Nature Reviews Molecular Cell Biology | AOP, published online 14 October 2009; doi:10.1038/nrm2789

Journal club

35 YEARS LATER, MRNA CAPS STILL MATTER

Whereas some important discoveries shine sudden and unexpected light on a research area, other seminal advances result from the contributions of several groups, and the realization of their impact comes years after the initial breakthrough. The discovery of the mRNA cap offers one example of growing realization.

In the mid 1970s, biochemical analyses, such as those carried out by Wei *et al.* and Furuichi *et al.*, revealed that certain viral and eukaryotic mRNAs have a cap — a methylated guanosine residue linked to the 5′ end of mRNA through an inverted 5′ to 5′ triphosphate bridge. The cap was found to have a crucial role in mRNA translation, and eukaryotic translation initiation factor 4E (EIF4E) was the first protein identified to bind directly to the cap to recruit numerous other important translation factors and ribosomes to mRNA.

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The regulation of translation by EIF4E activity has since become an important area of research. Multiple intracellular signalling pathways converge on this protein, and several studies suggest that EIF4E activity is deregulated in various diseases, including cancer. The cap structure was later shown to also be required for efficient mRNA processing, export, stabilization and microRNA-mediated gene silencing. These cap functions are mediated by cap-binding proteins other than EIF4E.

Surprisingly, although it has been clear for many years that the cap is added to mRNAs during transcription, deep sequencing efforts from the Affymetrix and Cold Spring Harbour Laboratory ENCODE Transcriptome Project recently highlighted the widespread presence of short RNAs with a cap-like structure that is apparently added post-transcriptionally. This observation, as well as evidence from Otsuka *et al.* that a cytoplasmic complex can add caps to 5′-monophosphate RNAs, suggests that capping might be more complex than initially thought. How many more tricks will be pulled out of the cap?

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ORIGINAL RESEARCH PAPERS Wei, C. M. *et al.* Methylated nucleotides block 5′ terminus of HeLa cell messenger RNA. *Cell* **4**, 379–386 (1975) | Furuichi, Y. *et al.* 5′-Terminal m-7G(5′) ppp(5′)G-m-p *in vivo*: identification in reovirus genome RNA. *Proc. Natl Acad. Sci. USA* **72**, 742–745 (1975) | Affymetrix/Cold Spring Harbor Laboratory ENCODE Transcriptome Project. Post-transcriptional processing generates a diversity of 5′-modified long and short RNAs. *Nature* **457**, 1028–1032 (2009) | Otsuka, Y. *et al.* Identification of a cytoplasmic complex that adds a cap onto 5′-monophosphate RNA. *Mol. Cell. Biol.* **29**, 2155–2167 (2009).