PROSTATE CANCER

Myeloid-derived IL-23 drives CRPC

New research shows that myeloid-derived suppressor cells (MDSCs) drive progression to castration-resistant prostate cancer (CRPC) by secreting interleukin 23 (IL-23).

MDSCs were enriched in CRPC biopsy specimens compared with castration-sensitive prostate cancer (CSPC) specimens, and surgical castration increased tumour-infiltrating MDSC numbers in mouse models that develop CRPC upon androgen withdrawal. In vitro, MDSC-derived conditioned medium increased proliferation, survival, and androgen receptor (AR) target gene transcription under androgen-deprived conditions, suggesting that paracrine factors regulate CRPC emergence. Indeed, pharmacological depletion of tumour-infiltrating MDSCs delayed CRPC progression in castrated mice.

IL-23 was identified as the major MDSC-derived factor driving CRPC. Notably, MDSC-secreted IL-23 levels were markedly higher in mouse and human CRPC tumours than CSPCs. Plasma IL-23 levels were also increased in patients with CRPC and correlated with MDSC infiltration. In a functional validation, conditioned medium from MDSCs derived from *Il23*$^{+/+}$ mice, but not *Il23*$^{-/-}$ mice, induced proliferation, survival, and AR activity in androgen-dependent prostate cancer cells and organoids; similar findings were reported in vivo. Subsequent mechanistic experiments identified IL-23R–STAT3–RORγ signalling as the major pathway downstream of IL-23.

Notably, although treatment with AR antagonist enzalutamide alone was ineffective, the addition of an anti-IL-23 antibody reduced tumour volume, proliferation, and AR activity, and induced apoptosis, in mouse tumours, illustrating the therapeutic relevance.

These findings reveal a novel mechanism of immune-mediated resistance to androgen deprivation therapy (ADT) that could be exploited therapeutically. "Together with J. De Bono at ICR, we aim to run a clinical trial to assess if anti-IL-23 antibodies can improve ADT efficacy and revert ADT resistance in metastatic CRPC," concludes author Andrea Alimonti.

Conor A. Bradley

ORIGINAL ARTICLE Calcinotto, A. et al. IL-23 secreted by myeloid cells drives castration-resistant prostate cancer. *Nature* https://doi.org/10.1038/s41586-018-0266-0 (2018)

PROSTATE CANCER

FGFR1 reprogrammes cell metabolism

A new study reports that ectopic expression of fibroblast growth factor receptor 1 (FGFR1) reprogrammes energy metabolism in prostate cancer cells.

First, the effect of FGF signalling on cell metabolism was investigated. *Fgfr1*$^{-/-}$*Fgfr2*$^{-/-}$*Frs2a*$^{-/-}$ mouse embryonic fibroblasts (MEF$^{\Delta F}$ cells) had lower L-lactate dehydrogenase A chain (LDHA) and higher LDHB expression than parental MEFs, suggesting that FGF signalling regulates the reversible conversion of pyruvate to lactate via LDH isozymes. Indeed, further experiments revealed a shift from aerobic glycolysis to oxidative phosphorylation in MEF$^{\Delta F}$ cells and that FGFR1 enhances LDHA stability (via phosphorylation) and suppresses *Ldhb* transcription (via methylation).

In DU145 prostate cancer cells, *FGFR1* knockout decreased LDHA protein expression and increased LDHB mRNA and protein levels, consistent with a role for FGFR1 in the post-translational and transcriptional regulation of these respective isozymes. In line with MEF observations, depletion of *FGFR1* and *LDHA* induced a metabolic shift to oxidative phosphorylation, whereas *LDHB* depletion enhanced glycolysis. Subsequent DU145 xenograft experiments revealed that *LDHA* depletion reduced, but *LDHB* depletion enhanced, tumorigenicity.

Clinical relevance was assessed using a tissue microarray comprising 225 prostate cancer samples and 27 benign prostate tissue samples annotated with 15-year follow-up data. Compared with benign tissues, prostate cancer tissues had higher levels of total and phosphorylated LDHA, lower LDHB levels, and higher *FGFR1* expression, which were each associated with significantly shorter biochemical-recurrence-free survival.

The study shows that FGFR1 enhances aerobic glycolysis — the Warburg effect — to drive prostate cancer progression by differentially regulating LDHA and LDHB, which could be novel prognostic biomarkers.

Conor A. Bradley

ORIGINAL ARTICLE Liu, J. et al. Aberrant FGFR tyrosine kinase signaling enhances the Warburg effect by reprogramming LDH isoform expression and activity in prostate cancer. *Cancer Res.* https://doi.org/10.1158/0008-5472.CAN-17-3226 (2018)

PROSTATE CANCER

FGF2 causes genomic instability

Previously unaddressed questions concerning the role of fibroblast growth factor 2 (FGF2) in prostate cancer have been investigated in new research. The results of this study show that exogenous FGF2 causes chromosomal imbalances and DNA breakages in prostate cancer cells. Stromal FGF2 expression was positively associated with unfavourable clinico-pathological features. Treatments targeting the tumour stroma could have promise for patients with prostate cancer.

In vitro, treatment with recombinant FGF2 (rFGF2) increased the number of abnormal centrosomes and DNA-damage-associated foci in LNCAP and PC3 cells. Aberrant mitoses were also increased in these cells. In LNCAP cells, rFGF2 treatment caused increased numbers of chromosome 8. Co-treatment of LNCAP cells with rFGF plus the FGF receptor inhibitor dovitinib reduced the number of cells with abnormal centrosomes, chromosome 8 numbers, and DNA damage.

In vivo, bone-forming patient-derived xenografts (PDXs) with high endogenous FGF2 expression and hyperactivation of the FGF signalling axis exhibited increased mitosis and aberrant mitoses. These PDXs also had increased numbers of DNA-damage-associated foci.

In patient samples, immunohistochemical analysis showed that strong stromal FGF2 staining was associated with increased Gleason grade, pT stage, lymph node metastases, distant metastases, and biochemical recurrence.

Overall, these data show that FGF2 induces genomic instability in prostate cancer cells and that increased stromal FGF2 expression is associated with adverse clinicopathological features in patients with prostate cancer. Understanding the biological basis of these findings could lead to new treatments for this disease.

Louise Stone

ORIGINAL ARTICLE Pecqueux, C. et al. FGF-2 is a driving force for chromosomal instability and a stromal factor associated with adverse clinico-pathological features in prostate cancer. *Urol. Oncol.* https://doi.org/10.1016/j.urolonc.2018.05.020 (2018)