GENETICS

Conserved by evolution, but altered in cancer

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Some regions of the genome are 100% conserved between human, mouse and rat, suggesting that they have important functions. A new study shows that changes in the expression of these so-called ultraconserved regions (UCRs) are associated with various cancers.

Several recent studies have shown that, in addition to classical oncogenes and tumour suppressors, microRNAs (miRNAs) have a role in cancer. However, these are not the only type of non-coding RNA — many other parts of the genome appear to be expressed and functionally important, even though they do not encode protein. UCRs are one particular class of these whose functional importance has been demonstrated through deletion experiments in mice.

The authors used microarray profiling of UCRs in normal tissue to identify those that were transcribed — T-UCRs. More detailed study using quantitative PCR and northern blots showed that two particular T-UCRs differed significantly in their expression between normal lymphocytes and chronic lymphocytic leukaemia cells. The authors then explored whether T-UCR expression signatures could distinguish between a wide range of normal and cancer cells. Using a panel of 133 cancer samples and 40 corresponding normal controls, they showed that signatures of between 8 and 61 T-UCRs could distinguish specific cancer cells from their normal counterparts.

So what do these T-UCRs do and how are changes in their expression associated with cancer? First, the

authors showed that the locations of T-UCRs are correlated with regions that have previously been shown to be associated with cancer, such as fragile sites, amplified regions and regions with a loss of heterozygosity. In one particular case, no mutations were found in the protein-coding genes in the region, suggesting that the change in the T-UCR was what promoted cancer susceptibility. Second, they showed that the expression of several T-UCRs was negatively correlated with that of certain miRNAs, and that there was a significant antisense complementarity between several miRNA–T-UCR pairs, suggesting a functional link. In four cases these interactions were confirmed in an *in vitro* reporter system, and several were observed to function *in vivo*.

Finally, the authors demonstrated the oncogenic potential of one T-UCR. They chose one of the T-UCRs that is most significantly upregulated in colon cancer, and used small interfering RNAs to downregulate it. This decreased proliferation and increased apoptosis.

The role of T-UCRs in cancer is just beginning to be explored. They are unlikely to be the last new element with a role in tumorigenesis: as geneticists discover more functional elements in their increasingly detailed annotation of the genome, cancer biologists can expect many of them to have roles as oncogenes and tumour suppressors.

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ORIGINAL RESEARCH PAPER Calin, G. A. et al. Ultraconserved regions encoding ncRNAs are altered in human leukemias and carcinomas. *Cancer Cell* **12**, 215–229 (2007)

FURTHER READING Esquela-Kercher, A. & Slack, F. J. Oncomirs — microRNAs with a role in cancer. *Nature Rev. Cancer* **6**, 259–269 (2006)