TUMOUR MICROENVIRONMENT

External influences

Although it is generally accepted that the tumour microenvironment influences tumour formation and progression, how stromal cells communicate with epithelial tumour cells is not well understood. Gustavo Leone, Michael Ostrowski and colleagues have now shown that PTEN in stromal cells provides an important tumour suppressive link between these two cellular compartments.

The authors generated mice with a stromal fibroblast-specific deletion of *Pten* using a $Pten^{loxP}$ conditional allele and a mesenchymal-specific *Fsp-Cre* transgene. These mice had extracellular matrix (ECM) expansion but mammary epithelial cells were not transformed. The mice were then crossed with mice expressing *Erbb2* under the control of the mouse mammary tumour virus (*MMTV*) promoter (an established mouse model of breast cancer). The authors transplanted mammary glands from these and control mice into syngeneic wild-type recipient mice to prevent possible effects of *Pten* deletion in fibroblasts from other organs, and found that stromal *Pten* deletion increased ERBB2-driven mammary tumorigenesis.

How does stromal PTEN suppress tumours? Gene expression arrays showed that mouse mammary stromal fibroblasts lacking *Pten* had significant (greater than fourfold) changes in the expression of several genes linked to ECM remodelling, wound healing and chronic inflammation. Indeed, immunohistochemistry of *Pten*-deleted stroma indicated higher collagen deposition (primarily type I collagen) and macrophage infiltration than in stroma expressing *Pten*. PTEN loss also activated the Ras, Jun N-terminal kinase and Akt signalling pathways, as well as the transcription factor ETS2, which is downstream of these pathways. Therefore, the authors examined the consequences of *Ets2* deletion in mammary stromal fibroblasts in another mouse model of breast cancer, *MMTV*-polyoma middle T antigen (*PyMT*). Loss of stromal *Ets2* was sufficient to reduce tumour load and slow progression. Furthermore, deletion of both *Pten* and *Ets2* in mammary stromal fibroblasts significantly reduced tumour load, macrophage infiltration and angiogenesis following orthotopic injection of a tumour cell line expressing *Erbb2*, indicating that ETS2 is a crucial effector of tumorigenesis following stromal PTEN loss.

So how does ETS2 promote tumorigenesis? The transcription of two direct ETS2 targets, matrix metalloproteinase 9 (*Mmp9*) and the chemokine *Ccl3* (which affect ECM remodelling and macrophage recruitment, respectively), was upregulated in *Pten*-deleted stromal fibroblasts. MMP9 might contribute to ETS2-dependent tumour promotion by increasing the release of the active vascular endothelial growth factor A (VEGFA) isoform $VEGF_{164}$. The authors found lower $VEGF_{164}$ accumulation and vascular VEGF receptor 2 (VEGFR2) activation in *MMTV-PyMT* tumours that lacked stromal ETS2 than in those that expressed ETS2.

Comparison of the mouse stromal fibroblast PTEN expression signature with tumour stroma and adjacent normal stroma from human breast tumours allowed the derivation of a subset of 70 human genes that was sufficient to distinguish tumour stroma from normal stroma in patients with breast cancer. Furthermore, stromal PTEN expression was low in ~50% of 99 human invasive breast carcinoma samples, and this was negatively correlated with nuclear phosphorylated ETS2, indicating that the PTEN–ETS2 pathway is relevant to human breast tumorigenesis.

This mouse model, which reflects human breast cancer stroma at both the histological and molecular levels, could be useful for studying various roles of stroma–tumour communication in breast cancer.

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