P13 Proteomics- driven therapeutic agents for Prostate Cancer

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Introduction & Objectives: Prostate cancer is the second most commonly diagnosed malignancy, and the fifth leading cause of death in men. 50-60% of prostate cancer cases detected via PSA screening are over-diagnosed, which leads frequently to overtreatment. On the contrary, for patients progressing to metastatic disease after androgen deprivation therapy, there are no effective therapies, and the median survival is 2 years. This reflects the paradox that patients' who do not require treatment are over-treated, while for those that require immediate intervention, effective treatment options are not available. Driven by the unmet need to improve the therapeutic opportunities, the objective of this study is to characterize the molecular landscape of prostate cancer through the proteomics analysis of disease affected tissue, and consequently to predict putative therapeutic agents that are able to reverse the disease phenotype.

Materials & Methods: Twenty-two fresh-frozen tissue specimens (n=5 samples from patients with benign prostatic hyperplasia and n=17 samples from patients with prostate cancer) were analyzed using liquid chromatography coupled with tandem mass spectrometry. Ethical approval was obtained from Hannover Medical School. Mass spectrometry analysis was performed using an Orbitrap LTQ Velos (Thermo Finnigan, Bremen, Germany). Raw files were analyzed with Proteome Discoverer 1.4. Two missed cleavage sites, a precursor mass tolerance of 10 ppm and fragment mass tolerance of 0.05 Da were allowed. Individual data sets have been integrated using a clustering approach, followed by label-free quantification. Statistical analysis was performed using Mann Whitney. Connectivity Map analysis (CMap, http://www.broadinstitute.org/CMAP/) was employed to predict compounds/drugs that are able to reverse prostate cancer signature.

Results: 7,498 peptides were detected in at least 60% of benign and/or malignant samples and corresponded to 4,003 proteins including 1,106 identified based on at least 2 peptides. For the latter, statistical analysis revealed a significant change in the abundance of 254 proteins ($p<0.05$) including 55 proteins up- and 199 proteins down-regulated in cancer vs benign samples. Xenobiotic Metabolism, PTEN and Clathrin-mediated Endocytosis Signaling were found as the top 3 most significantly enriched pathways. Moreover, a total of 56 drugs/ compounds have been predicted ($p<0.05$) to reverse the disease signature. This includes among others drugs/ compounds that have shown to have a potential anti-cancer effect in vitro and/ or in vivo in the context of prostate cancer such as berberine or fulvestrant, supporting the validity of the analysis.

Conclusions: Tissue proteomics provides a direct link to disease pathophysiology, and in combination with CMap analysis allows predicting drugs/ compounds with the potential to reverse disease phenotype. Further validation of the findings in additional tissue proteomics data sets is ongoing.