METASTASIS

One step closer

One dangerous feature of melanoma is its rapid progression to metastatic disease. Does this characteristic arise from external factors, such as the effects of ultraviolet light exposure, or from intrinsic features of the melanocyte itself? In the October issue of *Nature Genetics*, Robert Weinberg and colleagues provide evidence that following transformation the inherent features of the melanocyte's differentiation programme places these cells one step closer to metastasis.

Dermal melanocytes arise from an especially migratory embryonic cell population called the neural crest. Weinberg's group set out to determine whether the properties of the neural crest cells that induce migratory behaviour during development could also underlie their highly metastatic behaviour. To examine the effects of cell-specific factors in melanoma progression, the authors transformed different types of primary human cells by expressing a combination of the simian virus 40 early region (SV40ER), the catalytic subunit of the telomerase reverse transcriptase holoenzyme (TERT) and an oncogenic form of RAS.

Melanocytes transformed with these three genes formed high-grade, well-vascularized melanomas in mice. These melanomas rapidly underwent widespread metastatic dissemination to the lungs, lymph nodes, liver, spleen and small bowel — much as human melanomas do. Human fibroblasts and mammary epithelial cells transformed in the same manner, however, formed primary tumours that did not become metastatic. The polyclonal nature of the melanocytes that formed the metastases and their lack of any significant genomic alterations indicated that transformed melanocytes probably possessed the ability to form metastases before their introduction into mice. In fact, based on the rate of metastasis, the authors predicted that it was unlikely that additional genetic alterations beyond the SV40ER, TERT and RAS oncoproteins used to transform the melanocytes were required for tumour spread.

So, what are the features of melanocytes that make them so ready to move? Gene expression analysis revealed that the transcription factor SLUG, which mediates neural crest cell migration, was expressed in the transformed metastatic melanocytes. In addition, SLUG was also expressed in human naevus samples (benign melanocyte tumours) where its expression correlated with other genes known to be involved in neural crest cell motility. So, the components of an embryonic differentiation programme involved in neural crest cell motility and migration were already expressed in benign human melanocyte lesions before neoplastic transformation. Furthermore, short interfering RNA (siRNA) knockdown of *SLUG* expression reduced the metastatic tumour burden of the transformed melanocytes tenfold in mice.

The authors conclude that the rapid progression of human melanomas to a metastatic state can be attributed, in part, to lineage-specific factors associated with the melanocyte differentiation programme. Therapies aimed at downregulating SLUG or its target genes might therefore be useful in treating or preventing tumour metastasis.

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References and links

ORIGINAL RESEARCH PAPER Gupta, P. B. *et al*. The melanocyte differentiation program predisposes to metastasis following neoplastic transformation. *Nature Genet.* 4 September 2005 (doi:10.1038/ng1634).