Low expression of PCA3 in localized prostate tumors is associated with clinical recurrence and metastatic progression

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Background: The long non-coding RNA, Prostate cancer antigen 3 (PCA3), is a prostate-specific diagnostic biomarker that has been clinically validated in urine samples. While PCA3 scores have clear diagnositic utility, the prognostic value of PCA3 scores is unclear. Here, we quantified PCA3 in radical prostatectomy (RP) specimens to determine if PCA3 expression correlated with clinical or pathological features such as risk, tumor progression and treatment outcome.

Methods: A total of 4,143 gene expression profiles from RP patients with high risk tumors were obtained from the Decipher GRID™ prostate cancer database for both multi-institutional retrospective and prospective cohorts. The primary clinical endpoint for this study was distant metastasis-free survival. Both univariable and multivariable logistic regression analyses were used to evaluate the association of PCA3 with clinical variables. Finally, Cox proportional hazards models were used to determine the performance of PCA3 in predicting risk of metastasis.

Results: We observed significantly increased PCA3 expression levels in malignant tissue compared to benign tissue ($p<0.0001$). In primary tumors, PCA3 demonstrated a bimodal distribution where low PCA3 expression was significantly associated with adverse pathological variables ($p<0.001$). Moreover, low PCA3 was associated with clinical recurrence outcome and a greater probability of metastatic progression ($p<0.001$). Functional analysis revealed that low PCA3 is enriched with low AR signaling score ($p<0.0001$), expression profiles similar to basal-like PCa cells ($p<0.0001$) and inversely correlated with processes involved in invasion and metastasis.

Conclusions: Analysis of PCA3 expression in over 4000 prostate cancer tumors revealed an unexpected binomial distribution ith low expression associated with unfavorable patient outcome and increased risk of cancer progression and potential metastatic development. These findings may aid to identify patients with increased metastatic risk.

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