

Cancer's insatiable appetite

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Seemingly unrelated mutations that drive cancer share the ability to promote nutrient uptake and metabolism conducive to cell growth.

Human cancers occur as a consequence of genetic alterations that promote uncontrolled cell proliferation outside the context of normal tissues. Mutations in oncogenes and tumor suppressor genes influence various cellular processes, such as signal transduction and gene expression, but it remains unclear how different combinations of diverse genetic alterations synergize to cause unrestricted cell growth. Two recent reports^{1,2} in *Science* provide new evidence that otherwise unrelated oncogenic events elicit the common effect of facilitating glucose uptake and metabolism (Fig. 1). The studies provide further insights into the central role of nutrient uptake and altered metabolism in early tumorigenesis and suggest that treatment strategies that exploit the unique metabolic needs of cancer cells may be less susceptible to the development of drug resistance.

In one study, Hao *et al.*¹ showed that the nuclear mitochondrial gene *SDH5* is frequently mutated in a form of hereditary paraganglioma, a rare neuroendocrine tumor. *SDH5* is not part of a signaling pathway that controls cell growth but an essential component of central carbon metabolism. The authors found that *SDH5* is indispensable for the assembly of a functional succinate dehydrogenase complex, which acts both as the electron transport chain complex II (ETC II) and as an enzyme in the tricarboxylic acid cycle, where it catalyzes the oxidation of succinate to fumarate. As a consequence, the loss-of-function mutations identified in *SDH5* will disrupt tricarboxylic acid cycle flux and likely cause succinate accumulation.

Interestingly, mutations in three subunits of the succinate dehydrogenase complex, all

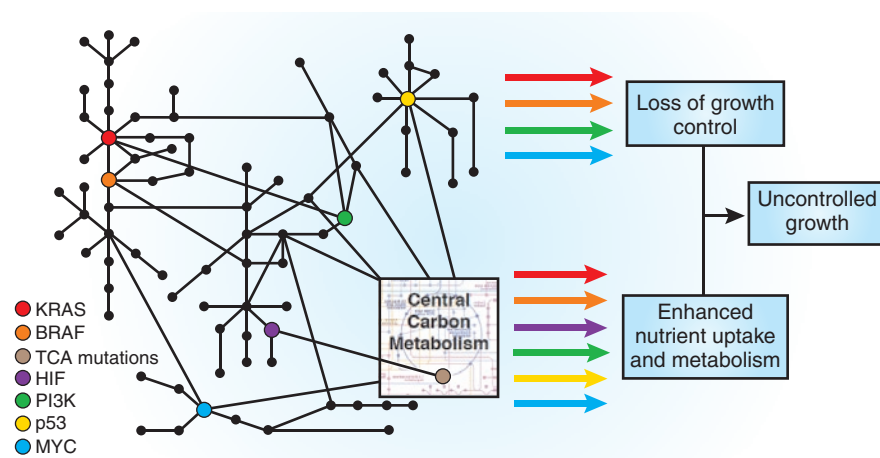


Figure 1 Genetic events shown to be important in human cancer influence signal transduction through a complex network that results in inappropriate cell proliferation. Arrow colors depict signal outputs that correspond to the various oncogenic mutations. These mutations lead to a dysregulation of cell growth control as well as alterations in central carbon metabolism. One consequence that is shared among the various mutations in oncogenes and tumor suppressor genes is promotion of nutrient uptake. Acquiring sufficient nutrients to allow accumulation of biomass is essential for cell proliferation and provides an attractive target for novel therapeutics. “TCA mutations” includes mutation of *SDH5*.

of which decrease the activity of ETC II, are associated with forms of hereditary paraganglioma^{1,3}. The oncogenic effects of ETC II mutations are thought to occur through indirect stabilization of the hypoxia-inducible transcription factor (HIF)⁴. The α subunit of HIF is hydroxylated in an oxygen-dependent reaction and targeted for degradation. However, the catalytic mechanism of HIF hydroxylation requires decarboxylation of α -ketoglutarate to form succinate, such that succinate accumulation can also inhibit HIF hydroxylation through product inhibition⁵. Thus, either depletion of oxygen or build-up of succinate resulting from decreased ETCII activity despite normal oxygen levels stabilizes HIF and induces the expression of hundreds of genes, including the glucose transporter *GLUT1* and enzymes involved in glycolysis⁶. All mutations known to cause hereditary paraganglioma therefore lead to altered gene expression that drives glucose uptake and metabolism and promotes cancer cell proliferation. Similarly, mutations in other components of the tricarboxylic acid cycle increase HIF expression and are believed to be oncogenic in other cancer types⁷.

In a separate study, Yun *et al.*² studied pairs of constructed isogenic cell lines that differ

only in the mutational status of *KRAS* and *BRAF*. The *KRAS* and *BRAF* genes encode signal transduction proteins and frequently acquire mutations in human cancer that render their products constitutively active⁸. However, mutations in these oncogenes are mutually exclusive, suggesting that the advantage they provide for tumor growth is redundant. The authors showed that *GLUT1* was one of only three genes consistently upregulated in cell lines harboring one of these mutations. They then focused on a *KRAS*-mutated cell line and subjected a wild-type version of these cells to glucose deprivation. Although most of the cells perished in this environment, a significant fraction of the ones that survived spontaneously acquired new *KRAS* mutations, and all of them increased *GLUT1* expression.

