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CELL SIGNALLING

Breaking down the defenses

Mutations in *PTEN* are the most common genetic alterations in human prostate cancer; however, it is still unclear which other genetic alterations might promote metastases and progression in this disease.

The group led by Sophia Tsai and Ming-Jer Tsai has now reported that the expression of the nuclear receptor COUP-TFII is increased in patients with primary prostate cancer and further enhanced in patients with metastatic disease. To further define the role of COUP-TFII in prostate cancer progression, the authors used *PTEN*-mutant mice to examine the effect of loss or gain of function of COUP-TFII on tumour growth. Loss of COUP-TFII compromised prostate tumour progression, whereas overexpression of COUP-TFII resulted in a rapid acceleration of tumour progression, with prostate intraepithelial neoplasia (PIN) developing at 4 months of age and progressing to high-grade PIN by 12 months.

"Although loss of PTEN will induce tumours in mice, these tumour are indolent due to enhanced TGFβ signalling, which sets up a growth barrier to prevent further tumour growth and metastasis," explains Tsai, "given that TGFβ signalling is crucial for prostate cancer progression, we examined whether COUP-TFII potentiated prostate tumorigenesis through TGFβ signalling." Indeed, the authors observed that COUP-TFII interacted with SMAD4—a mediator of TGFβ signalling—directly inhibiting TGFβ signalling and disrupting the growth barrier to promote tumour growth and metastasis.

As COUP-TFII is a nuclear receptor, Tsai and argues that "if we can identify small molecules that can serve as antagonists to inhibit COUP-TFII activity, we may be able to use them for therapeutic purposes."

M. Teresa Villanueva

Original article Qin, J. *et al*. COUP-TFII inhibits TGFiβ-induced growth barrier to promote prostate tumorigenesis. *Nature* doi:10.1038/nature11674