Preview

Starving lethal prostate cancer by targeting heat shock proteins and glycolytic enzymes

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Metastatic prostate cancer remains uncurable. In this issue of *Cell Reports Medicine*, Rice et al. present an assessment of a compound (SU086) demonstrating activity in prostate cancer models through heat shock protein 90 inhibition and cell metabolism changes.

Prostate cancer is the most common noncutaneous malignancy in men in the Western world and accounts for more than 33,000 annual deaths in the United States alone.[1] Despite therapeutic advances over the past years, metastatic prostate cancer remains uncurable.[2] Therefore, there is an urgent need to develop novel therapeutic approaches and define new targets for the treatment of advanced prostate cancer.

In this issue of *Cell Reports Medicine*, Rice et al. describe a compound (SU086) that demonstrates promising pharmacological properties and activity in preclinical models of advanced prostate cancer.[3] SU086 is a chalcone derivative that shows toxicity in a variety of cancer cell lines, including prostate cancer. In *in vitro* experiments, SU086 suppresses prostate cancer cell growth and invasion independent of the androgen receptor (AR), an important oncogenic lineage transcription factor in prostate cancer. Furthermore, in several cell-line- and patient-derived xenograft models, SU086 suppresses tumor growth *in vivo* at low micromolar concentrations without overt systemic toxicities. In addition, SU086 shows improved tumor control *in vivo* in combination with AR signaling inhibitors enzalutamide and abiraterone suggesting a benefit of combining SU086 with standard of care AR targeted therapies.

To determine the molecular targets of SU086, Rice et al. performed a series of elegant biochemical experiments demonstrating that the compound shows prefer-

ential affinity to the heat shock protein HSP90. HSP90 is an ATP-dependent molecular chaperone that controls folding, activity, and stability of a large number of proteins.[4] To further delineate which proteins are most affected by SU086-mediated HSP90 inhibition, global mass-spectrometry analyses were performed, which revealed a strong enrichment of proteins involved in the regulation of glycolysis (PGK1, YWHAZ, and HSPB1). Rice et al. functionally corroborated this observation by Seahorse assays demonstrating altered glycolytic flux and glycolysis rates upon SU086 treatment. Furthermore, desorption electrospray ionization/mass spectrometry imaging of SU086-treated tumor xenografts showed a shift in glucose metabolism, supporting the notion that SU086 could at least in part act through inhibition of glycolysis. Collectively, these data suggest that SU086 is a putative HSP90 inhibitor with efficacy in advanced prostate cancer models and therefore could address the aforementioned need for advanced prostate cancer therapies.[3]

HSP90 has been exploited as a drug target for several decades. Initially skepticism related to the toxicity of HSP90 inhibitions slowed their development, but currently there are several small-molecule inhibitors under clinical investigation.[4] It is worth noting that HSP90 is a chaperone for many proteins involved in prostate cancer biology including MYC and AR; therefore it will be important to further characterize the effect of SU086 on other

signaling pathways to comprehensively understand its mechanism of action. Despite the potentially broader molecular action of SU086, which could be a unique therapeutic benefit, the activity of SU086 on glycolytic pathways is of particular interest.

Otto Warburg first proposed the concept that anaerobic glycolysis was a unique feature of altered ATP production in cancer 100 years ago. Although this concept has undergone multiple renditions, therapeutically targeting the various enzymes involved in the glycolytic pathway is an attractive approach to treating cancer.[5] However, the metabolism of prostate cells appears to be fundamentally different from that of many other cell types and context-dependent requirements need to be considered when studying prostate cancer metabolism.

