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The mesenchymal-to-epithelial reverting transition is enriched in metastatic castration resistant prostate cancer and correlates with poor survival

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Objective: Despite recent recognition that the epithelial-mesenchymal transition (EMT) program acts in a dynamic manner (termed Epithelial to Mesenchymal Plasticity or EMP) during carcinoma metastasis, it has largely been ignored in the discovery and development of EMT-targeted therapies. In part, this has stemmed from a lack of preclinical models that can mimic the full dynamic nature of EMP and the perception that the EMT-reverting transition [or mesenchymal-epithelial reverting transition; (MErT)] is a mere antithesis of EMT. The objective of this study was to develop the first PCa model capable of recapitulating the dynamic nature of EMP.
Methods: The LNCaP cell line was utilised to develop a reversible model of SNAI1-mediated EMT. Transcriptional profiling and an array of biological assays were performed to assess the role of EMT and MErT on phenotypes relevant to cancer progression.
Results: Temporal transcriptional profiling of EMT-induced tumour cells during their active reversion to an epithelial phenotype, revealed MErT to be enriched in clinical samples of lethal metastatic castration resistant prostate cancer. A MErT signature was identified to correlate with faster prostate cancer patient relapse and poor survival across multiple carcinoma types. MErT is not simply the mirror image of EMT and reveal unique transcriptional subprograms operating during MErT.
Conclusions: In this study we have identified a MErT associated with carcinoma metastasis and poor clinical outcome, and reveal unique transcriptional networks activated during the reversion of EMT. This study highlights the need to consider the dynamic nature of EMP during the metastatic process for the application of potential EMT-targeted therapies into the clinic, as inhibiting EMT (i.e. activating MErT) may reawaken dormant disseminated cells and be detrimental to the patient.

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The essential role of ARF in prostate cancer microenvironment

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Objective: Prostate cancer is the leading cause of cancer-related deaths among men, in particular, the fourth most common cause of death from cancer among Asian/Pacific men. Tumor microenvironment contributes to the origin, restriction, invasion and progression of prostate cancer. Oncogenic insults induced by gene mutation may promote or restrict tumor progression depending on activation of cellular senescence such as Pten loss induced p53-dependent tumor restriction. ARF plays an important role in senescence but its function in genetic context of Pten loss is largely unknown. p53 mutation is frequently found in various cancers and PTEN mutation or inactivation is found in 90% cases of prostate cancer. Genetic engineering mouse model with Pten loss would allow us to explore novel signaling and avenues for targeted therapy.
Methods: Pten/Trp53 knockout mouse model, cell line culture, immunofluorescence, immunohistochemistry were applied for investigation.
Results: ARF expression is found in both epithelial and stromal cells in prostate cancer of Pten/Trp53 null mice. ARF overexpression decreased cellular adhesion through targeting extracellular matrix via matrix metalloproteinase (MMP)7 in human prostate cancer PC3 cells. ARF associates with MMP7 in PC3 and DU145 cells. MMP7 expression was positively correlated with ARF elevation in human prostate cancer specimens.
Conclusions: Oncogenic insults may cause damages to cellular matrix and regulate cancer progression through changes in microenvironment. Combined targeting of ARF with MMP7 inhibitor would be a novel avenue for treatment of aggressive prostate cancer.

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Resistance to abiraterone based castration is not predicted by ARv7 status in high-risk prostate cancer

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Purpose: Androgen receptor splice variants (ARvs) are upregulated in response to castration, and can activate transcription in the absence of ligand. Recent evidence suggests that ARv7 expression predicts resistance to abiraterone and enzalutamide. We were therefore interested to determine the expression of ARv7 in localized prostate cancer, and correlate this with response to an abiraterone-containing castration regimen.
Patients and Methods: We performed an open label Phase II neoadjuvant study of degarelix, abiraterone, bicalutamide and prednisolone for 24 weeks in men with high-risk clinically localized prostate cancer using an optimal 2-stage design. The primary endpoints were safety/tolerability and pT0 response rate. ARv7 expression was determined by immunohistochemistry and qRT-PCR in both pre- and post treatment tumor specimens, and correlated with pathological response.