MICRORNA

Served with a TWIST

DOI:
10.1038/nrc2264

The role of small cellular RNAs, called microRNAs (miRNAs), in specific steps of tumour progression is unknown. Li Ma, Julie Teruya-Feldstein and Robert Weinberg have now shown that miRNA-10b (miR-10b) initiates invasion and metastasis in non-metastatic breast cancer through a previously undescribed pathway involving the transcription factor TWIST.

The authors examined miRNAs that had been previously identified as differentially expressed between primary breast cancer and normal mammary tissue, and found that only one of these, miR-10b, was highly expressed in cancer cell lines with metastatic capacity. Having shown that silencing of this miRNA by antisense oligonucleotides in metastatic breast cancer cells reduced their invasive properties, and that overexpression of miR-10b in immortalized human mammary epithelial cells (HMECs), which have low levels of miR-10b, increased invasiveness, Ma *et al*. went on to look at the role of this miRNA *in vivo*.

When miR-10b was overexpressed in non-metastatic breast cancer cells that were then implanted into mammary fat pads of immunocompromised mice, the primary breast cancers that grew were a similar size to those that grew in mice implanted with control cells. However, only the miR-10b-expressing tumours were invasive — the invasive fronts were enriched with proliferating cells and were highly vascularized, and lung micrometastases were seen only in these mice.

So, how is miR-10b expression regulated? Ma *et al*. found that miR-10b expression correlated with the metastatic potential of the four mouse mammary tumour cell lines that had been used previously to identify the metastasis-promoting TWIST1 basic helix-loop-helix transcription factor. Indeed, when TWIST1 was expressed in immortalized HMECs, expression of miR-10b was increased, and chromatin immunoprecipitation showed that TWIST1 binds to a specific E box in the putative *mir-10b* promoter. If antisense to miR-10b was introduced into the TWIST1-overexpressing HMECs, the motility and invasiveness of these cells were reduced.

Which genes does miR-10b regulate? Computational analysis predicted approximately 100 targets for miR-10b, among which was the homeobox gene *HOXD10*, which has been implicated previously in suppression of migration and invasion in breast tumours. Ma and colleagues found that miR-10b binds to a site within the 3′ untranslated region of the *HOXD10* mRNA and inhibits its translation. As HOXD10 is known to repress expression of RHOC, a Rho family GTPase involved in cell migration and invasion, the authors examined expression of RHOC in the cells overexpressing miR-10b — RHOC expression was high compared with control cells. If HOXD10 was constitutively expressed or *RHOC* small interfering RNA was added to the miR-10b-overexpressing cells, miR-10b-induced cell motility and invasiveness was greatly reduced.

The authors also measured miR-10b expression in primary breast-tumour samples and found that it was higher in the tumours of patients who had metastases than in those who did not.

This new regulatory pathway for cancer-cell migration and invasion demonstrates the contribution of miR-10b to metastasis. Studies of the roles of other miRNAs in tumour progression are eagerly awaited.

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ORIGINAL RESEARCH PAPER Ma, L., Teruya-Feldstein, J. & Weinberg, R. A. Tumour invasion and metastasis initiated by microRNA-10b in breast cancer. *Nature* 26 September 2007 (doi:10.10.38/nature06174)