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PROSTATE CANCER

Novel subtyping could aid stratification and therapy


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New results show that RNA expression data can be used to categorize prostate cancer into three distinct molecular subtypes that can be used to detect aggressive tumours and improve diagnostics.

You *et al.* mapped pathway activation gene expression signatures into three categories: prostate-cancer-relevant signalling pathways, genetic and genomic alterations, and biological features related to aggressive prostate cancer progression. Pathway activation scores were then computed in each specimen in the DISC cohort ($n = 1{,}321$). Using these pathway activation profiles, a consensus map of non-negative matrix factorization (NMF) clustering showed that the samples could be split into three groups that correspond to three subtypes: PCS1, PCS2, and PCS3. PCS1 displayed high activation scores for EZH2, PTEN, PRF, ES, AV and AR-V pathways. PCS2 was characterized by ERG pathway activation, as well as AR, FOXA1, and SPOP. By comparison, PCS3 showed high activation of RAS, PN, and MES, but low activation of AR and AR-V pathways. Validation using a 14-pathway classifier was able to accurately classify tumours in the DISC cohort into these three subtypes.

Comparison with other categorization methods showed that the PCS1 group contained the largest number of Gleason ≥8 tumours and also the poorest outcomes. However, these factors did not seem to be linked, with PCS1 tumours having poorer metastasis-free survival regardless of whether they were classified as Gleason score ≤7 or ≥8. Further analysis showed that PCS1 was the most aggressive of the three subtypes.

The team then went on to study whether the subtypes corresponded to specific cells of origin according to expression of genes characteristic of luminal or basal cells. PCS1 and PCS2 showed strong associations with luminal genes, whereas PCS3 could be designated as a basal subtype. A 37-gene panel built by You *et al.* was able to distinguish significantly different gene expression patterns between the three subtypes. Interestingly, this panel was able not only to differentiate between subtypes but was also able to assign tumours to the PCS1 group using tissue and circulating tumour cells, suggesting that it could be used as a noninvasive method to classify prostate tumours and guide therapy decisions.

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ORIGINAL ARTICLE You, S. *et al.* Integrated classification of prostate cancer reveals a novel luminal subtype with poor outcome. *Cancer Res.* http://dx.doi.org/10.1158/0008-5472.CAN-16-0902 (2016)