Prostate cancer affects one in eight men in the developed world, and now accounts for more cancer related deaths in men than females dying of breast cancer. Despite improvement in patient survival with novel androgen receptor inhibitors and taxane chemotherapy, a significant proportion of patients with advanced disease still dies within five years of diagnosis. Our recent research applied a range of preclinical models to investigate molecular drivers of treatment resistance, aimed at the discovery of new therapeutic strategies.

In this report, we describe our recent advances in multi-omics and network-based analyses to probe the molecular basis of advanced prostate cancer including castration resistant disease. Our findings support the idea that Prostate Specific Membrane Antigen (PSMA) may have a potentially functional role in promoting treatment resistance in prostate cancer in addition to its role as an imaging marker.

Castration-resistant prostate cancer (CRPC) is incurable and remains a significant challenge worldwide. Using a panel of isogenic human prostate cancer models of hormone naïve and castration resistant disease, we have developed matching 2- and 3-dimensional in vitro cultures and in vivo orthografts to model clinical prostate cancer. We initiated deep quantitative proteomic analysis to characterise proteins of interest in castration resistant prostate cancer (CRPC). As a result, we identified several key players in CRPC and reported our findings recently (Blomme et al., 2020, 2022; Martinez et al., 2021). In these early studies, we have adopted a relatively focussed platform (for instance, the proteome) as a starting point for investigating the molecular basis driving CRPC, which will inevitably result in a relatively narrow perspective of the underlying biology. To provide an added dimension of our knowledge in CRPC, we have now carried out a multi-omic analysis of our orthotopic models of hormone naïve and castration resistant prostate cancer as well as network-based regulon analysis of CRPC.

Multi-omics analysis identifies potential roles for tumour N-acetyl aspartate accumulation in Castration Resistant Prostate Cancer

Untargeted RNA sequencing, proteomics, and metabolomics analyses were performed on xenografts derived from three independent sets of hormone naïve and matched CRPC human cell line models grown as murine orthografts. We tested the feasibility of multi-omic analyses on models of CRPC in revealing pathways of interest for future validation investigation (Figure 1). Untargeted metabolomics revealed N-acetylaspartate (NAA) and N-acetylaspartylglutamate (NAAG) commonly accumulating in CRPC across three independent models, while proteomics analysis showed upregulation of related enzymes, namely N-Acetylated Alpha-Linked Acidic Dipeptidases (FOLH1, NAAAL1L2; also commonly referred to as Prostate-Specific Membrane Antigen/PSMA). Based on pathway analysis integrating multiple omic levels, we hypothesise that increased NAA in CRPC may be due to upregulation of NAAG hydrolysis via NAAAL1Lases providing a pool of Acetyl Co-A for upregulated sphingolipid metabolism and a pool of glutamate and aspartate for nucleotide synthesis during tumour growth.

Our findings are highly relevant to clinical prostate cancer. PSMA is an important imaging marker of prostate cancer. PSMA based PET imaging is rapidly transforming the detection of low burden prostate cancer metastatic lesions as well as cancer recurrence (both hormone naïve and castration resistant disease) (Figure 2). In addition, PSMA-based therapy is rapidly gaining momentum as part of an effective treatment for advanced metastatic disease. Here, our data supports the idea that PSMA may functionally contribute to disease progression and represents a valid target for therapy.

Transcriptomic gene regulation network analysis of human prostate orthografts

We exploited a graph-based enrichment score to integrate transcriptomic data from gene regulation network identified in our prostate orthografts and differentially expressed genes in clinical resected prostate tumours (Figure 3). We tested whether a network of genes similarly regulated from our preclinical prostate cancer models and further evaluated the top ranked JUMO6 gene regulated network in three independent clinical patient cohorts.

JUMO6 belongs to the Jumonji domain-containing family of proteins. JUMO6 is thought to function mainly as a lysyl 5-hydroxylase. Its ability to regulate the transcriptional activity of p53 through hydroxylation of a lysine in the p53 C-terminus is highly relevant in cancer biology. Upregulated JUMO6 expression has been implicated in tumour growth, tumour metastasis and high tumour pathological grades. Our transcriptomic network analysis highlighted the value of future studies on JUMO6 mediated function in prostate cancer biology.

Concluding comment

The use of a multi-omics approach and the application of a network-based analysis have potential in revealing important insight into CRPC.

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Figure 1

Figure 2

Figure 3

Abstract

Graphical