PROSTATE CANCER

Lineage predicts ADT response

The commercial, high-throughput PAM50 gene expression classifier can identify basal-like and luminal-like prostate cancer subtypes, which have differing clinical behaviour and response to androgen deprivation therapy (ADT). These findings give new insights into prostate cancer biology and indicate an opportunity to predict patient responses to ADT.

PAM50 is used in breast cancer to categorize tumours into luminal A, luminal B, HER2, and basal subtypes. Similar lineages have been suggested in prostate cancer and a team from multiple institutions in the USA sought to clarify the applicability of PAM50 (excluding the HER2 subtype) and relevance of this classification in prostate tumours. In a set of 1,567 postprostatectomy tumour samples, PAM50 categorized 34.3% as luminal A, 28.5% as luminal B, and 37.1% as basal. In comparison with men with luminal A and basal cancers, those with luminal B cancers had worse clinical outcomes (for example, distant-metastasis-free survival (DMFS), prostate-cancer-specific survival, and overall

survival). In addition, men with luminal B tumours had the highest preoperative PSA levels, Gleason scores, extracapsular extension, and lymph node invasion rates.

Investigation of molecular lineage markers showed that the 91-gene CD49f signature, which is characteristic of basal lineage, was more common in basal tumours, whereas expression of the luminal markers *NKX3.1*, *KRT18*, and *AR* was increased in the luminal subtypes. Gene set analysis demonstrated positive enrichment of androgen activity and MYC pathways in luminal subtypes compared with the basal subtype. Interestingly, the PAM50 proliferation score was lower for luminal A than for luminal B tumours, which might explain the differing clinical outcomes despite molecular similarities in these two subtypes. Findings in 2,215 prospectively collected samples were similar.

The disparity in androgen activity between the luminal and basal subtypes prompted the researchers to evaluate whether subtype characterization could enable prediction of ADT responses. Matched

subgroup analysis, in which luminal A and basal subtypes were merged owing to similar outcomes of ADT, showed that men with luminal B tumours who received ADT had better DMFS than those who did not receive ADT, whereas those who received ADT in the other subgroups had worse DMFS. Thus, tumour classification based on these molecular subtypes might be a possibility to personalize the use of ADT.

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