

Putting Prostate Cancer Metabolism into the Right Context

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Prostate cancer (PCa) is the most commonly diagnosed cancer in the USA and there is considerable evidence that metabolic alterations underpin the emergence and progression of the disease. In this issue of *European Urology Oncology*, Giunchi et al [1] present a review of the recent literature and highlight 50 publications, the majority of which relate to fatty acid and cholesterol metabolism, to illustrate metabolic alterations in PCa. The review considers fatty acid, cholesterol, one-carbon, and glucose metabolism in distinct sections, and covers general metabolic concepts, the impact of metabolic alterations, potential biomarkers linked to these changes, and the potential for therapeutic interventions for each process. In addition, one section addresses the interplay predominantly between one-carbon metabolism and epigenetic changes. In their article the authors make reference to some of the relationships between PCa drivers and genomic hallmarks (such as PTEN loss and *TMPRSS2-ERG* gene fusion) and the expression of metabolic enzymes and concomitant metabolic changes. These relationships are also highlighted in the schematic figures that summarise ester/fatty acid metabolism and one-carbon metabolism. The article highlights burgeoning research on metabolic aspects of PCa. While metabolism is undoubtedly fundamental to sustaining all stages of PCa, it remains challenging to present ongoing research in a single integrated model that captures the stages in disease progression and the contribution of various established genomic drivers and candidate molecular subtypes to metabolic changes. Metabolic dysregulation can be exquisitely dependent on environmental factors, including aspects of tissue architecture, diet, and the partitioning of metabolic processes between cell subpopulations within tissue samples. This makes it difficult to define the most robust clinical context in which to focus on a particular metabolic process and propose a therapeutic intervention. However, this is no more challenging than resolving issues of genomic heterogeneity emergent in sequencing studies on tissue samples.

Furthermore, some features are rather consistent, including the need to maintain tricarboxylic acid cycle activity in PCa cells, be that through β -oxidation of fatty acids or amino acid metabolism. This facet of PCa biology appears to be supported by c-Myc overexpression and PTEN mutation/loss, high-incidence events that have in some studies been linked to the emergence of poor-prognosis disease. Another broad impact of these metabolic changes that will prove to be somewhat conserved is feedback effects on the epigenetic landscape of PCas. One-carbon metabolism is of course the natural place to start in considering how this might work [2]. Alterations in DNA methylation remain some of the highest-incidence early-stage genomic changes in PCas, even accounting for the discovery ETS fusions [3]. Furthermore, the androgen receptor profoundly influences the expression of enzymes involved in one-

carbon metabolism, and metabolites synthesised via these metabolic pathways, principally polyamines such as spermine, are hallmarks of the secretome of healthy prostates [2]. However, given that chromatin opening and aberrant enhancer function are characteristics of poor prognosis/progressing PCas, and that these features are in turn characterised by altered histone acetylation, it is likely that other metabolic pathways and feedback effects will prove to be equally or more important perturbation factors promoting epigenetic reprogramming [4].

A recent study on pyruvate dehydrogenase function in PTEN-null PCas revealed a nuclear role for this enzyme complex as a source of acetyl groups affecting the chromatin landscape of progressing tumours [5]. Given that other studies in other cancer types have highlighted ATP citrate lyase as a source of acetyl groups for chromatin modification, we can expect to see further studies that address the interplay between metabolic activities and chromatin modification [6,7]. This in turn may help to position metabolic drugs in combination with epigenetic and DNA damage repair pathway inhibitors to improve the outcome for PCa patients with progressing disease. Metabolism should conceptually have feedback effects on chromatin and transcriptional capacity/activity and these processes should be tightly co-regulated. Aberrant metabolism arguably supports the proliferative potential of cancer cells and their capacity to generate new membranes and biomass to support cell division, and may also sustain the mutagenic potential of cancer cells by affecting the accessibility of chromatin to oxidative and other DNA-damaging stressors without activating cell death pathways. Given the relatively low proliferative index of many PCas, the latter possibility is perhaps the more biologically interesting, but is currently far harder to model preclinically. That possibility speaks for the notion that aberrant lipid turnover and amino acid metabolism in PCa cells support NADPH homeostasis and a redox balance in synchronisation with changes in chromatin modifications and accessibility [8]. This in turn might be further affected by age-associated changes in circulating hormones and by dietary factors. Collectively this would support the more rapid acquisition of DNA damage and the emergence over time of pro-proliferative mutations in tumour suppressors and DNA repair pathways, the frank/“true” drivers of cancer progression. In a preclinical setting it is possible to isolate some limited aspects of this hypothesis and test them in controlled settings, but often in the presence of some of these strong oncogenic drivers. To more thoroughly decipher these interplays we will need to embrace tissue-based preclinical models on a scale that fully captures PCa heterogeneity and supports a range of genetic and chemical perturbations that cover the full spectrum of metabolic and genomic changes. Tissue explants offer the best chance of achieving this at present, but lack the temporal follow-up to assess how these perturbations might impact on the evolution of the tissue and the progression of aggressive PCa [9,10,]. Giunchi et al have provided a present-day snapshot of the intensive research focus on metabolic changes in PCa and highlighted the ever growing need to better understand the interplay among metabolic pathways and between metabolism and other key events that support disease progression. Our focus has long been on identifying genomic cancer drivers. Owing to the unpredictable progression characteristics of PCa and its heterogeneity we now need to embrace the challenges of studying gene-environment and genome-metabolism interactions to complete the picture.

Conflicts of interest: The author has nothing to disclose.

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