**Glycolysis and lipid metabolism as predictors of prostate cancer aggressiveness**

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**Objective:** To assess expression profiles of glycolytic and lipid metabolism genes as predictors of poor prognosis and of extraprostatic extension (EPE) observed in radiology scans for PCa.

**Methods:** mRNA and protein expression data from tumour tissues for genes involved in KEGG glycolytic and lipid metabolism pathways (total 215 genes) was downloaded for 498 PCa patients from the Cancer Genomics Atlas (TCGA). Unsupervised clustering of the data resulted in six patient clusters (C1-C6) and identified an optimal subset of 15 genes with each gene being altered in ≥16% patients. The enrichment of these clusters for EPE as seminal vesicles, regional lymphadenopathy and distant metastasis was computed using results from radiology scans (MRI, pelvis and bone CT). The clusters were used to train a multinomial classifier based on expression levels of the 15 genes, and the classifier was validated on an independent dataset from Taylors et al. (2010)[1].

**Results:** Cluster C1 presented a high-risk patient subgroup with the poorest outcome – disease-free survival (DFS) probability of <40% at 80 months and Cox proportional hazards ratio (HR) 3.27 – whereas C5 presented the lowest risk subgroup with DFS ~85% at 80 months. C1, C3 and C5 showed the most differences between their DFS (logrank-test p=0.018). While the overall proportion of patients with EPE was 14.87%, C1 was significantly enriched with 24.56% EPE (hypergeometric-test p=0.0193). The average accuracy of the classifier using 80-20 cross-validation on TCGA was 0.76, and its application to the Taylors et al. data identified similarly prognostic clusters (p=0.0093) with C1 displaying the poorest (~40% at 50 months, HR: 3.31) and C5 the most favourable DFS (>60% even at 125 months).

**Conclusions:** In agreement with recent studies in the area[2], our study indicates a significant link between expression of glucose and lipid-metabolism pathways and poor prognosis in PCa. Additionally, our study also suggests that EPE in radiology scans could be an important determinant of this link. Towards this end, we are developing radiology image segmentation software using deep learning, in particular, to quantify the EPE and microenvironmental factors including peri-prostatic adipose tissue (PPAT) which is posited feed the metabolically active PCa cells[3]. PPAT measurements will be integrated with glucose and lipid profiles measured from blood to predict patient risk and to guide surgical decisions.

[1] Taylors et al., Cancer Cell 2010, 18(1):11-22.

[2] Latonen et al., Nature Comms 2017, 9:1176.

[3] Nassar et al., BJUI 2018, doi.org/10.1111/bju.14173.