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Messenger RNA – Measured and Trimmed to Size

Researchers from the Max Planck Institute of Biochemistry reveal the structure of a ribonucleotide-trimming machinery with a central role in cell biology.

- **Messenger RNAs (mRNA) transfer genetic information from the cell nucleus and to the site of protein synthesis.**
- **mRNAs are modified with a chain of adenines (poly(A)-tail) that has regulatory functions.**
- **Study solves the structure of the complex that controls trimming of the poly(A)-tail to the optimal size.**
- **Proteins binding to the poly(A)-tail measure its length and in parallel control the affinity of the enzymes degrading the poly(A)-tail.**

Messenger RNAs (mRNAs) are the functional link between the genetic information in the cell nucleus and ribosomes, where proteins are synthesized. The structure of mRNAs can be differentiated into translated and untranslated regions. The translated regions serve as templates for the synthesis of proteins, while the untranslated regions have regulatory functions. The untranslated regions of mRNAs of all higher developed cells – from yeast to plants and humans – contain similar characteristic elements. One such element is the poly(A)-tail: a long chain of adenine molecules, one of the RNA building blocks. These tails are added to the end of the mRNA after their synthesis and fulfil many functions e.g. control stability, translation into proteins and localization of the mRNA. Nascent mRNAs have a long tail of up to several hundred adenines, which is then reduced to a species-specific length by enzymes called deadenylases.

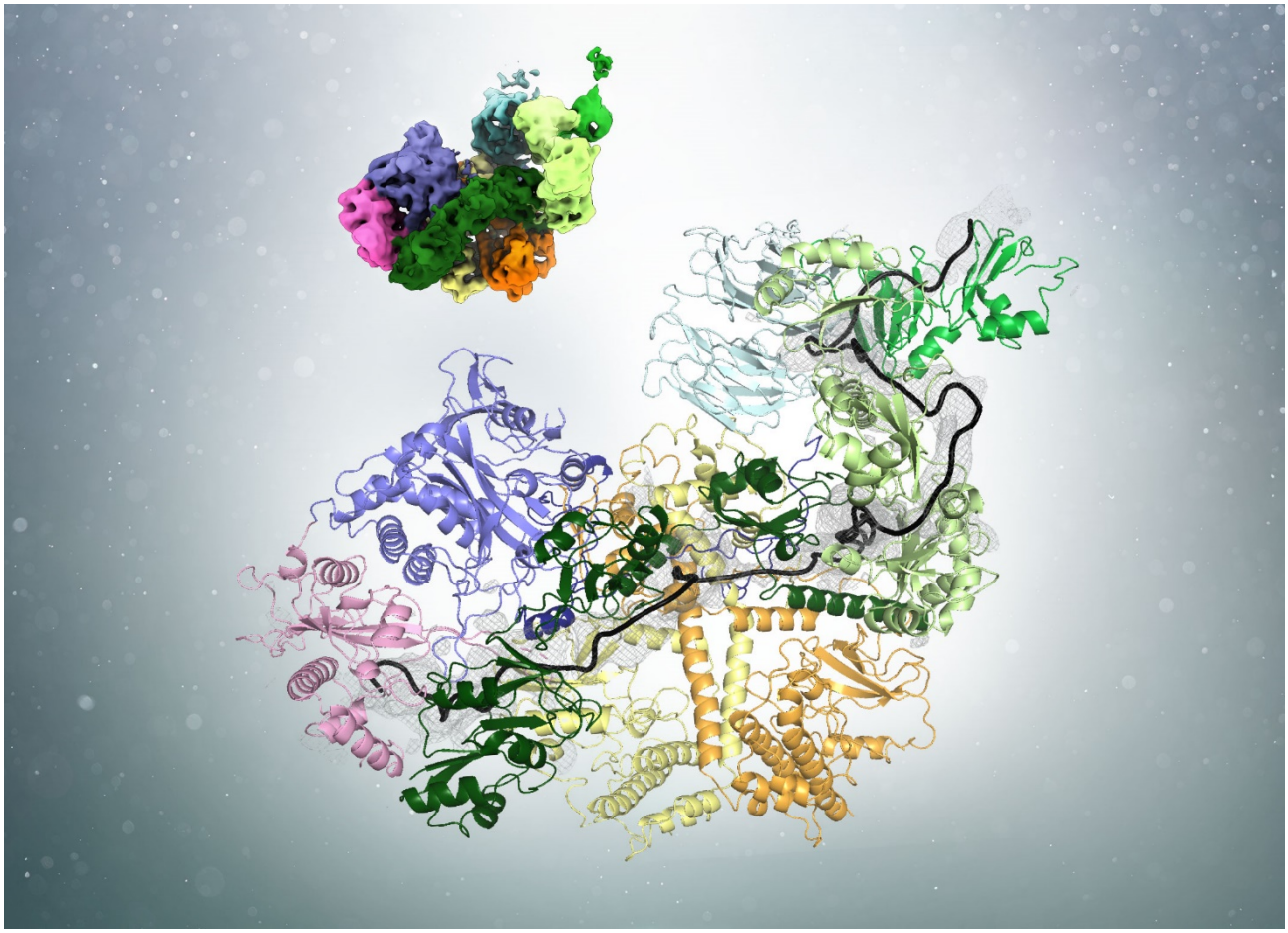
In a recent publication in the journal *Cell*, researchers led by Elena Conti at the Max Planck Institute of Biochemistry (MPIB) in Martinsried have demonstrated how poly(A)-tail shortening is controlled. “The poly(A)-tail is synthesized to a length much longer than we eventually find in cells. The presence of a poly(A)-tail-trimming mechanism has therefore been long suggested but the details were unclear”, says Ingmar Schäfer, a postdoctoral researcher in Elena Conti’s Department and first

