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MICROENVIRONMENT

HSF1, the troublemaker next door

It is well known that stromal cells within the tumour microenvironment can contribute to tumour formation and progression, but the mechanisms through which these cells promote malignancy in their neighbours are less well understood. Scherz-Shouval *et al.* have described a transcriptional programme that is frequently activated in cancer-associated fibroblasts (CAFs) and driven by heat shock factor 1 (HSF1) that promotes malignancy in adjacent cancer cells.

Previous results indicated that the transcription factor HSF1 indirectly promotes tumorigenesis in several types of cancer cells by enabling proliferation, invasion and metastasis, so the authors hypothesized that HSF1 might have a similar role in making normal stroma pro-tumorigenic. Activated HSF1 accumulates in the nucleus, and, indeed, stromal cells found close to malignant cells in tumour samples from patients with breast cancer showed strong nuclear HSF1 staining.

> HSF1 … promotes malignancy in adjacent cancer cells

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But how does HSF1 promote tumour growth in neighbouring cells? To address this question, the authors analysed the RNA extracted from murine mammary cancer cells (D2A1) grown in co-culture with primary mouse embryonic fibroblasts (MEFs) and compared it with that of cancer cells grown alone or in the presence of MEFs lacking *Hsf1*. Cancer cells that were co-cultured with wild-type MEFs showed upregulation of approximately 200 genes encoding proteins involved in development, cell proliferation and invasion — such as dentin matrix protein 1 (*Dmp1*), Dickkopf homologue 3 (*Dkk3*), secreted acidic cysteine-rich glycoprotein (*Sparc*), matrix metalloproteinase 2 (*Mmp2*) and *Mmp3* — that were not upregulated in cancer cells co-cultured with *Hsf1*-null MEFs. In the cancer cells that were co-cultured with *Hsf1*-null MEFs, approximately 750 genes were upregulated, including those encoding pro-inflammatory cytokines — such as CC chemokine ligand 5 (*Ccl5*) and *Ccl8* — and other genes involved in immune responses. The authors concluded that the activation of HSF1 in the stroma contributes to reprogramming of cancer cell gene expression in at least two ways: by upregulating genes that promote the malignant phenotype and by downregulating genes that might trigger an anticancer immune response.

Does HSF1 also influence the phenotype of stromal cells? Analysis of mRNA from wild-type MEFs co-cultured with cancer cells compared with MEFs alone showed that HSF1 in stromal cells upregulated the expression of a cluster of genes involved in development, proliferation and wound healing — transforming growth factor β1 (*Tgfb1*) and vascular cell adhesion molecule 1 (*Vcam1*), among others — and downregulated genes involved in cellular immune responses. This gene expression analysis also showed that TGFβ signalling was one of the pathways most extensively regulated by HSF1. Adding TGFβ1 and stromal cell-derived factor 1 (SDF1) — both known to promote CAF phenotypes — as purified recombinant proteins to co-cultures of cancer cells and *Hsf1*-null MEFs restored cancer cell growth to levels achieved by co-culture with wild-type MEFs. In addition, knocking down the expression of SMAD2, a signalling molecule downstream of TGFβ, in MEFs (but not in cancer cells) impaired the growth of cancer cells, showing that TGFβ and SDF1 are mediators of the tumour-promoting activity of stromal HSF1.

Furthermore, an analysis of tumour samples from patients with breast or early stage non-small-cell lung cancer showed that HSF1 nuclear localization in the stroma was associated with reduced disease-free survival and overall survival, suggesting that an HSF1-based biomarker could help to predict patient prognosis. Although directly inhibiting a transcription factor such as HSF1 is challenging, the dual role of HSF1 opens the possibility of treating cancer more effectively by targeting both the malignant cells and the more genetically stable stroma supporting them.

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ORIGINAL RESEARCH PAPER Scherz-Shouval, R. *et al.* The reprogramming of tumor stroma by HSF1 is a potent enabler of malignancy. *Cell* **158**, 564–578 (2014)

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