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RESEARCH HIGHLIGHT

COUP-TFII, a prognostic marker and therapeutic target for prostate cancer

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The absence of a biomarker to predict the aggressiveness of prostate cancer patients is the major obstacle in deciding which prostate cancer patient should be treated. In this report, we show that COUP transcription factor II (COUP-TFII), a member of the nuclear receptor superfamily, antagonizes the transforming growth factor (TGF)-β-induced growth barrier to facilitate tumor metastasis and provide a molecular mechanism for how PTEN indolent tumors acquire metastatic potential. More importantly, we identify that COUP-TFII expression or its signature serves as a predictor to stratify risk of biochemical recurrence in patients. Collectively, our findings identify a prognostic marker and therapeutic target for metastatic prostate cancer.

Despite much recent progress, prostate cancer is still the most common malignancy in men of the Western world. Most prostate tumors are initially indolent, but some of them rapidly become aggressive and metastatic. The absence of an effective prognostic marker to distinguish the aggressive versus the indolent tumors has led to a major concern for the accuracy of the diagnosis of prostate cancer in patients.[1] This prognostic challenge could be addressed by further understanding the underlying mechanism of prostate cancer malignance. PTEN mutation and genomic alterations in the PI3K-signaling pathway are the most common genetic alterations reported in prostate cancer patients. However, tumors bearing PTEN mutations in mice are indolent, which barely develop into the invasive carcinoma and display a minimal metastatic incidence.[2] Recently, Ding *et al.*[3] demonstrated that breakdown of the PTEN mutation-induced transforming growth factor (TGF)-β barrier is a rate limit step for prostate cancer metastasis, underscoring the notion that the feedback pathways suppressing progression might be activated in indolent PTEN-null tumors, and inhibition of such progression barriers would develop aggressive metastasis-prone cancer. Therefore, it is important to identify the pathways or players serving as the 'second hit' to abrogate the TGF-β-dependent growth barrier and enable PTEN-null tumors to acquire fully penetrated metastatic potential, which will have important therapeutic implications for the development of new targets or biomarkers for cancer intervention and clinical diagnosis.

Nuclear receptors, whose activity can be regulated by small molecular compounds, are ideal targets for drug development. COUP-TFII, also known as NR2F2, is a member of the nuclear receptor superfamily and plays a critical role in angiogenesis and organogenesis during embryonic development.[4] Our findings highlighted that the destruction of the TGF-β-dependent barrier by COUP-TFII is critical for the progression of well-confined prostate cancer to life-threatening metastatic disease.[5] We identified that COUP-TFII is aberrantly upregulated in prostate tumors, and further increased in metastatic prostate cancer patients. More importantly, COUP-TFII expression in prostate tumor cells is predictive of increased risk of tumor recurrence and decreased survival after prostatectomy, suggesting a causal role of COUP-TFII in disease progression. Further genetically engineered mice models revealed that COUP-TFII is crucial for PTEN-mediated prostate cancer malignance. Prostate-specific overexpression of COUP-TFII cooperates with PTEN loss to produce an invasive cancer and enables the tumor cells to metastasize to distant tissues including the lung and lymph nodes, indicating that COUP-TFII serves as the 'second hit' to drive the indolent tumors to aggressive tumors. Conversely, conditional inactivation of COUP-TFII in the prostate epithelium arrests tumor progression at the hyperplasia stage in comparison with high-grade prostatic intraepithelial neoplasia lesions or adenocarcinomas observed in PTEN-null mice. This result provides us a rational basis for future targeting of COUP-TFII for cancer intervention. Further mechanistic investigation indicated that COUP-TFII associates and inhibits Smad4 transcriptional activity, and consequently counteracts the TGF-β signaling-induced growth barrier for PTEN-null indolent tumors. The functional antagonism between COUP-TFII and Smad4 is further evidenced by genetically engineered mice models, in which conditional loss of Smad4 rescues the invasive tumor growth in mice lacking COUP-TFII, and overexpression of COUP-TFII does not exacerbate tumor malignance further in the absence of Smad4. In support of this observation, COUP-TFII expression inversely correlates with TGF-β signaling in human prostate tumors. More importantly, multivariate analysis revealed that the COUP-TFII signature carries the independent predictive capacity to further enhance the prognostic accuracy of four genes' prediction, including PTEN, Smad4, p21 and CyclinD1, suggesting the genetic cooperation between COUP-TFII and TGF-β signaling in PTEN-mutated prostate tumors. Taken together, our results demonstrate that COUP-TFII-mediated inhibition of TGF-β signaling is necessary for PTEN-null prostate cancer malignance and suggest that blockage of this nuclear receptor may limit metastasis. However, present studies do not elucidate which oncogenic signal is responsible for the increase of COUP-TFII expression in prostate tumors, which might be important for the further understanding the underlying mechanism for how prostate cancer becomes aggressive. In

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addition, it would be interesting to address whether COUP-TFII is implicated in castration resistance, the major reason for the death of prostate cancer patients.

In summary, our findings identified the potential biomarker that predict poor prognosis, and highlights the importance of COUP-TFII to disrupt the TGF-β-dependent growth barrier for prostate cancer malignance. Given that COUP-TFII also plays a crucial role in the tumor microenvironment to modulate tumor angiogenesis,[6,7] future targeting of COUP-TFII might have added values for therapeutic implications since antagonists will inhibit both the tumor microenvironment and tumor cells to curb tumor malignance. In addition, since COUP-TFII is a member of the nuclear receptor family whose activity can be regulated by small molecules,[8] our findings not only advance the understanding of prostate tumorigenesis, but also provide a potential new drug target for intervention of metastatic prostate cancer.

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