TUMORIGENESIS

Alternative view

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URLs

SFRS1
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uids=6426

RPS6KB1
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uids=6198

The splicing of human genes increases the variety of mRNAs and therefore proteins that one gene can encode. Adrian Krainer and colleagues show that, like deregulated transcription and translation, deregulated splicing can lead to tumour formation.

Evidence for a connection between aberrant splicing and tumorigenesis is not new; some alternative splicing factors are overexpressed in tumour cells and can serve as diagnostic and prognositc markers. The SR family of alternative splicing proteins show increased expression in some tumours and decreased expression in others, so Krainer and colleagues examined whether the SR protein SFRS1 (also known as SF2 and ASF) can influence tumour formation.

Initially they screened 300 human tumour samples, including breast, lung and colon, and found increased expression of both SFRS1 protein and mRNA in many tumour types, and amplification of *SFRS1* in 4 of 50 breast tumours. The authors showed that the increased expression of SFRS1 can transform NIH3T3 and Rat1 cells *in vitro*, and NIH3T3 cells that express SFRS1 produce tumours *in vivo*.

So, does the splicing profile of specific genes change in cells that express SFRS1? The authors looked at the splicing of genes involved in the Ras–mitogen-activated protein kinase (MAPK) and the phosphatidylinositol 3-kinase (PI3K)–mammalian target of rapamycin (mTOR) pathways, which are often deregulated in cancer. The overexpression or knockdown of *SFRS1* using short interfering RNA (siRNA) resulted in specific splicing changes in a number of genes involved in these pathways. For example, SFRS1 is known to regulate the splicing of the gene that encodes the mTOR substrate RPS6KB1 (S6K1) in mouse cells, but only the expression of isoform 1 has been shown in human cells. However, the authors found that, like mouse cells, human cells that overexpress SFRS1 predominantly express isoform 2 of S6K1. Moreover, they found that isoform 2 is oncogenic, as NIH3T3 cells that express this isoform produce tumours in immunocompromised mice. The authors also showed that short-hairpin RNA (shRNA)-mediated knockdown of either *SFRS1* or isoform 2 of S6K1 prevented growth in immunocompromised mice of NIH3T3 cells expressing SFRS1 or a human lung cancer cell line with increased SFRS1 expression.

These results show that changes in the expression of specific splicing factors can alter the mRNA expression profile of genes involved in the Ras–MAPK and PI3K–mTOR pathways. As a result, SFRS1 can promote tumorigenesis.

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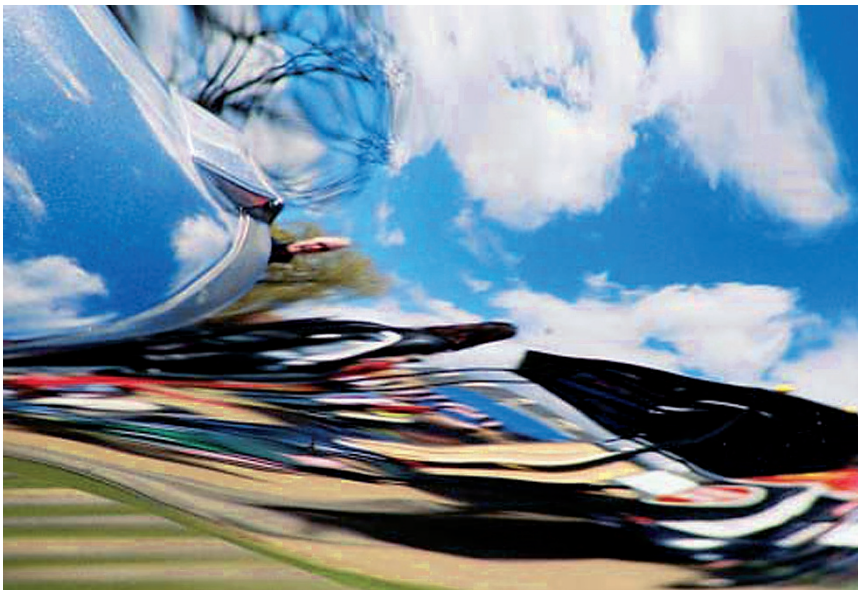
ORIGINAL RESEARCH PAPER Karni, R. *et al.* The gene encoding the splicing factor SF2/ASF is a proto-oncogene. *Nature Struc. Mol. Biol.* **14**, 185–193 (2007)



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