, a HECT-domain containing E3 ligase, which binds and inhibits p53. We found that, upon glutamine deprivation, PP2A-B55α dephosphorylates EDD and allows for p53 activation, leading to a metabolic checkpoint similar to glucose deprivation (Fig. 1). This p53 activation was enhanced in cells with ectopic expression of α4 and dependent on B55α.4 Although the exact role of p53 in terms of key target gene activation and cell survival mechanism in response to glutamine depletion is unclear, we have observed B55α-dependent induction of p53 target cell cycle arrest genes such as Cdkn1 (p21) and Gadd45a, suggesting that activation of a proliferative block may be a key component for low-glutamine cell survival.

How cells survive transient periods of nutrient starvation remains a critical and open question for the progression of cancer therapies. Targeting glutamine metabolism with specific glutaminase inhibitors has been attempted in the clinical, but high toxicity and severe side effects have curbed...
the enthusiasm for such drugs. It is possible that glutaminase inhibitor treatment leads cells to behave similar to glutamine deprived conditions in that they activate a survival mechanism. Our study suggests a more efficient therapeutic strategy may include a combination of glutamine metabolism inhibitors while subsequently blocking the survival mechanism. In addition, our study also highly suggests that disrupting glutamine metabolism in p53-deficient tumors may have strong therapeutic benefit.

References
1. Vander Heiden MG, et al. Science 2009; 324:1029-33; PMID:19460998; http://dx.doi.org/10.1126/science.1160809
2. DeBerardinis RJ, et al. Proc Natl Acad Sci USA 2007; 104:19345-50; PMID:18032601; http://dx.doi.org/10.1073/pnas.0709747104
3. Urasaki Y, et al. PLoS One 2012; 7:e36775; PMID:22615809; http://dx.doi.org/10.1371/journal.pone.0036775
4. Jones RG, et al. Mol Cell 2005; 18:283-93; PMID:15866171; http://dx.doi.org/10.1016/j.molcel.2005.03.027
5. Sen N, et al. Mol Cell 2011; 44:621-34; PMID:22099309; http://dx.doi.org/10.1016/j.molcel.2011.08.044
6. Roberts E, et al. Cancer Res 1949; 9(3 pl):645-8, 3; PMID:15392817
7. Kong M, et al. Mol Cell 2009; 36:51-60; PMID:19818709; http://dx.doi.org/10.1016/j.molcel.2009.09.025
8. Reid MA, et al. Molecular Cell 2013; In press