

Integration of stress response biology multi-omic datasets decodes prostate cancer dynamic disease progression and places IRE1 activity at the epicentre of acquired treatment resistance

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Introduction:

Prostate cancer (PCa) is an androgen receptor (AR) driven, high-incidence disease significantly contributing to cancer mortality. PCa is in need of better risk stratification at diagnosis and treatment outcomes in patients at high risk of metastasis. The unfolded protein response (UPR) is an AR-dependent process. However, the impact of the UPR transducer IRE1 on AR-dependent biology and treatment resistance has not been defined.

Material and method:

We use diverse pre-clinical models of stress response (2D and 3D) to describe IRE1 activity impact on multiple disease stages and demonstrate its involvement with poor prognosis (RB1 loss), and cell lineage determination (club phenotypes). We genetically and pharmacologically perturbed AR and IRE1 activity in multiple pre-clinical PCa models and observed that long-term adaptation to IRE1 activity loss, leads to a lineage shift that confers treatment resistance characteristics in AR sensitive models.

Result and discussion:

In parallel, we show that castration resistant PCa (CRPC) models have low IRE1 activity and that androgen deprivation therapy (ADT) suppresses IRE1 activity. By treating these CRPC models with an IRE1 activator, we sensitised them to both physiological and pharmacological (Enzalutamide) ADT. Integrating clinical, pre-clinical, bulk, single cell and spatial transcriptomic datasets, we chart IRE1 activity throughout PCa evolution by developing an IRE1 activity gene set (IRE1_sig1.0) reflecting both tumoral and micro-environmental niches. IRE1_sig1.0 has distinct expression profiles in AR positive (HSPC and CRPC) and AR negative (CRPC) disease reflecting tumoral identity as well as tumoral content. Using diverse datasets such as the Dream Team West Coast, META855 and 55K GRID cohorts we validated IRE1_sig1.0 against multiple clinical correlates in more than 55000 patients and found that it significantly correlates with response to ARSI, grade group, NCCN and Decipher scores.

Conclusion:

As such, IRE1_sig1.0 prognosticates localised and metastatic disease independently from AR activity in terms of metastatic progression, biochemical recurrence, prostate cancer specific mortality and consequently, may guide IRE1 modulation as a novel combination therapeutic. Our study showcases a forward translation, data integration pipeline which may distil actionable targets and biomarkers from studying a fundamental biological homeostatic mechanism that represents cells in both the tumour and the microenvironment.

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