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Editorial

JunB and PTEN in prostate cancer: 'loss is nothing else than change'

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Prostate cancer (PCa) is the second most common cause of death in men worldwide and ~72 000 die from PCa in the European Union each year (http://seer.cancer.gov/statfacts/html/prost.html). Owing to its heterogeneous nature, no clear disease pathways have been defined to date, but both genetic and environmental factors appear to be crucial for PCa development. Although most PCas show relatively slow growth and can be controlled by androgen depletion, sometimes for decades, patients may develop a highly aggressive PCa with often fatal outcome. Currently, no suitable prognostic biomarkers are available to distinguish nonaggressive tumors from those that will progress to lethal disease. As a result, patients suffer from substantial and expensive overtreatment with deleterious effects on quality of life such as incontinence and/or impotence.[1,2]

The early stages of prostate carcinogenesis feature alterations in several signaling pathways, the most prominent of which is the PI3K–AKT pathway. In human cancer, PI3K is most frequently activated by the inactivation of its negative regulator PTEN. Expression of PTEN inversely correlates with the stage of prostate cancerogenesis, and PCas are often associated with monoallelic PTEN mutations.[3] Complete loss of PTEN expression is generally associated with metastatic cancers, and several mouse models of PCa are based on conditional deletion of *Pten* in the prostate epithelium. These mouse models have provided valuable insights into the disease.[4]

PTEN cooperates with a number of signaling pathways, such as the JNK stress kinase pathway, to modulate PCa progression to invasive adenocarcinoma. Thus, PTEN inactivation in human prostate tumors is accompanied by increased JNK activity.[5] Conversely, JNK ablation in mouse prostate epithelium results in invasive PCa, when combined with PTEN loss.[6] Thus, JNK signaling via its downstream targets, which includes members of the activating protein 1 (AP-1) family of transcription factors, might have tumor modulating functions.[7] The AP-1 members c-Fos, c-Jun as well as phosphorylated-c-Jun are elevated in human PCa samples and lead to the increased proliferation and invasiveness of PCa cell lines.[8] Conversely, depletion of JunB in prostatic transient amplifying cells *in vitro* promoted escape from senescence through the inactivation of p16/pRb.[9] This is consistent with the tumor-suppressive functions of JunB in the myeloid and lymphoid lineages.[10,11]

In this issue, Thomsen *et al*. investigated the role of JunB in the *PSA-Cre* mediated *Pten* knockout mouse model, which enables the investigation of the time window from low-grade prostate intraepithelial neoplasia (PIN) to high-grade PIN lesions, which is of special human relevance.[12] Their results provide yet another *in vivo* hint as to the tumor-suppressive function of mitogenic signaling mediators. The authors demonstrate that combined knockout of *Pten* and *JunB* in prostate epithelial cells results in formation of invasive cancers *in vivo.* Moreover, the deletion of *Pten* and *JunB* by orthotopic delivery of adenoviral Cre recombinase in a subpopulation of adult prostate epithelial cells also resulted in invasive tumor formation. Previous studies showed that PTEN induces the activation of a p53-dependent cellular senescence response.[13] In the present study, Thomsen *et al*. observed increased cellular proliferation after the loss of both *Pten* and *JunB* and decreased expression of the cell cycle inhibitors $p16^{Ink4a}$ and $p21^{CIP1}$, which are key inducers of cellular senescence (Figure 1).[14] These findings were supported by data from three different gene expression data sets of human PCa samples, were low-grade tumors express JUNB, but high-grade and metastatic tumors are devoid of JUNB and $p21^{CIP}$ expression. Intriguingly, the authors do not observe any similar effect on PIN development by codeletion of *Pten* and *c-Jun*, suggesting a specific role for JunB only in limiting PIN progression. It might still be worthwhile to explore the function of c-Jun in a more aggressive PCa mouse model such as the *Pb-Cre*.[15]

