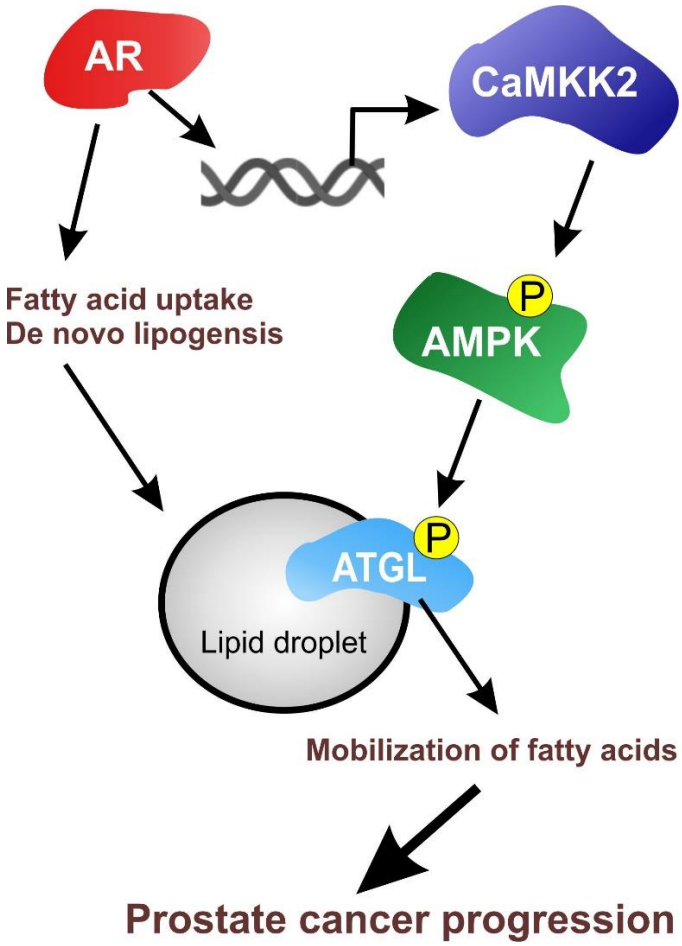
The AR-CAMKK2-AMPK signaling axis regulates adipose triglyceride lipase in prostate cancer, controlling access to intracellular lipid depots and promoting disease progression

Background: Late-stage prostate cancer patients are treated with androgen deprivation therapy. However, the majority will relapse within 2-3 years. The androgen receptor (AR) and the processes downstream of the receptor remain viable therapeutic targets in prostate cancer. We previously identified the AR-CAMKK2-AMPK signaling axis as a major driver of prostate cancer metabolism. To identify, in an unbiased manner, AMPK downstream targets potentially involved in prostate cancer progression, we leveraged an improved AMPK substrate motif to mine phosphoproteomics data obtained from men with benign disease, localized, hormone-sensitive or metastatic, castration-resistant prostate cancer (mCRPC) samples. Using this approach, we were able to identify high-confidence AMPK targets across subgroups. The screen revealed that phosphorylation of adipose triglyceride lipase (ATGL), the rate-limiting step in the breakdown of triglycerides in lipid droplets, tracks with disease progression.

Methods: A battery of molecular (inducible shRNAs), biochemical (kinase activity), genetic (CRISPR/add-backs) and pharmacological approaches were used to investigate ATGL's regulation and role in prostate cancer cell biology.

Results: Increased AR-CAMKK2-AMPK signaling increased ATGL phosphorylation and subsequent lipolysis. Conversely, knockdown or knockout of ATGL led to an accumulation of neutral lipids in various prostate cancer cell models and inhibited proliferation and migration of CRPC cell models. Using pharmacological or genetic approaches, we were able to show that the inhibition of ATGL impaired intracellular lipid shuttling that could be exploited therapeutically.

Conclusions: Research on lipid metabolism in prostate cancer has centered on lipid uptake and *de novo* lipogenesis, little consideration has been given to how cancer cells accommodate and later access these new lipids. Our study gives important insights into how intracellular fat depots are accessed during prostate cancer progression and suggests that regulation of ATGL is a key mediator of this step. Hence, ATGL represents a potential novel therapeutic target for the treatment of advanced prostate cancer.


AR
CaMKK2
Fatty acid uptake
De novo lipogensis
P
AMPK
P
ATGL
Lipid droplet
Mobilization of fatty acids
Prostate cancer progression