Result: We showed that in the presence of PSP, γ-T3 treatment induce a drastic activation of AMP-activated protein kinase (AMPK). This was accompanied with inactivation of acetyl-CoA carboxylase (ACC), as evidenced by the increased phosphorylation levels at Ser 79. In addition, PSP treatment also sensitized cancer cells toward γ-T3-induced cytotoxicity. Furthermore, we demonstrated for the first time that combination of PSP and γ-T3 treaments significantly reduced the growth of prostate tumor in vivo.
Conclusion: Our results indicate that PSP and γ-T3 treaments may have synergistic anti-cancer effect in vitro and in vivo, which warrants further investigation as a potential combination therapy for the treatment of cancer.

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Kallikrein-related peptidase 4 induces tumour microenvironment alterations that support tumour growth

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Objective: Kallikrein-related peptidase 4 (KLK4) is a protease with elevated production in prostate cancer versus benign tissue. KLK4 expression is associated with prostate cancer risk, and its activity favours tumour progression through increasing cell motility and growth. Importantly, over-production of KLK4 in prostate glandular cells precedes tumour formation, positioning the enzyme to play a role in early remodelling of the tumour microenvironment, a process essential for tumour growth. We sought to identify the proteins and downstream signalling pathways targeted by KLK4 activity, to define its role in tumour microenvironment remodelling and evaluate the efficacy of KLK4 inhibition as a cancer therapy.
Methods: KLK4-induced gene expression changes in prostate myofibroblasts, abundant cells in the tumour microenvironment, were assessed by microarray. Complementary proteomic approaches were employed for high-depth identification of KLK4 targets in cell secretions. Ingenuity Pathway Analysis software and in vitro validation was used to determine the resulting effect on cell function.
Results: KLK4 induced extensive gene expression changes in prostate myofibroblasts, through activation of transforming growth factor beta 1 (TGFβ1) and protease activated receptor-1 (PAR-1) signalling. Forty-five novel KLK4 substrates were also identified, some of which regulate the activity of TGFβ1, a key factor in tumour microenvironment remodelling. KLK4 has before been shown to activate PAR-1 on prostate myofibroblasts, and herein we showed this to induce expression of fibroblast growth factor-1 and -5.
Conclusions: KLK4 appears to initiate microenvironment remodelling via proteolytic activation of TGFβ1 and PAR-1 signalling. KLK4 is a promising target for inhibition as cancer therapy.

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A 3D in vitro model reflecting the androgen deprivation state in prostate cancer bone metastasis

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Objective: In castrate-resistant prostate cancer (CRPC), the prevailing organ for metastasis is bone, where the survival of cancer cells is regulated by the permissive metastatic niche offered by the bone marrow. The tumour microenvironment and cellular interactions with the matrix and bone cells enable metastasis and lead to cancer cells becoming androgen resistant. Hence, 3D models that mimic CRPC in terms of an androgen deprivation state (ADS) are needed to identify the mechanisms for CPRC growth in bone and further develop therapeutic strategies.
Methods: A humanised 3D bone model was engineered from melt electrospun fibres and seeded with patient-derived osteoblastic cells. The construct was osteogenically differentiated over 8 weeks in culture. Prostate cancer cells, such as LNCaP, C4-2B and PC3 were seeded ($3 \times 105/cm^2$) on the construct and co-cultured in FBS or CSS – representative of ADS in vivo.
Results: The bone construct exhibited a dense extracellular matrix (SEM, immunohistochemistry). Constructs were viable up to 21 days and a mixed population composed of osteoblasts and osteocytes was observed. When seeded on the bone constructs, cancer cells were shown to colonise the neo-bone matrix with LNCaP cells cultured in CSS displaying a more mesenchymal morphology. The expression of alkaline phosphatase in media was significantly altered from day 7 to day 21 and differences in the expression of bone and cancer genes were observed by qRT-PCR.
Conclusions: This model has proven to replicate CRPC in vitro and will be useful to assess the relevance of standard treatments and unravel new treatment approaches for CRPC.

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MSH2 translocations are associated with clinically aggressive prostate cancer

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Background: Chromosomal translocations between distinct gene loci are now recognized as a molecular hallmark of prostate cancer. More than 50% of all primary prostate cancers harbour an androgen induced TMPRSS2-ERG gene fusion. Recently, it has been noted that advanced prostate cancers have genomic re-arrangements that disrupt the DNA mismatch repair gene MSH2. To date it is unknown whether translocations in MSH2 occur via the same mechanism as TMPRSS2 and if they are androgen induced.

