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PROSTATE CANCER

A prognostic pathway signature for personalizing therapy

The DNA damage and repair (DDR) pathway signature of high-risk prostate tumours shows a strong correlation with prognostic outcomes, and DDR pathway profiling could be useful prognostic tool for stratifying patients with this disease, according to new data reported in *JAMA Oncology*.

Evans and colleagues developed a patient-level gene set enrichment analysis (GSEA)–based pathway profiling approach for predicting patient prognosis. Initial pathway profiling and GSEA was conducted using individual patient gene rank profiles as input for a preranked GSEA algorithm with 1,000 permutations, which generated individual patient DDR profiles with normalized gene enrichment scores.

DDR pathway profiling was conducted for 1,090 men and revealed individual variation in the DDR pathway. Analysis of DDR gene set enrichment and standard clinical variables revealed weak but significant correlation of Gleason score with 16 of 17 gene sets, age with seven gene sets, and serum PSA level with three gene sets. *AR* expression was significantly, but weakly, correlated with all DDR gene sets, with *AR* transcriptional activity showing stronger correlation, and *ERG* expression was significantly correlated with 13 of 17 DDR gene sets.

Investigation of the prognostic potential of individual pathways revealed that, on univariate analysis, Seven of nine pathways had significant correlation with worse metastasis-free survival. Individual pathways were also examined using multivariate analysis, to control for confounders, which showed that four of nine pathways significantly correlated with clinical outcomes.

The investigators then developed a prognostic signature of combined DDR pathways using metastasis-free survival data from a training cohort of 545 men. As well as significantly correlating with metastasis-free survival in this cohort, this signature correlated with biochemical-recurrence-free survival and overall survival, and this association was independent of standard clinical variables on multivariate analysis.

Further examination showed that this DDR pathway signature significantly correlated with biochemical-recurrence-free, metastasis-free and overall survival in three pooled validation cohorts (n = 232, 130, and 183), and remained significant independent of standard clinical variables on multivariate analysis.

This novel GSEA-based profiling approach revealed patient-level variations in the DDR pathway in tumours from men with high-risk prostate cancer. These pathway profiles have prognostic value and correlate with survival outcomes.

The DDR pathway signature could be a useful tool for identifying men at risk of disease progression and select patients for treatment intensification, further helping to personalize therapy for men with high-risk prostate cancer. To this end, Evans and colleagues have constructed a nomogram for predicting metastasis-free survival at 10 years, based on these models, to support the clinical use of these findings.

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ORIGINAL ARTICLE Evans, J. R. *et al.* Patient-Level DNA damage and repair pathway profiles and prognosis after prostatectomy for high-risk prostate cancer. *JAMA Oncol.* http://dx.doi.org/10.1001/jamaoncol.2015.4955 (2016)