Regulation of cellular metabolism by manipulating signal transduction pathways: Akt and c-Myc promote an anabolic phenotype favoring cell growth

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OBJECTIVE: Most therapies for inborn errors of metabolism (IEMs) aim to maximize nutritional management and prevent catabolism. However, cellular metabolism is orchestrated primarily by growth factor signal transduction. This suggests that intervening in signaling pathways can provide a novel therapeutic approach, possibly stabilizing anabolism and growth. We studied the effects of Akt and c-Myc, two downstream effectors of growth factor signaling, on the metabolic activities that support lipid synthesis in growing cells. METHODS: We used radioactive tracers, NMR spectroscopy and mass spectrometry to examine metabolism in proliferating cells. We used inhibitors of the Akt pathway, conditionally active c-Myc alleles and RNA interference to study the role of Akt and c-Myc in cell metabolism. Transcriptional effects of c-Myc were determined using quantitative RT-PCR. RESULTS: During growth factor stimulation, human glioblastoma cells rapidly consumed glucose and glutamine. Glucose was the preferred carbon source for fatty acid synthesis whereas glutamine metabolism supplied both the anaplerotic flux and the NADPH needed to synthesize fatty acids. The majority of glutamine carbon and nitrogen was secreted rather than incorporated into macromolecules. Inhibition of Akt limited glucose utilization and cell proliferation but did not affect glutamine utilization. By contrast, enhanced c-Myc activity in fibroblasts increased glutamine consumption, glutaminase activity, ammoniagenesis and triglyceride synthesis. These effects were accompanied by increased gene expression of nutrient transporters and enzymes for glutamine metabolism and fatty acid desaturation. RNA interference against c-Myc suppressed these genes and decreased proliferation. CONCLUSIONS: In proliferating cells, Akt and c-Myc can exert complementary effects culminating in a metabolic platform that facilitates lipid biosynthesis. The data suggest that Akt exerts control over glucose metabolism while c-Myc's effects on transcription direct glutamine utilization. A deeper understanding of the interplay between signal transduction and anabolic metabolism may lead to new therapeutic opportunities in IEM patients in whom catabolic states are life-threatening.