Second, efforts should be put at all levels to improve the preclinical representation of the complexity and heterogeneity of human cancer. One major requirement is to attain a large number of models. Because cancer is a highly heterogeneous disease, the only way to estimate the relevance and impact of a preclinical result is to gather an epidemiological contextualization of it. Indeed, to identify small subsets of rare or very rare variants, harbored by tiny patient subpopulations (which is very likely), population-scale studies (both in vitro and in vivo) are needed to guarantee the statistical power required to discriminate relevant correlations. Beside this, the experimental models per se should be refined to augment their intrinsic predictive proficiency. In vitro, promising results have been recently obtained in the setup of short- and long-term tissue cultures that better preserve the genetic and phenotypic features of cancer cells while maintaining the scalability typical of cell line studies (7). In vivo, host humanization approaches and complex models of genetically modified mice are paving the way for improved modeling of tumor–host interactions and for better prediction of activity when developing microenvironment-targeted drugs (8).

Third, but not less important, is the absolute need to leverage the informative potential of negative results. Historically, negative results have always been difficult to publish, leading to two harmful consequences: on one side, the widely diffuse habit of partial reporting, which introduces a highly distortive filter in the interpretation of an already very complex system; on the other, the impossibility to normalize the relevance and the consistency of new preclinical findings against the general level of experimental noise typical of biological systems. More open publishing policies, emphasizing the balancing role and the informative value of negative results (when obtained through robust methodologies), would certainly increase the overall reliability of preclinical studies.

References

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Metastatic Castration-Resistant Prostate Cancer Hunger for Leucine
Andrew R. Tee

Unfortunately, the current treatment for metastatic castration-resistant prostate cancer remains mostly palliative with little additional benefit. In this issue of the Journal, Wang and colleagues (1) present a landmark article that uncovers the Achilles heel of prostate cancer, which is cleverly disguised as the system L-type transporters (LATs). The LATs are amino acid exchangers that import the branched chain amino acids (such as leucine) in exchange for other intracellular amino acids (such as glutamine). The “Warburg effect” is a term often used to describe cancer cells that have an adapted metabolic profile. Such cancer cells have enhanced glucose uptake and even in the presence of oxygen, glucose is rapidly broken down by anaerobic metabolism. In a manner analogous to the dependency upon glucose in the Warburg effect, metastatic prostate cancer has an appetite for leucine. The research led by Dr. Jeff Holst reveals that metastatic castration-resistant prostate cancer cells are highly dependent on amino acid uptake through LATs for their growth and proliferation, as well as their malignant transformation (1). Discovery of this leucine hunger in metastatic prostate...
cancer (or, if I can be prudent and say the “Holst effect”), opens up a new therapeutic option to treat prostate cancer by inhibiting amino acid transporters.

As well as being essential for de novo protein synthesis, amino acids can be used as a source of fuel. Cells can make acetyl CoA from leucine to directly generate energy via the Krebs cycle. In addition, amino acids can be channeled into anabolic pathways to generate nucleotide and membrane biomolecule precursors that are required for rapidly proliferating cells. Another mechanism by how leucine drives cell growth is through the Ragulator complex, which recruits mammalian target of rapamycin complex 1 (mTORC1) to lysosomes where mTORC3 is activated (2). In a leucine-dependent manner, mTORC1 orchestrates cellular growth through energy-consuming processes such as protein translation. mTORC1 also drives cell growth and proliferation through the generation of membrane (3) and nucleotide biomolecule precursors (4), respectively. Herein, work by Holst and colleagues (1) reveals that progression of prostate cancer is directly linked to amino acid uptake through LATs.

It is well known that androgen potently drives prostate cancer. However, the exact mechanisms by which androgen promotes cell growth of prostate cancer cells are not yet fully understood. It was, therefore, of interest that LAT3 protein expression remained highly elevated in all stages of prostate cancer but was highly sensitive to androgen ablation. This finding supports previous work by this group showing that LAT3 is an androgen-responsive gene (5), implying that androgen might (in part) exert prostate cancer growth through LAT3 expression. Expression of LAT1 was quite different from that of LAT3, as LAT1 protein levels were markedly enhanced and directly associated with the Gleason score. Upon leucine deprivation, by blocking LAT amino acid uptake, ATF4 was translationally upregulated and drove LAT1 gene expression through an amino acid response element. Of interest, upregulation of ATF4 genes such as LAT1 (as well as SNAT2, which works cooperatively with LAT1 for glutamine/leucine exchange) was strikingly evident in metastatic castration-resistant prostate cancer but not in either benign or primary prostate cancer tissue. This work implies that malignant prostate cancer typically possesses an amino acid–starved gene expression profile, and to compensate, increases amino acid uptake through LAT1/SNAT2. Such new evidence explains why malignant prostate cancer has an appetite for amino acids, where these amino acids are quickly utilized to drive their growth and proliferation. Furthermore, these novel findings imply that LAT1 might be a good predictive biomarker for prostate cancer malignancy.

An important finding was that LAT inhibition (and sequentially reduced amino acid uptake) repressed E2F-driven M-phase cell cycle genes in prostate cancer cell lines. Such a finding revealed that leucine uptake via LATs can potently drive a highly proliferative signal in prostate cancer. Analysis comparing metastatic prostate cancer vs primary prostate cancer further confirmed exclusive enrichment of E2F–regulated genes in malignant prostate cancer samples. In addition, an upregulation of E2F genes was directly associated with patients with recurrent cancer and poor survival. Finally, to confirm that amino acid uptake through LATs was necessary in prostate cancer development, this group utilized a bioluminescent xenograft mouse model to examine tumor formation of a prostate cancer cell line with either LAT1 or LAT3 knockdown. Indeed, knockdown of either LAT1 or LAT3 statistically significantly reduced tumor formation, impaired cellular proliferation (via loss of E2F gene expression), and importantly diminished metastasis. Such key experiments revealed that prostate cancer requires the expression of both LAT1 and LAT3 to have the capacity to grow and to metastasize. This dependency upon both LAT1 and LAT3 expression for transformation reemphasizes the “hunger” that malignant prostate cancer appears to have for amino acids.

This pioneering piece of cancer research has huge clinical implications for future prostate cancer studies and therapies through targeting LATs. Furthermore, this study indicates that amino acid transporters can potently drive cell growth, proliferation, and metastasis. This work is likely to impact research on other sporadic cancers, which may be equally as reliant on amino acids for their growth and sequential transformation. It would be of considerable interest to see how malignant prostate cancer utilizes leucine for their growth—that is, whether leucine is catabolized for energy or is used to make biosynthetic precursors required for rapid proliferation. Undoubtedly, further research is still required, but this innovative study opens up a new area of investigation that focuses on amino acid uptake as a facilitator of prostate cancer progression and a potential new avenue for therapy.

References


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