As opposed to oxidative phosphorylation, which is used for ATP production in most glandular tissues, benign prostate epithelial cells use anaerobic glycolysis[6,7] (Figure 1A). This pathway is efficiently utilized in the benign prostate because of active transport of zinc into normal prostate cells. The elevated level of zinc in benign prostate cells (the prostate contains the highest levels of zinc of any human tissue) inhibits the activity of aconitase, which "short-circuits" the TCA (tricarboxylic acid) cycle, resulting in a shunting of citrate, conversion to acetyl coenzyme carboxylase, and subsequent increased synthesis of fatty acids.[6,7]
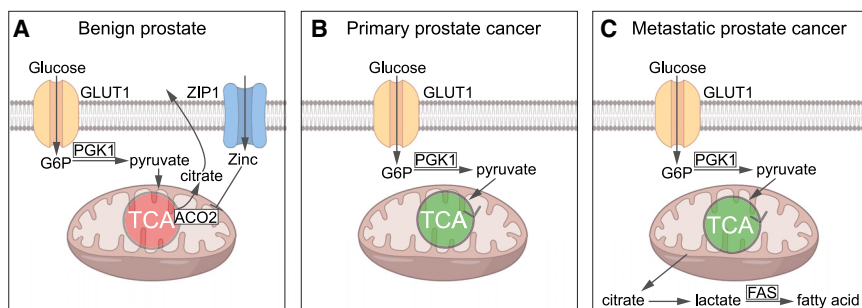
Figure 1. Glucose metabolism is uniquely different in prostate epithelial cells when compared to other cell types

In the benign prostate luminal epithelial cell (A), the zinc transporter ZIP1 transports zinc into the cell. In the cell, zinc inhibits the enzyme aconitase in the mitochondria, stopping the metabolism of citrate derived from glucose from entering the tricarboxylic acid (TCA) cycle as pyruvate to generate ATP. In primary prostate cancer (B), ZIP1 expression is markedly suppressed and pyruvate now enters the TCA cycle. Finally, in metastatic prostate cancer (C), the enzymes involved in glycolysis are markedly elevated whereas ZIP1 is further suppressed, thus allowing for increased ATP production through the TCA cycle but also providing materials necessary for cell membrane synthesis in rapidly proliferating tumor cells from endogenous synthesis of fatty acids.

In early primary prostate cancer, zinc and citrate levels are reduced (Figure 1B). These changes permit the TCA cycle activation and oxidative phosphorylation becomes the primary source of energy in the form of ATP. Clinically this is reflected in the low detection rate of 18-FDG PET activity (a clinical measure of glycolysis) in primary prostate cancers.

However, in the progression to metastatic disease, glycolysis along with lipogenesis and oxidative phosphorylation supply the increased energy demands of prostate cancer cells (Figure 1C). This can be clinically monitored by increased 18-FDG PET avidity in advanced metastatic prostate cancer. The relevance of this switch to a glycolytic state is highlighted by several recent reports in which total lesion glycolysis determined by 18-FDG PET uptake in metastases was associated with significantly shortened survival.[8] These findings suggest that tumors with a higher level of glycolysis are biologically more aggressive, but also provides a potential imaging biomarker for therapies that interfere with glycolytic pathways, such as SU086.

Warburg initially proposed that the development of glycolysis in tumors was a "metabolic switch" needed to drive the cancer. However, because benign prostate epithelial cells use anaerobic glycolysis, it has been suggested that the "metabolic switch" does not occur in prostate cancer. The results from Rice et al., as well as new clinical and *in vitro*

and *in vivo* data, suggest that the switch occurs as prostate cancer enters its therapeutic and lethal stages.[6,7] In fact, it appears that prostate cancers undergo two metabolic switches, first from anaerobic glycolysis to oxidative phosphorylation (benign glands to primary cancers) and then, in lethal metastatic disease, re-aquire anaerobic glycolytic activity and enhanced fatty acid oxidation.

This increased glycolytic dependence has spurred drug development; preclinical studies targeting glycolytic enzymes, including Glut 1, hexokinase 2, phosphogluco-isomerase, phosphoglycerate kinase, and enolase, have shown promising results.[9,10] However, glycolysis is an important function in most benign tissues and as a result, development of direct inhibitors of glycolytic pathway components that do not exhibit prohibitive toxicity has been challenging. Therefore, future detailed *in vivo* studies of SU086 will need to carefully dissect the toxicity profile and optimize dosing. Given the paucity of therapeutic targets for advanced lethal prostate cancer, the discovery of SU086 with its broad mechanisms of action has highlighted several important therapeutic strategies and will certainly motivate future investigations.

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