ATP Consumption Promotes Cancer Metabolism

William J. Israelsen and Matthew G. Vander Heiden

Cancer cells metabolize glucose by aerobic glycolysis, a phenomenon known as the Warburg effect. Fang et al. (2010) show that the endoplasmic reticulum enzyme ENTPD5 promotes ATP consumption and favors aerobic glycolysis. The findings suggest that nutrient uptake in cancer cells is limited by ATP and satisfies energy requirements other than ATP production.

Mounting evidence suggests that cancer cells engage in a unique metabolic program that allows for rapid cell proliferation. Nonproliferating cells can use glycolysis products to generate ATP for their energy needs. Such cells generally have low rates of glycolysis followed by oxidation of pyruvate in the mitochondria, leading to efficient generation of ATP. Dividing cells, in contrast, also use glycolysis intermediates for the synthesis of macromolecules and must therefore balance their ATP requirements and biosynthetic needs (Vander Heiden et al., 2009). Metabolism of glucose by aerobic glycolysis, a phenomenon known as the Warburg effect, may help dividing cells strike this balance.

The phosphoinositide 3-kinase (PI3K) signaling pathway, which is activated in many cancers, regulates cell growth and survival. PI3K signaling has been implicated in the altered glucose metabolism of cancer cells, and the serine/threonine kinase AKT, a major PI3K effector, promotes glucose uptake and increases the activity of glycolytic enzymes (DeBerardinis et al., 2008). In this issue of Cell, Fang et al. (2010) report an important mechanism by which AKT signaling leads to increased aerobic glycolysis. They show that AKT activation promotes protein glycosylation in the endoplasmic reticulum, which elevates ATP consumption and derepresses a rate-limiting enzyme in glycolysis that is otherwise inhibited by an elevated ratio of ATP to AMP. This work suggests how proliferating cells may integrate growth signals with energy status to enable increased glucose uptake to support cell proliferation.

Activation of the PI3K pathway in cancer can occur via genetic alterations that allow growth factor-independent kinase activation or via the loss of PTEN, a lipid phosphatase that attenuates PI3K signaling. Fang et al. now find that cell extracts from PTEN-deficient cells have an enhanced ability to generate AMP from ATP. Subsequent purification and biochemical characterization of this activity led to the identification of ectonucleoside triphosphate diphosphohydrolase 5 (ENTPD5) as the enzyme associated with the ATP hydrolysis activity. PI3K signaling leads to upregulation of ENTPD5, a UDPase that promotes the N-glycosylation and folding of glycoproteins in the ER by hydrolyzing UDP to UMP (Trombetta and Helenius, 1999) (Figure 1). UDP hydrolysis in the ER is a reaction necessary to promote protein folding via the calnexin/calreticulin pathway. It is linked to ATP hydrolysis in the cytosol by a cycle of glucose and phosphate transfer reactions. As part of this cycle, the UDP-glucose/UMP antiporter exports UMP out of the ER in exchange for importing UDP-glucose into the ER (Hirschberg et al., 1998). The UGGT enzyme then uses UDP-glucose to transfer glucose to proteins in the ER (Vembar and Brodsky, 2008). This glucose addition to nascent glycoproteins is necessary for their calnexin/calreticulin-mediated protein folding. Thus, disruption of ENTPD5 in PTEN-deficient cells results in decreased protein N-glycosylation and causes ER stress.

Cell surface proteins, including many growth factor receptors, are N-glycosylated. Fang et al. show that disruption of ENTPD5 leads to decreased levels of several growth factor receptors, including epidermal growth factor receptor (EGFR), insulin-like growth factor receptor β (IGFR-β), and Her2/ErbB2. Given that growth factor signaling plays an important role in increasing nutrient metabolism in rapidly proliferating cells (DeBerardinis et al., 2008), these new findings suggest that cellular ATP levels can influence the folding and expression of growth factor receptors, perhaps ensuring that cells do not attempt to grow when ATP is limiting. Furthermore, because glucose metabolism by the hexosamine biosynthesis pathway provides the carbon for these receptor glycosylation events, the availability of glucose may provide a means to couple nutrient levels with growth factor receptor expression. These feedbacks may exist to prevent a metabolic catastrophe caused by activation of the cell growth machinery when the supply of nutrients or ATP is limiting.

How does ENTPD5 regulate ATP levels? Fang et al. find that reconstitution of the ATP consuming activity also requires the presence of UMP/CMP kinase-1 and adenylate kinase-1. UMP/CMP kinase-1 catalyzes the rephosphorylation of the UMP generated by ENTPD5 into UDP (Figure 1), in the process converting ATP to ADP. Adenylate kinase-1 then converts ADP molecules into ATP and AMP, thus allowing the cycle to continue. Surprisingly, this cycle involving ENTPD5 is a major source of ATP consumption in PTEN-deficient cells. Furthermore, these reactions directly affect the cell’s glycolytic rate. Whereas increased ENTPD5 expression has no

Fang et al. (2010) show that the endoplasmic reticulum (ER) UDPase ectonucleoside triphosphate diphosphohydrolase 5 (ENTPD5) is expressed in response to phosphoinositide 3-kinase (PI3K) signaling. Activation of PI3K results in FOXO phosphorylation by AKT and loss of ENTPD5 transcriptional repression. This leads to increased ENTPD5 enzyme activity in the ER, where UGGT transfers glucose to an unfolded N-glycoprotein and produces UDP. Properly folded N-glycoproteins, such as growth factor receptors, exit the cycle, whereas unfolded proteins undergo further folding attempts or are degraded. ENTPD5 activity enables this process by hydrolyzing UDP to provide the UMP necessary for exchange with UDP-glucose in the cytosol. The activities of UMP/CMP kinase-1 and adenylate kinase-1 couple the energetic requirements of this cycle to the net conversion of ATP to AMP. Thus, increased ENTPD5 activity leads to a decrease in the cellular ATP/AMP ratio. Because this ratio is the major determinant of glucose flux through the phosphofructokinase (PFK) step in glycolysis, a lowered ATP/AMP ratio increases glycolysis, elevates lactate production, and provides glycolytic intermediates for biomass production.

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**REFERENCES**