In addition, the authors observed alterations in gene expression in the tumor stroma of *Pten; JunB* double-knockout mice, suggesting that the genetic alterations within *Pten*-deleted tumors can influence the tumor microenvironment. Specifically, the authors describe increased SPP1/Osteopontin and S100A8/A9 expression in monocytes and macrophages of the tumor stroma derived from double-knockout mice. This finding is of considerable interest, as increased expression of the SPP1/Osteopontin has been linked to prostate cancerogenesis and metastasis in previous studies.[16,17] Furthermore, Osteopontin induces a strong potential for intravasation in LNCaP tumor cells.[18] S100A8/A9 are members of the S100 low-molecular weight calcium binding proteins and were shown to be upregulated

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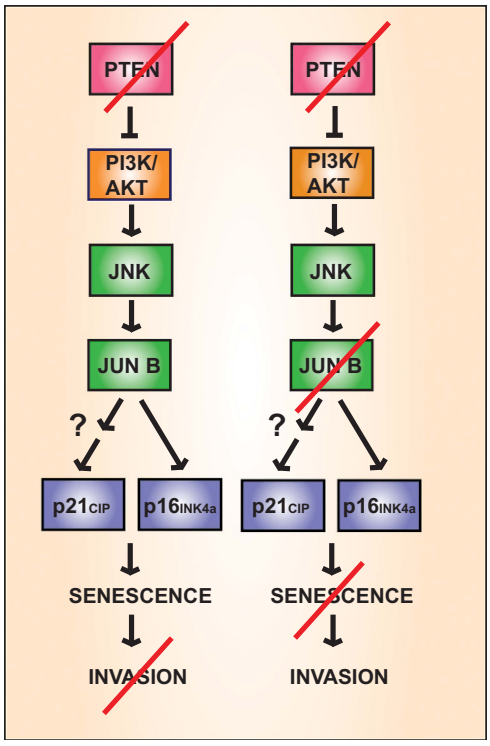

Figure 1 Loss of PTEN and JUNB results in invasive prostate cancer. PTEN deletion is associated with increased PI3K/AKT and mitogenic signaling via JNK and JUNB, which results in oncogene-induced senescence and upregulation of p21 and p16INK4a (left panel). Co-deletion of PTEN and JUNB abrogates senescence, due to downregulation of the cell cycle inhibitors p21 and p16INK4a, and causes invasive prostate cancer

upon loss of JunB in psoriasis.[19] Increased expression of S100A8/A9 in PCa epithelial cells causes enhanced infiltration of immune cells and stimulates lung-colonization by cancer cells.[20] The exact mechanism of how the loss of epithelial JunB results in induction of stromal SPP1/Osteopontin and S100A8/A9 expression needs to be further investigated, but possible disruption of this pathway might represent a novel therapeutic opportunity.

Taken together, the present study by Thomsen *et al.* shows that the combined loss of *Pten* and *JunB* has a major impact on the transformation of PIN to invasive PCa, which displays high histological and molecular similarities to human PCa. Although this study adds some fascinating findings to PCa research, it also generates several new questions as to the diagnostic relevance of JunB loss and to the mechanisms of how JunB and its AP-1 partners influence PCa progression. One very important regulatory mechanism certainly includes the direct transcriptional regulation of $p16^{INK4a}$ by JunB.[21] However, repression of cell cycle regulators and senescence-associated genes including $p16^{INK4a}$ has also been associated with epigenetic silencing in diverse tumors.[22] Two independent silencing mechanisms based on DNA methylation and Polycomb group silencing are both effective in tumors. C-Jun has been shown to protect the promoter of the $p16^{INK4a}$ gene from DNA methylation, whereas the loss of c-Jun evokes DNA methylation of the promoter.[23] It will be of great interest to investigate how AP-1 can signal to the epigenome and whether direct mechanisms are involved *in vivo*.

Related to clinical aspects JUNB could provide a novel biomarker for PCa diagnosis and might help to predict whether a primary tumor has the potential to become invasive and disseminate to distant sites. Thus, mitogenic signaling pathways are central to the regulation of diverse cellular pathways including proliferation and senescence and can have opposing effects on tumorigenesis depending on the stage, by provoking tumor promotion or suppression. We can expect that additional partners of these pathways are important to balance proliferative versus cell cycle inhibitory effects, and an elucidation of the underlying mechanisms will increase our understanding of tumorigenesis.

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