

Title: Genomic drivers of lipid metabolism in prostate cancer

CANCER METABOLISM

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Dysregulated lipid metabolism is a prominent feature of prostate cancers. Two papers in this issue identify novel genomic drivers of lipid metabolism in prostate cancer with implications for the subtyping and treatment of the disease.

Prostate cancer is a high-incidence cancer characterised in part by dysregulated lipid metabolism is a prominent feature which encompasses increased *de novo* lipogenesis including steroid hormone biosynthesis as well as beta-oxidation of fatty acids¹. In imaging prostate cancer the importance of lipid metabolism is evidenced by the adoption of choline- and acetate-based tracers for the detection of alterations in situ². Furthermore fatty acid synthase has previously been reported to have the properties of prostate cancer oncogene as assessed in a transgenic mouse model of prostate cancer³. In addition fatty acid synthase inhibitors can restrict prostate cancer growth at least in pre-clinical cancer models and this has prompted considerable interest in drug repurposing and further development of these therapeutics^{4,5}. Epidemiological data implicate obesity as a risk factor for aggressive prostate cancer⁶. Collectively this implies that lipid metabolism is a significant contributor to sustaining prostate cancer development and there is a major need for further mechanistic insights into the drivers of lipid metabolism, be they genetic or environmental.

In this issue two studies identify novel regulatory impacts of genomic changes in the prostate cancer on the capacity of prostate cancer cells to metabolise lipids (**Figure 1**)^{7,8}. Both studies utilise the same prostate-specific Pten-null transgenic mouse model of prostate cancer which gives high-grade intraepithelial prostate tumours at an early age and invasive prostate cancer at a late age^{7,8}. One study focuses on the frequent amplification and overexpression of subunits of the pyruvate dehydrogenase complex (PDC), a complex with a gatekeeper function in converting pyruvate into acetyl-CoA for entry into the TCA Cycle in mitochondria⁷. Having established that overexpression of subunits of the PDC are features both of clinical prostate cancer and of the Pten-null transgenic mouse model they go on to show that inactivation of *Pdha1* can restrain prostate growth at early ages in this model⁷. The mechanistic basis of this involves both nuclear and mitochondrial functions of this complex⁷. Previous studies have reported that acetyl-CoA is not merely required to sustain the metabolic activity of mitochondria but also required in the nucleus to support histone acetylation and enhancer activity⁹. By employing a combination of metabolomic and transcriptomic profiling the authors show that a principle impact of targeting the PDC complex, and in particular PDHA1, is to suppress lipid biosynthesis. At the nuclear level this was found to be due to a reduction in histone acetylation at regulatory regions bound by the SREBP transcription factor and at the mitochondrial level due to a reduction in citrate production⁷. This study identifies the PDC complex and in particular PDHA1 as a potential therapeutic target through which to restrain prostate cancer development by impacting directly and indirectly on the metabolic capacity of prostate cancer cells⁷.

In the other study the authors set out to explore the impact of co-deletion of Pml and Pten on the phenotype of Pten-null prostate cancers and identify lipid metabolism as the amplified biological process arising from coordinate targeting of these tumour suppressors⁸. They determine that this metabolic change reflects hyperactivation of an SREBP-dependent pro-metastatic lipogenic program, reminiscent of the nuclear/transcriptional changes observed in the PDC paper^{7,8}. The route to the enhanced transcription of SREBP target genes is however not via histone acetylation as reported in the other study but rather through the hyperactivation of MAPK signalling otherwise restrained by Pml⁸. requires MAPK signalling. The metastatic impact of these changes can be blocked with an inhibitor of SREBP, fatostatin, but importantly can also be replicated by feeding the Pten-null mice a lard-based high-fat diet without targeting Pml⁸. This points to a synergy between genetic and environmental factors in promoting prostate cancer progression which needs to be evaluated more widely in *in vivo* models of the disease. The identification of Pml deletion as driver for MAPK signalling, which has previously been associated with castrate-resistant prostate cancer, and aberrant lipid metabolism may provide an additional patient classifier for treatment or dietary intervention. As with the study focussing on the PDC complex many of the mechanistic aspects of this work have been built on lipidomic and transcriptomic profiling of the pre-clinical models and comparisons with clinical datasets highlighting the importance of data integration and multi-omic studies^{7,8}. In this case this has also yielded an SREBP target gene signature which is enriched in a subgroup of human castrate-resistant prostate tumours⁸. Given that other transcriptomic signatures are now being used to risk stratify tissue biopsies there is a translational precedent^{10,11} for evaluating this further and particularly in the context of the genomic amplifications and deletions examined in these back-to-back papers.

These papers significantly enhance our understanding of the mechanistic basis for dysregulated lipid metabolism in prostate cancer and will motivate further clinical and pre-clinical studies. It will be of particular interest to determine overexpression and activation of the PDC complex in a Pten-null background and Pml-deletion in the same background are promoting the same lipogenic biology but also whether other prostate cancer drivers have similar impacts. There are certainly indications that this is true for c-Myc and ETV1^{12,13}. The longer term challenge will then be to implement strategies based on this information to improve patient stratification and clinical outcomes.

