⮕ PROSTATE CANCER

Prostate quartet

Current methods to measure aggressiveness of prostate adenocarcinoma (PCA) are based on pathological and clinical characteristics of the tumour cells — such as Gleason score or levels of prostate-specific antigen (PSA) — but these are often inadequate given the heterogeneity of this type of cancer. Ron DePinho and colleagues have now identified a four-gene signature that is able to predict recurrence and metastasis more accurately in human PCAs.

Given that PTEN loss is associated with prostate cancer, the authors used a mouse model of PCA in which deletion of Pten in the prostate ($Pten^{pc-/-}$) results in prostate intraepithelial neoplasia (PIN), which can progress to PCA after a long latency period. To determine what drives this progression, the authors analysed the transcriptome of PIN from $Pten^{pc-/-}$ mice and found increased transforming growth factor-β (TGFβ)–bone morphogenetic protein (BMP) signalling when compared with the transcriptome of normal prostate epithelium in wild-type mice. Accordingly, they identified high levels of SMAD4 — a mediator of TGFβ and BMP signalling — in PIN from $Pten^{pc-/-}$ mice. Interestingly, SMAD4 is downregulated in human metastatic PCA, and when SMAD4 was knocked down in xenografts derived from PC3 prostate cancer cells, an increased frequency of metastases to the lung occurred. This led the authors to speculate that SMAD4 might inhibit progression from PIN to PCA. To further investigate this hypothesis, they engineered another mouse model lacking both Pten and Smad4 in the prostate ($Pten^{pc-/-}$;$Smad4^{pc-/-}$). Whereas $Pten^{pc-/-}$ mice developed invasive features after 19 weeks of age and survived beyond 1 year of age, $Pten^{pc-/-}$;$Smad4^{pc-/-}$ mice acquired highly aggressive and invasive PCA by 15 weeks of age and most died by 32 weeks of age.

How does SMAD4 prevent progression to a more aggressive phenotype of PCA? The authors analysed the PCA transcriptomes from both models, and in $Pten^{pc-/-}$;$Smad4^{pc-/-}$ mice they observed an enrichment of genes of two categories: cell division and cellular movement. Among the genes within the cell division category, cyclin D1 (Ccnd1) was the only one which was not only expressed in human metastatic PCA but which also had a SMAD-binding element (SBE) in its promoter. Consequently, overexpression of CCND1 in PC3 cells enhanced xenograft tumour growth. In turn, when SMAD4 was expressed in tumour cells from $Pten^{pc-/-}$;$Smad4^{pc-/-}$ mice, CCND1 expression was downregulated on treatment with TGFβ. Next, the authors validated the ability of ten of the 84 cellular movement genes to enhance invasive properties of human prostate cancer cells. From these, secreted phosphoprotein 1 (Spp1) was selected for further analysis, as this gene has been associated with PCA progression and has a conserved SBE in the promoter. Accordingly, knock down of Spp1 in $Pten^{pc-/-}$;$Smad4^{pc-/-}$ tumour cells inhibited the invasive activity of these cells, whereas SPP1 overexpression in PC3 cell xenografts increased metastasis formation in the lumbar lymph node and the lung.

Finally, the authors investigated whether the expression of the four genes — *PTEN*, *SMAD4*, *SPP1* and *CCND1* — could be used as a predictive tool for survival based on two independent cohorts of patients with prostate cancer and through immunohistochemical staining of tumour tissue microarrays of 405 tumour samples of prostate cancer. Indeed, this model enhanced the prognostic accuracy of the Gleason score and also acted as an independent prognostic factor with improved precision.

This study identifies *PTEN*, *SMAD4*, *CCND1* and *SPP1* as drivers of PCA progression and as a four-gene signature with prognostic value for predicting the risk of developing metastatic PCA that may complement the currently available methods to improve the evidence-based management of patients.

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