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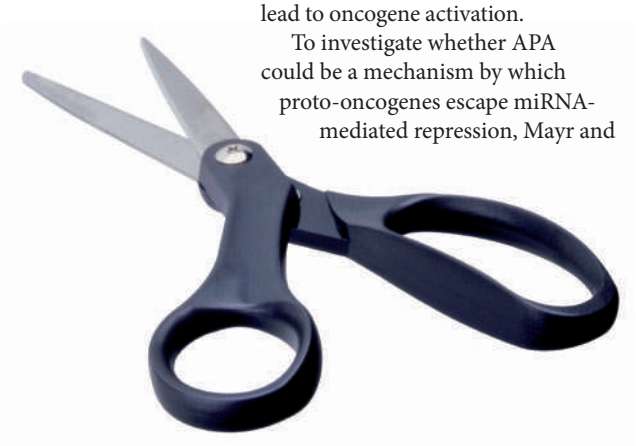
GENE REGULATION

UTR cutbacks give free rein to oncogenes

Although alterations in proto-oncogenes can explain their hyper-activation during tumorigenesis, oncogene overexpression can occur even in the absence of mutations at these loci. Christine Mayr and David Bartel now present evidence that the shortening of 3′ UTRs — which often harbour post-transcriptional regulatory elements — contributes to oncogene activation in tumorigenesis.

Many genes contain alternative polyadenylation (APA) signals within the 3′ UTR that, when used, result in cleavage and eliminate part of the 3′ UTR along with any regulatory components that it contains. MicroRNAs (miRNAs) specify post-transcriptional repression by pairing to complementary sites within the 3′ UTR, and loss of these sites can lead to oncogene activation.



To investigate whether APA could be a mechanism by which proto-oncogenes escape miRNA-mediated repression, Mayr and Bartel compared mRNA transcripts that were expressed in various normal and cancer cell lines. Northern blotting was used to probe 27 cancer cell lines for 16 candidate genes, all of which contained miRNA-binding sites in their 3′ UTRs. Six of the candidate genes, including cyclin D1 (*CCND1*) and fibroblast growth factor 2 (*FGF2*), had a shorter mRNA isoform that was more prominent in the cancer cell lines. Moreover, 3′ rapid amplification of cDNA ends (RACE) confirmed that these shorter isoforms arose from APA, which lends weight to the argument that APA-mediated shortening of 3′ UTRs is a cancer-associated phenomenon.

The authors then investigated the functional consequences of APA-mediated 3′ UTR shortening. The decay of the mRNA isoforms in eight of the cancer cell lines was assessed by northern blot analysis, and the shorter isoforms were substantially more stable than their full-length counterparts. In addition, reporter assays revealed that the shorter isoforms typically produce tenfold more protein. However, when the contribution of miRNA regulation was assessed by the mutation of miRNA-binding sites in the full-length isoforms, more modest increases in protein expression were seen, which indicates that other regulatory elements within the 3′ UTR also contribute to the net repressive effect.

Nonetheless, the results so far suggest that cancer-associated shortening of 3′ UTRs by APA could activate proto-oncogenes. In support of this, the short mRNA isoform of the proto-oncogene insulin-like growth factor 2 mRNA-binding protein 1 (*IGF2BP1*) was shown to promote transformation of fibroblast or human breast epithelial cell lines more efficiently than its full-length counterpart.

It remains to be established exactly which mechanisms underlie the recognition and increased utilization of APA signals in cancer cells, but this novel mode of oncogene activation suggests potential new approaches to cancer therapy.

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ORIGINAL RESEARCH PAPER Mayr, C. & Bartel, D. P. Widespread shortening of 3′UTRs by alternative cleavage and polyadenylation activates oncogenes in cancer cells. *Cell* **138**, 673–684 (2009)