⮕ **METASTASIS**

Which way to the lungs?

Why are metastases from primary tumours restricted to specific organs? Prompted by rich yet contradictory evidence, David Padua and colleagues set out to clarify the role of transforming growth factor β (TGFβ) in primary breast cancer metastasis.

TGFβ is secreted by the tumour microenvironment under hypoxic conditions, and has been shown to support as well as to inhibit tumour growth. The authors defined a TGFβ response signature (TBRS) — a set of 153 genes shown to be targets of the TGFβ signalling pathway — to grade the effects of the cytokine on cancer development. Importantly, the TBRS was highly expressed in oestrogen receptor-negative (ER⁻) breast cancer samples from patients who later developed lung metastases. To corroborate the connection between TGFβ signalling and lung metastasis, Padua *et al*. disrupted components of the TGFβ signalling pathway in LM2 breast cancer cells that are known to metastasize to the lungs. This drastically reduced LM2 lung invasion after injection into mice. By contrast, incubating unmodified LM2 cells with TGFβ accelerated their dissemination to the lungs, but not to bone.

But which target of TGFβ signalling confers metastatic behaviour to ER⁻ breast cancer cells? The authors noticed that the cytokine angiopoietin-like protein 4 (*ANGPTL4*) belonged to both the TBRS and a set of genes proposed to be characteristic for cancer cells with a propensity for lung metastasis. The authors showed that expression of ANGPTL4 can disrupt endothelial cell–cell junctions, and that breast cancer cells overexpressing ANGPTL4 can pass through an endothelial layer twice as fast as unmodified tumour cells. Two findings indicated a direct connection between ANGPTL4 and TGFβ signalling. First, ANGPTL4 expression was drastically enhanced when ER⁻ primary mammary tumour cells were incubated with TGFβ. Second, knockdown of *Angptl4* in mice led to a 10-fold decrease in lung metastases. These findings indicate that the upregulation of ANGPTL4 expression by TGFβ leads to lung metastasis through the disruption of endothelial cell contacts. The authors hypothesize that blood vessel walls in bone are different to those in the lung, so ANGPTL4 is unable to aid the invasion of ER⁻ breast cancer cells into bones.

Aside from a clarification of the role of TGFβ in ER⁻ breast cancer progression, the authors delineate a molecular mechanism by which these cells metastasize to the lungs. Priming of cancer cells towards organ-specific invasion by cytokine secretion from the tumour environment signals new possibilities for cancer drug development.

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