Martin Raff⁹ proposed a number of years ago that multicellular organisms control tissue size by requiring cells to compete for limited amounts of survival signals provided by growth factors and/or contact with the extracellular matrix. This is in contrast to unicellular organisms, which regulate cell proliferation by nutrient availability. It has been suggested that the same survival signals that regulate mammalian cell number also control nutrient uptake¹⁰.

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Thus, for cells in a tissue to proliferate autonomously and survive outside of their normal environment, they must acquire mutations that further increase nutrient uptake. This idea is highlighted by a recent study demonstrating a requirement of altered metabolic activity for survival when cells are detached from the extracellular matrix¹¹.

Accumulating evidence therefore supports the theory that seemingly disparate genetic alterations known to promote cancer lead to a single converging metabolic phenotype characterized by enhanced nutrient uptake. The studies by Hao *et al.*¹ and Yun *et al.*² raise the intriguing possibility that specific environmental perturbations facilitate adaptation to hyperactive metabolic states by selecting for mutations that enhance nutrient uptake and reorganize metabolism. In Hao *et al.*¹, a state of pseudo-hypoxia caused by defective mitochondrial respiration resulted in the activation of oncogenic transcription factors that control glucose metabolism. In Yun *et al.*², glucose deprivation drove the emergence of cells harboring a constitutively active *KRAS* gene that allowed these cells to compensate by increasing *GLUT1* expression. In several cancers, various major oncogenic events, such as PI3K pathway activation and loss of the tumor suppressor p53, have been associated with increased glucose uptake and metabolism^{12,13}. In addition, uptake of the nutrient glutamine can be driven by the *MYC* oncogene¹⁴. This suggests that reorganization of metabolic pathways by genetic alterations in cancer cells supports cell-autonomous metabolism with biosynthetic capabilities necessary for the rapid production of a new cell.

Attempts at therapies that target one or two signaling proteins have met with limited success in the clinic, in part because cancer cells use redundant pathways to circumvent target inhibition. The finding that cells in which mutant *KRAS* has reverted to wild type are selected to acquire new *KRAS* mutations implies that *KRAS* mutation may impose dependencies that can be exploited for therapy, although a majority of the clones acquired the ability to proliferate by unidentified genetic means. However, in all cases upregulation of *GLUT1* was observed. This suggests that many if not all mutations that permit continued cell proliferation enhance glucose metabolism. Targeting this common metabolic dependency may prove less susceptible to development of drug resistance.

Yun *et al.*² found that targeting metabolic pathways could be successful in treating *KRAS* mutant tumors. The alkylating agent 3-bromopyruvate (3BrPA) selectively inhibited cancer

cell proliferation both in culture and *in vivo*, (using tumor xenografts), presumably through effects on glucose metabolism, and might be effective against any tumor with a genetic alteration that increases glucose uptake and metabolism. 3BrPA has been proposed to act through inhibition of hexokinase, although some reports suggest that it is an effective antiproliferative agent in concentrations at which no hexokinase inhibition is observed¹⁵. Understanding the exact mechanism by which 3BrPA disrupts cellular metabolism may provide valuable insight into metabolic targeting as an antitumor therapy.

Our understanding of cancer cell metabolism is complicated by the enormous complexity of the interaction between metabolic pathways and the genetic aberrations that alter these pathways. Future progress will require new technologies and conceptual frameworks, such as high-throughput metabolomics and mathematical models that can parse the effects of many simultaneous interactions. Nevertheless, the insights of Hao *et al.*¹ and

Yun *et al.*² provide validation that investing this effort could result in potent new treatments for people with cancer.

COMPETING INTERESTS STATEMENT

The authors declare competing financial interests: details accompany the full-text HTML version of the paper at <http://www.nature.com/naturebiotechnology/>.

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Introducing the acetylome

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Mass spectrometry reveals protein acetylation to be as widespread as phosphorylation.

Acetylation of proteins was discovered over 40 years ago¹, but much remains to be learned about the extent of this post-translational modification and its roles in cellular processes. In an important advance reported in *Science*, Choudhary *et al.*² have now carried out the first global analysis of acetylated proteins in human cells. The authors mapped 3,600 acetylation sites in proteins and also identified proteins that are acetylated after treatment with deacetylase inhibitors, one of which is approved for clinical use.

Acetylation is regulated by the counteracting activities of acetyltransferases and deacetylases. Before the work of Choudhary *et al.*², relatively few acetylated proteins and acetylation sites were known. Acetylation has been best characterized for histones, where it is implicated in processes such as gene expression, the cell cycle, DNA replica-

tion and DNA repair. Acetylated histones are thought to alter chromatin structure and to serve as docking sites for protein complexes that remodel nucleosomes or further modify histones^{3,4}. However, the roles of acetylation of other targets, such as the tumor suppressor p53 (ref. 5), are only beginning to be understood.

Choudhary *et al.*² studied acetylated proteins in three human cell lines (MV4-11, Jurkat and A549) by immunoprecipitation followed by further enrichment with isoelectric focusing and high-resolution mass spectrometry. They identified 3,600 acetylation sites in 1,750 human proteins, increasing the number of known acetylation sites by about sixfold. These striking results indicate that protein modification by acetylation is nearly as abundant as by phosphorylation, which is estimated to occur on >2,000 proteins⁶.

Many of the acetylation sites discovered by Choudhary *et al.*² were on proteins in multi-subunit complexes. The prevalence of acetylation on 40 subunits of acetyltransferase

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