Nature Reviews Urology | Published online 22 December 2015; doi:10.1038/nrurol.2015.305

PROSTATE CANCER

Proteomics provides a prognostic marker

The most comprehensive analysis of the proteome of primary prostate cancer to date has been published in *European Urology*.

Using mass spectrometry, Iglesias-Gato and colleagues performed genome-scale quantitative proteomic profiling of formalin-fixed paraffin-embedded prostatectomy samples from tumours and neighbouring nonmalignant tissue.

In total, 28 tumour samples and eight samples from adjacent tissue were analysed and the investigators observed that 649 proteins were differentially expressed between these sample types. Comparison of the profile of these proteins with transcriptome studies showed statistically significant but limited concordance between changes in protein and corresponding mRNA expression and a stronger concordance for downregulated proteins and mRNA, specifically. A significant correlation between hypermethylation of gene promoters and a reduction in the corresponding protein levels was also observed.

Levels of proteins involved in cell adhesion and glycolytic enzymes were considerably reduced in cancer tissue, but proteins associated with mitochondria, vesicular transport, ribosomal biosynthesis, and RNA processing were increased. Further analysis revealed elevated complex IV Cytochrome C oxidase activity in tumour samples, suggesting that mitochondrial oxidative phosphorylation capacity is increased in prostate cancer and contributes to the energy needs of the tumour. *In vitro* treatment of 22rv1 prostate cancer cells with the carnitine palmitoyltransferase II inhibitor L-aminocarnitine, or the fatty acid oxidation inhibitor trimetazidine, both of which target mitochondrial bioenergetic function, reduced cell proliferation.

Comparison of the proteome of tumours with a primary Gleason score of 4 with those with a primary score of 3 revealed that only a small number of proteins were differentially expressed between these tumour types. Of these proteins, pro-neuropeptide Y (pro-NPY) had the highest measurable increase and also showed significantly increased expression in tumour tissue compared with benign tissue. In a panel of 400 tumour samples from 10 cancer types, immunohistochemical staining for pro-NPY showed specificity for prostate cancer.

Analysis of independent tissue microarray samples from 289 patients (196 of which had associated benign tissue available) showed significant pro-NPY staining in tumour tissue compared with benign tissue. Patients whose tumours exhibited moderate to high pro-NPY staining were at a significantly increased risk of prostate-cancer-specific mortality. When stratified by histological score, pro-NPY levels were no longer predictive of mortality for patients with high-grade tumours, but they were for low-grade tumours. Of the tumours that were positive for ERG expression, 52% also had high pro-NPY levels and multivariate analysis showed that high expression of ERG and pro-NPY combined were predictive of cancer-specific mortality independently of Gleason score. The prognostic value of pro-NPY in combination with ERG was then validated in a independent patient cohort.

This study is the first system-wide analysis of changes to the proteome in localized prostate cancer. This proteomics-based approach has identified pro-NPY as a new prognostic marker for prostate cancer and offers great possibilities for translational research and precision medicine.

Louise Stone

ORIGINAL ARTICLE Iglesias-Gato, D. *et al.* The proteome of primary prostate cancer. *Eur. Urol.* http://dx.doi.org/10.1016/j.eururo.2015.10.053