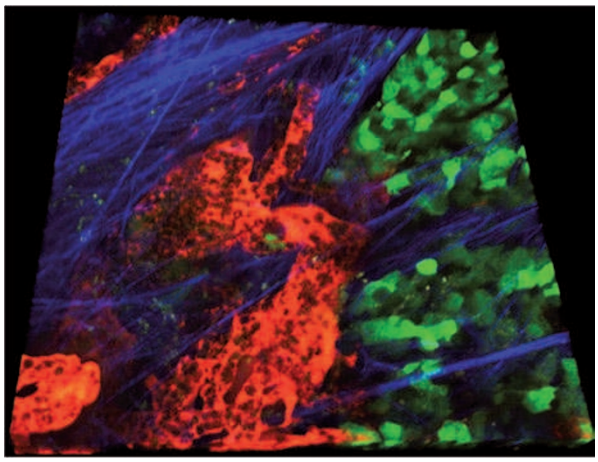
CELL MIGRATION

The benefit of being single

> TGFβ promotes single cell motility *in vivo*.

Regulation of cell motility is important for the metastatic dissemination of tumour cells from their primary location to lymph or blood vessels. Transforming growth factor-β (TGFβ) signalling — which is mediated by Smad transcription factors — enhances cell motility and tumour progression. Erik Sahai and colleagues now report that the transient and local activation of TGFβ signalling in breast cancer cells causes a switch from cohesive movement to single cell motility and promotes haematogenous metastasis.

Intravital imaging of mammary carcinoma cells shows that only 5% of primary tumour cells are motile and that they move either singly or collectively. Imaging of fluorescent reporter genes reveals that TGFβ is active primarily in single cells and that this correlates with the nuclear localization of SMAD2 and SMAD3, which are phosphorylated in response to TGFβ and form a complex with SMAD4 that accumulates in the nucleus. Interestingly, the increase in TGFβ activity is not maintained in lymph node and lung metastases, suggesting that TGFβ is only activated transiently.



In vivo image of mammary carcinoma cells showing cancer cells in green, the lymphatic vessel in red and collagen in blue. Image courtesy of E. Sahai, Cancer Research UK London Research Institute, London, UK.

So, how does TGFβ affect the mode of tumour cell migration? Tumour cells that are cultured in the presence of TGFβ move as single cells instead of growing in colonies. Cell scattering is inhibited on SMAD4 knockdown, suggesting a role for TGFβ-mediated transcription in determining the mode of migration. Using microarray analysis, the authors identified several genes that are upregulated in cells treated with TGFβ. Knockdown studies revealed that these genes have distinct roles in the switch from collective to single cell motility.

Intravital imaging also shows that expression of a dominant-negative TGFβ receptor in cancer cells triggers a switch back to cohesive movement, whereas overexpression of TGFβ promotes single cell motility. This suggests that TGFβ promotes single cell motility *in vivo*. But how does this switch in cell motility affect metastasis?

Cells lacking TGFβ signalling and moving collectively can only enter lymphatic vessels and disseminate to the lymph nodes. Conversely, cells with permanently hyperactive TGFβ signalling enter the blood efficiently, but are ineffective at forming lung metastases, as prolonged TGFβ signalling inhibits growth. Thus, the transient activation of TGFβ enables single cells to enter the blood and its subsequent inactivation allows growth at secondary sites.

This study demonstrates that dynamic TGFβ signalling regulates both the mode of cancer cell migration and the metastatic route.

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ORIGINAL RESEARCH PAPER Giampieri, S. *et al.* Localised and reversible TGFβ signalling switches breast cancer cells from cohesive to single cell motility. *Nature Cell Biol.* 18 Oct 2009 (doi:10.1038/ncb1973)
FURTHER READING Friedl, P. & Gilmour, D. Collective cell migration in morphogenesis, regeneration and cancer. *Nature Rev. Mol. Cell Biol.* **10**, 445–457 (2009) | Schmierer, B. & Hill, C. S. TGFβ–SMAD signal transduction: molecular specificity and functional flexibility. *Nature Rev. Mol. Cell Biol.* **8**, 970–982 (2007)