author of the study. The researchers now solved the structure of the involved components and show how measuring the length and trimming of the poly(A)-tail are coupled. The process requires the interplay of three components: the poly(A)-tail, poly(A)-tail-binding proteins (PABP) and the Pan2-Pan3 complex of deadenylases.

Using cryo-electron microscopy (cryo-EM), the researchers found that PABP forms arches that cover approximately 25 to 30 bases of the poly(A)-tail. Ingmar Schäfer uses an analogy from everyday life to illustrate the process: “Before cutting hair, a hairdresser uses his fingers to physically determine how much of the hair will be left standing.” Similarly, the PABP arches act as a rulers to determine the length of the poly(A)-tail. “But unlike our hair at the hairdresser, the poly(A)-tail is not trimmed with one cut but rather ‘nibbled off’ from the end by the deadenylase enzyme.”

Interestingly, the number of bound PABP alters the affinity of the deadenylase for the poly(A)-tail. In yeast, the most common poly(A)-tail length is around 30 nucleotides. On longer poly(A)-tails, several PABP can be bound and the adenine chain is quickly degraded. Shorter poly(A)-tails approaching the optimal length can only bind one ruler protein. This corresponds with a lower affinity for the deadenylases. “Hence, PABP is not only the tool measuring the poly(A)-tail, but also acts as a brake on the deadenylases when the optimal length is reached”, explains Schäfer. Eventually, when the mRNA is no longer needed, it is further degraded by a different set of deadenylases.

Polyadenylation is a basic principle of cell biology used to control mRNA stability and protein synthesis. “The structure of the poly(A)-tail ‘trimming tool’ will impact research on a broad variety of aspects of cell biology”, puts MPIB Director Elena Conti the study in a larger context. She highlights that the mechanism is highly conserved between yeasts and humans. “Now that we have solved the structure of the deadenylation machinery in yeast, we want to understand how the system works in human cells, where the optimal poly(A)-tail length differs from yeast.”



Caption:

The length of the poly(A) tail (black) in complex with the poly(A) binding protein (green) is measured by Pan2-Pan3(shades of blue, yellow and orange).

Original publication:

I.B. Schäfer, M. Yamashita, J.M. Schuller, S. Schüssler, P. Reichelt, M. Strauss, E. Conti:
Molecular basis for poly(A) RNP architecture and recognition by the Pan2-Pan3 deadenylase *Cell*, May 2019
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About Elena Conti

Professor Elena Conti studied Chemistry at the University of Pavia in Italy. She received her PhD in Protein Crystallography at Imperial College, London in 1997. After a Postdoctoral fellowship in John Kuriyan's lab at The Rockefeller University, New York, USA, she was appointed Group leader at the European Molecular Biology Laboratory (EMBL) in Heidelberg, Germany in 1999. There she focused her research interest on mechanisms of RNA export to the cytoplasm and the structure and function of the molecular machines involved. Conti has followed the fate of RNA in the cytoplasm since then. She was appointed Director and Scientific Member at the Max Planck Institute of Biochemistry, Martinsried near Munich, Germany in 2006 where she leads the department of "Structural Cell Biology". Since 2007, she is Honorary Professor at the Ludwig Maximilian University in Munich. Conti received numerous awards, among others the Gottfried Wilhelm Leibniz Prize 2008 and the Louis-Jeantet Prize for Medicine 2014. More information you find here.

About the Max Planck Institute of Biochemistry

The Max Planck Institute of Biochemistry (MPIB) belongs to the Max Planck Society, an independent, non-profit research organization dedicated to top-level basic research. As one of the largest Institutes of the Max Planck Society, about 800 employees from 45 nations work here in the field of life sciences. In currently about 35 departments and research groups, the scientists contribute to the newest findings in the areas of biochemistry, cell biology, structural biology, biophysics and molecular science. The MPIB in Munich-Martinsried is part of the local life-science-campus in close proximity to the Max Planck Institute of Neurobiology, a Helmholtz Center, the Gene-Center, several bio-medical faculties of the Ludwig-Maximilians-Universität München and the Innovation and Founding Center Biotechnology (IZB). (http://biochem.mpg.de)

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