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TUMORIGENESIS

Dangerous micromanagement

> miR-21 and miR-181b-1 are key regulators of tumour suppressor genes and activators of an inflammatory feedback loop

Although the deregulation of microRNAs (miRNAs) has frequently been linked to tumorigenesis, the underlying molecular mechanisms responsible have been challenging to elucidate. Recent work reveals that oncogenic miRNAs can be transcriptionally activated by signal transducer and activator of transcription 3 (STAT3) and exert their oncogenic effects by disabling the expression of tumour suppressor proteins.

A team led by Kevin Struhl has established a mammary tumorigenesis model in which the immortalized breast cancer cell line MCF10A becomes fully transformed on the expression of an inducible *SRC* oncogene. SRC activates nuclear factor-κB (NF-κB), which triggers a positive inflammatory feedback loop involving interleukin-6 (IL-6) and STAT3.

In their latest work, the authors searched for miRNAs with altered expression levels during SRC-induced transformation; they identified miR-21 and miR-181b-1 as two of the most upregulated. To confirm that their upregulation had a causative role in transformation, antisense oligonucleotides targeting miR-21 or miR-181b-1 blocked colony formation in soft agar, *in vitro* invasion and the growth of xenografted MCF10A cells in mice. Surprisingly, even transient overexpression of miR-21 or miR-181b-1 was sufficient for sustained cellular transformation, indicating that these miRNAs are integral components of the self-reinforcing feedback loop that is induced by SRC.

What causes upregulation of these miRNAs? Sequence analysis revealed the presence of STAT3 binding sites in the promoters of *miR-21* and *miR-181b-1*, and promoter binding of STAT3 was confirmed by chromatin immunoprecipitation experiments. Small interfering RNA-mediated knock down or chemical inhibition of STAT3 prevented both cellular transformation and the upregulation of miR-21 and miR-181b-1, which is consistent with STAT3 being a direct transcriptional activator of *miR-21* and *miR-181b-1*.

Is there a mechanistic explanation for the oncogenic functions of miR-21 and miR-181b-1? During transformation, there was an inverse correlation between expression levels of miR-21 and PTEN, supporting the recognized role of miR-21 as a negative regulator of PTEN expression. Additionally, putative binding sites for miR-181b-1 were found in cylindromatosis (*CYLD*) mRNA, and further functional experiments confirmed miR-181b-1 as a negative regulator of CYLD expression. CYLD, a deubiquitylating enzyme, causes NF-κB degradation, which explains the activation of the NF-κB feedback loop by STAT3. Finally, knock down of miR-21 or miR-181b-1 prevented the transformation and xenograft growth of a subset of human cancer cell lines, although the reasons for the variable responses are currently unknown.

This work suggests that miR-21 and miR-181b-1 are key regulators of tumour suppressor genes and activators of an inflammatory feedback loop during SRC-mediated transformation. It also raises interest in these miRNAs as putative therapeutic targets for cancer, although the underlying genetics that determine the response will be crucial to decipher.

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ORIGINAL RESEARCH PAPER Iliopoulos, D. *et al.* STAT3 activation of miR-21 and miR-181b-1 via PTEN and CYLD are part of the epigenetic switch linking inflammation to cancer. *Mol. Cell* **39**, 493–506 (2010)