The activity of the Unfolded Protein Response Transducer IRE1 is a predictor of treatment resistant disease and a proxy of NEPC and RB1-loss like phenotypes

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Background: Prostate cancer (PCa) is androgen receptor (AR) driven, high incidence, significantly contributing to male cancer mortality through treatment resistant, metastatic disease. There is a need to improve risk stratification at diagnosis and treatment outcomes in patients at high-risk of metastasis. Through chromatin immunoprecipitation and bulk transcriptomics, we identified AR-regulated gene networks and AR-dependent PCa-development drivers, evaluating clinically available genomic scores in patient spatial transcriptomic (ST) datasets. The unfolded protein response (UPR) emerged as a biology that could be a proxy of PCa progression in both cancer cells and the tumour microenvironment. Consequently, we investigated whether a UPR activity score can accurately predict histological and biological heterogeneity in increasing levels of resolution; from single cell (SC) to ST and bulk datasets.

Methods: The UPR is a process that sustains AR activity and, several regulators of the IRE1-XBP1 axis (main UPR transducer) are AR targets. To test the effect of IRE1 modulation on AR naïve and CRPC settings we knocked out or mutated IRE1 in multiple cells lines and compared the effects of these genetic perturbations to cell lines resistant to androgen deprivation (ADT). We pharmacologically and physiologically perturbed AR (Charcoal Strip, R1881, Enzalutamide), IRE1 and Stress Responses (MKC8866, Thapsigargin, Tunicamycin, glutamine deprivation) in these lines as well as in P20-11 organoids carrying out single cell (scRNAseq) and bulk RNAseq. Integrating our datasets with publicly available ones we derived an IRE1 activity signature acting as a proxy of multiple driving PCa biologies. We then spatially assigned distinct subcompartments of the signature using v1/v2 Visium ST2 and Xenium 10X on FFPE/fresh frozen specimens derived from radical prostatectomies. Finally, we tested A) the prognostic value of our signature in localised and metastatic publicly available (TCGA, PCF/SU2C) and in-house generated patient cohorts as well as B) the ability of our signature to distinguish between tumoral and non-tumoral tissue in matched benign-malignant tissue samples.

Results: We have generated an IRE1-dependent transcriptomic score as proxy of multiple driving biologies (AR, Inflammation, DNA repair, Cell Cycle, EMT), multiple histological features (stroma, varying histological tumour grades, varying benign structures, PIN), and can prognosticate bulk datasets from large cohorts both in localised (TCGA) and metastatic (PCF/SU2C) cohorts (CamCapp, cBIOPORTAL). This score may be used as a tool alongside imaging AI and other multiomic modalities to inform neoadjuvant therapeutic formulations.

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