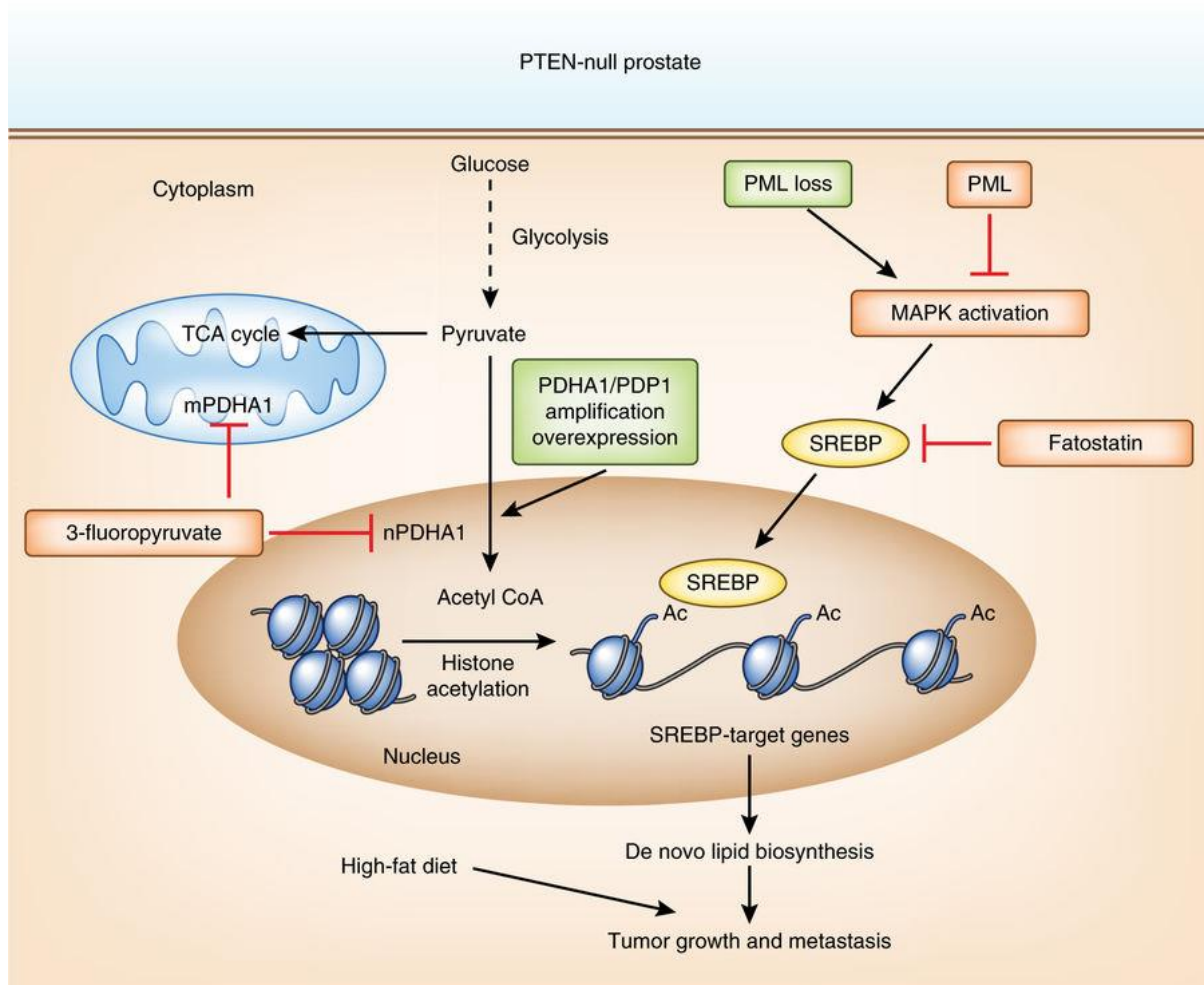


Figure Legend

Schematic diagram showing two genomic drivers of aberrant lipid metabolism contributing to tumour growth and metastasis in prostate cancer (CaP). Both pathways target SREBP dependent lipogenic program at the downstream level. Frequent amplification/overexpression of PDHDA1 seen in CaP affects tumor metabolism by regulating acetyl CoA production and histone acetylation at regulatory regions bound by SREBP at the nuclear level, and by flux through TCA cycle at the mitochondrial level, through nuclear PDHA1 (nPDHA1) and mitochondrial PDHA1 (mPDHA1) respectively. Genetic loss of PML leads to hyperactivation of SREBP dependent transcription through enhanced MAPK signaling. Both lipid biosynthesis and tumor growth can be inhibited by fatostatin, a direct inhibitor of SREBP or by genetic inactivation of PDHA1 or through 3-fluoropyruvate, a competitive inhibitor of PDHA1. On the other hand, a high fat diet induces lipid accumulation which is sufficient to drive metastasis in PTEN-null genetic background. Green boxes indicate genetic background. Green arrows indicate activation and red lines indicate inhibition.

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