GENE EXPRESSION

Something for a stressful day

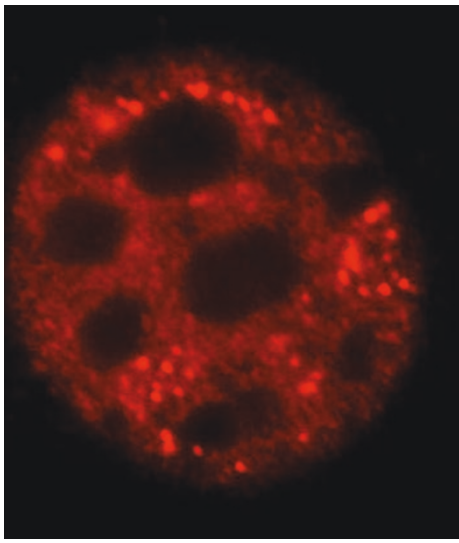
The genome has developed numerous ways to regulate the expression of the genes it harbours, and a new mechanism has now been uncovered by David Spector and colleagues, as reported in *Cell*. They identified an RNA that is normally retained in the nucleus but, in response to stress, is cleaved to release a translation-competent mRNA into the cytoplasm, which is subsequently translated into protein. This indicates a role for the nuclear retention of RNA in controlling gene expression.

Intrigued by the earlier observation that poly(A)$^+$ RNA is enriched in distinct subnuclear structures known as nuclear speckles, the Spector group set out to isolate and characterize the population of poly(A)$^+$ RNAs in nuclear speckles. They showed that one RNA, which they named CTN-RNA and is encoded by the mouse cationic amino-acid transporter-2 (*mCAT2*) gene, colocalizes only partially with nuclear speckles but colocalizes completely with an adjacent nuclear domain, known as paraspeckles.

The mechanism for nuclear retention of RNAs is unknown, but it could occur as a result of an RNA-editing process known as adenosine (A) to inosine (I) editing. The authors therefore investigated whether CTN-RNA might be a target for RNA editing. Sequence comparison of several CTN-RNA clones revealed that A-to-I editing takes place in the 3′ untranslated region (3′ UTR). Reporter-gene analysis showed, however, that the CTN-RNA 3′ UTR is not sufficient for retention, but that the entire transcript is required. This could indicate that specific folding of the entire RNA, as well as A-to-I editing of the 3′ UTR, is important for nuclear retention.

To explore the function of CTN-RNA, Spector and colleagues knocked down CTN-RNA using antisense oligonucleotides, and found that this was accompanied by a reduction in the level of *mCAT2* mRNA. The mCAT2 protein functions in the nitric-oxide synthesis pathway, which is induced by stress conditions. Cells exposed to stress showed a decrease in the level of CTN-RNA, which was accompanied by an increase in the level of *mCAT2* mRNA. Northern-blot analysis revealed that, under stress conditions, the CTN-RNA is cleaved at its 3′ UTR, releasing the protein-coding mRNA. So, in unstressed cells, CTN-RNA is nuclear retained and regulates the level of *mCAT2* mRNA, whereas in stressed cells, the CTN-RNA is released as translation-competent mRNA for the rapid production of mCAT2 protein.

The identification of CTN-RNA and its mechanism of action unveils a new paradigm in the regulation of gene expression, and Spector and colleagues propose that this type of regulation allows for a rapid response to environmental signals. These findings also implicate A-to-I editing as a mechanism for nuclear retention of RNA, and indicate a role for paraspeckles as a reservoir for A-to-I-edited nuclear RNAs.



RNA fluorescent *in situ* hybridization (FISH) showing the diffuse nuclear localization of CTN-RNA as well as its presence in paraspeckles in a mouse-embryo fibroblast. Image courtesy of Kannanganattu V. Prasanth and David L. Spector, Cold Spring Harbor Laboratory, USA.

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References and links

ORIGINAL RESEARCH PAPER Prasanth, K. V. *et al*. Regulating gene expression through RNA nuclear retention. *Cell* **123**, 249–263 (2005)
FURTHER READING Bass, B. L. *et al*. A nuclear RNA is cut out for translation. *Cell* **123**, 181–183 (2005)
WEB SITE
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