Micromanaging metastasis

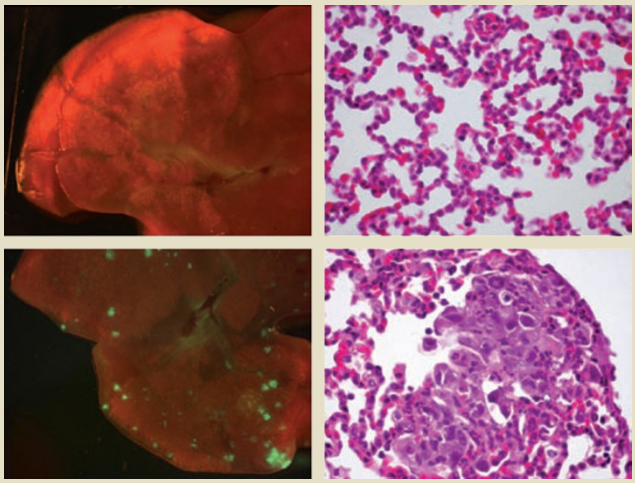
The idea that microRNAs have a hand in tumour development has been further cemented with the finding that miRNA-10b is upregulated by Twist to drive breast cancer cell invasion and metastasis through effects on HoxD10 and RhoC.

Weinberg and colleagues (*Nature*, doi:10.1038/nature06174) set out to address how miRNAs might affect metastasis, and homed in on miR-10b as an RNA that is differentially expressed in breast carcinomas. By comparing its levels in different cancer cell lines, they found that it is upregulated specifically in metastatic cells. Inhibiting miR-10b decreased the invasive behaviour of breast cancer cells *in vitro*, whereas overexpression of miR-10b was sufficient to induce both motility and invasiveness.

Next they turned to a mouse model and showed that implanting cells overexpressing miR-10b into the mammary fat pad increased tumour cell invasion (without affecting tumour growth itself) and also seemed to indirectly promote vascularization. In addition, the presence of miR-10b increased the likelihood of distant metastases. By repeating this experiment with non-invasive cells, they found that overexpressed miR-10b was sufficient to drive metastasis.

A key question is how miRNAs intersect with signalling pathways. Weinberg and colleagues noted that the expression levels of miR-10b mirrored that of Twist, a transcription factor that promotes metastasis. Indeed, they found that overexpression of Twist increased the induction of miR-10b and that Twist interacts with the putative miR-10b promoter in living cells. Consistent with the idea that Twist drives miR-10b expression, inhibiting miR-10b was sufficient to block the effects of Twist on motility and invasion.

From computational analysis, miR-10b is predicted to target about 100 genes, but one of these, HoxD10, caught their attention, given its links with invasion and tumour progression. Using reporter assays and mutational analysis, they found that miR-10b does repress HoxD10 through translational inhibition. Importantly, overexpression of HoxD10 prevents the effects of miR-10b on motility and invasion. HoxD10 is known to repress the pro-metastatic factor RhoC, and depletion of RhoC blocked the induction of migration by miR-10b.



Transplantation of SUM159 breast cancer cells overexpressing miR-10b into the mammary fat pad of mice results in numerous lung metastases (shown in the lower panels), which are readily detectable by GFP fluorescence (left panels) and histological analysis (right panels). Lungs isolated from mock-infected mice are shown in the upper panels.

HoxD10 is probably not the only target of miR-10b that is relevant for invasion and metastasis. Given that the authors observe increased expression of miR-10b in breast tumours from patients who are metastasis-positive, it will be important to identify these other targets so as to understand how this miRNA controls metastasis.

Alison Schuldt