antibodies did not block tumour-cell division or trigger apoptosis. They did, however, halt invasion of normal keratinocytes, and restore the invasiveness of RDEB^{Null} cells. Moreover, they stopped the expansion of tumours that were already established.

The FNC1 sequence contains a binding site for laminin-5, another extracellular protein that is found in SCC. Laminin-5 interacts physically with collagen VII, but the FNC1 antibodies disrupt this partnership. Moreover, it seems that laminin-5 is necessary for FNC1 to promote tumour invasion, as antibodies to laminin-5 inhibited this process.

Whether the presence of the FNC1 region in RDEB individuals is a reliable predictor that they will develop SCC has yet to be proven. But the authors suggest that as collagen VII and laminin-5 are extracellular, they will in principle be accessible to therapeutics such as antibodies.

Helen Dell

References and links

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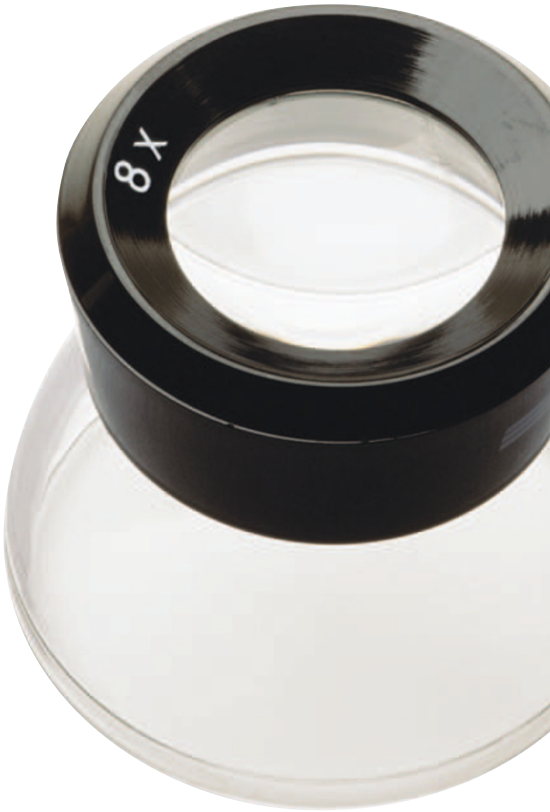
WEB SITE

Paul Khavari's lab: http://cmgm.stanford.edu/khavari/

TUMORIGENESIS

Micromanager



MicroRNAs (miRNAs) are now recognized to be key regulators of development and cell differentiation. Unsurprisingly, therefore, evidence is emerging that mi-RNAs can be mutated or abnormally expressed in human cancers. Steven M. Johnson *et al.* now provide a link between certain miRNAs and the notorious RAS oncogenic signalling pathway, suggesting a mechanism by which these miRNAs might regulate tumorigenesis.

Animal miRNAs are proposed to exert their regulatory effects by binding to complementary sequences in the 3′ untranslated regions (UTRs) of their target mRNA, thereby controlling translation. One of the first miRNAs to be discovered was *let-7* in the worm *Caenorhabditis elegans*, and there are now four *let-7* relatives known in these creatures. *let-7* controls cell fate in hypodermal seam cells, which are a type of epithelial cell, but the functions of the other family members are unknown. Johnson *et al.* searched the *C. elegans* genome for potential target genes, looking for sites complementary to a consensus *let-7* family sequence in the 3′ UTRs of their genes. The highest-scoring candidate was *let-60*, the *C. elegans* homologue of human *RAS*.

The authors found that *let-7* and *let-60* are both expressed in hypodermal seam cells, but in a reciprocal manner, so that during developmental stages when *let-7* is high, *let-60* is low, and vice versa. Moreover, the *let-60* 3′ UTR is sufficient to downregulate a reporter gene at the same developmental stage at which *let-60* expression normally drops off. Notably, in worms with *let-7* loss-of-function mutations, there was no decline in reporter-gene expression. All of which indicates that the *let-60* mRNA is a functional target of *let-7* in worms.

Moving into humans, Johnson *et al.* found several potential *let-7* complementary sites in the 3′ UTRs of the three *RAS* genes. Transfecting HepG2 cells with a *let-7* miRNA reduced the expression of *RAS* by ~70%. Moreover, the 3′ UTRs of *NRAS* and *KRAS* repressed the expression of a luciferase reporter in cells that have endogenous *let-7* (HeLa cells). Co-transfection of an antisense inhibitor of *let-7* relieved this repression.

Several human homologues of *let-7* reside in genomic regions that are deleted in cancer, and Johnson *et al.* suggested that the loss of regulation by *let-7* miRNA could cause overexpression of RAS and contribute to tumorigenesis. They analysed levels of *let-7* in a range of cancers from 21 patients. In lung cancers, *let-7* was reduced by an average of half, compared with normal adjacent tissue, and northern and western analyses revealed the reciprocal correlation between expression of *let-7* miRNA and RAS protein. However, the amount of RAS protein did not seem to reflect the amount of *NRAS* mRNA, indicating that expression of human *RAS* protein is regulated significantly at the level of translation — consistent with a control mechanism where the miRNA binds to the 3′ UTR. The authors concluded that *let-7* is strongly implicated as a tumour suppressor in lung tissue.

Helen Dell

References and links

ORIGINAL RESEARCH PAPER Johnson, S. M. *et al. RAS* is regulated by the *let-7* microRNA family. *Cell* **120**, 635–647 (2005)

FURTHER READING Downward, J. Targeting RAS signalling pathways in cancer therapy. *Nature Rev. Cancer* **3**, 11–22 (2003) | He, L. & Hannon, G. J. MicroRNAs: small RNAs with a big role in gene regulation. *Nature Rev. Genet.* **5**, 522–531 (2004)

WEB SITE

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