lacking. We wished to perform an unbiased screen of transcriptional and lipidomic changes present in adipose tissue associated with high-risk prostate cancer.
Methods: In 2011 we incorporated routine adipose tissue collection into our existing banking program, whereby fresh paired periprostatic (anterior fat pad) and subcutaneous (abdominal wall) adipose tissue was obtained from patients undergoing prostatectomy for localized prostate cancer. Transcriptional changes in subcutaneous and periprostatic adipose tissue associated with high (n = 24) and low (n = 24) risk prostate cancer were determined using the Illumina HT12v4 BeadChip. Differences in lipid speciation were determined by LC/MS.
Results: To date, clinically annotated adipose tissue samples have been collected on >400 patients with a variety of risk profiles, including post androgen deprivation therapy. Principal component analysis of global transcriptional profiles shows distinct clustering of individual tissue types (SC vs PP, high vs low), permitting the generation of a highly accurate gene classifier (AUC >0.95) based on as few as 5 transcripts. Significant pathways enriched on GSEA include Chemokine signaling (q = 0.006) and NF-kappa B signaling pathway (q = 0.02). Alterations in lipid speciation include significant decreases in the concentration of 20:4 containing PC lipids.
Conclusions: Adipose tissue from patients with high-risk prostate cancer demonstrates distinct transcriptional and lipidomic profiles compared to patients with low-risk disease. These changes are currently being orthogonally validated.

108
Investigating the role of neuroendocrine transdifferentiation in the progression to castration resistant prostate cancer

Ellca Ratther, Katrina Sweeney, Nataly Stylianou, Colleen C Nelson, Elizabeth D Williams and Brett G Hollier
Australian Prostate Cancer Research Centre – Queensland, Institute of Health and Biomedical Innovation, Queensland University of Technology, Princess Alexandra Hospital, Translational Research Institute, Brisbane, Australia

Objective: Androgen targeted therapies (ATT) are the most commonly used treatments in prostate cancer (PCa).While these therapies are initially effective, PCa cells are able to activate adaptive response pathways to survive these therapies and progress to castration resistant PCa (CRPC), a highly aggressive and ultimately lethal stage of the disease. Neuroendocrine transdifferentiation (NEtD), a process whereby PCa cells gain neuroendocrine-like characteristics, has been implicated in the development of CRPC. The objective of this study is to develop and characterise models of therapy-induced NEtD to investigate the role of this adaptive plasticity in the progression to CRPC.
Methods: NEtD was modelled in vitro using LNCaP cells treated with ATTs, including ARN509, Bicalutamide and Enzalutamide. An LNCaP-derived model of transient androgen receptor (AR) knockdown using an inducible shRNA system was also developed. Expression of neuroendocrine (NE) markers was assessed over time using quantitative RT-PCR (qRT-PCR), western blotting and FACS analysis. The expression of NE markers was compared to that of androgen regulated genes and key drivers of additional adaptive response pathways involved in PCa progression.
Results: Preliminary results have demonstrated that androgen deprivation, ATTs and AR knockdown induce varying temporal dynamics of NEtD in LNCaP cells. We observe substantial overlap of therapy-induced NEtD with additional adaptive response pathways. A number of these genes have been identified to have increased expression in metastatic and CRPC samples.
Conclusions: As the incidence of NEtD PCa is expected to rise rapidly through the prolonged and sequential use of new ATTs, there is an urgent clinical need to identify the molecular mechanisms involved in the development of NEtD PCa. The development and characterisation of models of NEtD will allow for the identification of novel biomarkers and therapeutic targets for the clinical management of advanced PCa.

110
Targeting neuropilin-1 to inhibit prostate cancer invasion and metastasis

Marianna Volpert[1], Brian W-C Tse[1], Nataly Stylianou[1], Ellca Ratther[1], Stephen McPherson[1], Taylor Costa[1], Kayla McGowan[1], Melanie L Lehman[1], Ladan Fazli[2], Martin E Gleave[2], Pamela J Russell[1], Jennifer H Gunter[1], Elizabeth Williams[1], Colleen C Nelson[1] and Brett G Hollier[1]
[1]Australian Prostate Cancer Research Centre – Queensland, Institute of Health and Biomedical Innovation, Queensland University of Technology, Princess Alexandra Hospital, Translational Research Institute, Brisbane, Australia
[2]Vancouver Prostate Centre, University of British Columbia, Vancouver, Canada

Objective: Recent reports provide evidence that the epithelial-to-mesenchymal transition (EMT) plays a key role in prostate cancer (PCa) metastasis and therapy resistance. We have recently identified the cell surface receptor, Neuropilin-1 (NRP1) to be increased during epithelial-mesenchymal transition (EMT) and this study aims to determine whether the inhibition of NRP1 will be a feasible therapeutic strategy for blocking PCa metastasis and therapy resistance.
Methods: qRT-PCR and western blotting was used to determine the expression levels of NRP1 in metastatic PCa cell lines. NRP1 expression in clinical samples was assessed using immunohistochemistry and bioinformatic analysis of multiple independent patient cohorts. RNAi approaches were used to assess the functional role of NRP1 in cell migration and invasion.
Results: NRP1 expression is elevated in metastatic PCa cells. In vitro studies have revealed the suppression of endogenous NRP1 levels to significantly inhibit the migratory and invasive behaviour of metastatic PCa cells. Importantly, NRP1 is increased in metastatic and therapy resistant clinical PCa samples and high NRP1 levels to be associated with shorter time to tumour relapse and shorter overall survival.
Conclusion: These results will provide the preclinical data necessary to rationalise the use of anti-NRP1 directed therapies for clinical use in PCa patients. Pharmaceutical companies currently have antibody and small molecule inhibitors under early development as anticancer therapeutics. This study will pave the way for larger scale preclinical and clinical trials in the PCa setting, with the ultimate goal of accelerating the translation of these therapeutics into the clinic for PCa patients.

