How quality control works in our cells

July 8 2013

A cellular control mechanism prevents the production of defective proteins in our cells. A team of researchers from Bern has now obtained valuable insights into this vital mechanism that could lead to new therapeutic approaches for genetic diseases.

A person has hundreds of thousands of different proteins that are constantly being produced and degraded. Like in any factory where raw materials are processed, there are various control mechanisms in the cell that check the quality of the products, namely the proteins.

This cellular quality check is referred to as "nonsense-mediated mRNA decay" (NMD) in the technical jargon. A team of researchers headed by Oliver Mühlemann at the University of Bern's Department of Chemistry and Biochemistry has now obtained valuable new insights into the molecular mechanics of this process. These findings could help to develope new therapeutic approaches towards genetic diseases. The research results have been published in two articles in the journal *Nature Structural & Molecular Biology*.

Control during protein production

The information on the production of all proteins in a cell is stored in the genetic material, the DNA. In order to produce a protein, the corresponding body plan encoded on a particular section of the DNA has to be copied in so-called messengerRNA (mRNA) and thus multiplied.

The cellular protein factories, the ribosomes, read these information

carriers – the mRNAs – based on the genetic code and produce the corresponding proteins. Errors regularly occur during this complex biochemical process, resulting in mRNAs carrying information for defective proteins. To prevent faulty proteins from being produced due to these corrupted mRNAs our cells developed the NMD control mechanism in the course of evolution, which recognises defective mRNAs and degrades them efficiently.

NMD also ensures that many mutations in our genes do not cause any disease symptoms – as long as the second copy of the gene affected is still intact and thus a correct version of the body plan is available.

For the NMD quality control mechanism to be triggered, a large number of factors have to coincide with the defective mRNA. When and how this happens, however, was unknown. Now, in collaboration with bioinformatics specialists from the Biozentrum Basel, biochemist David Zünd, a doctoral student in Oliver Mühlemann's team, has managed to demonstrate the contribution of a key protein: in the NMD process, the protein UPF1 (up-frameshift1) is recruited by all mRNAs, irrespective of whether they are in working order or damaged.

While on viable mRNAs UPF1 is removed by the protein factories, the ribosomes, it remains bound to defective mRNAs and recruits additional enzymes that cause the degradation of the mRNA "The protein UPF1 bound to the mRNA acts as an armed trap that only has to be triggered when needed to degrade the defective mRNA," says Zünd.

Molecular biologist Simone Rufener, who is also a doctoral student in the same lab, was able to solve another mystery surrounding NMD. Earlier results by American researchers indicated that, unlike in single-cell organisms, defective mRNAs in multicellular organisms can only be recognised and degraded by NMD for a short time period directly after their production.

This would mean that older defective mRNA molecules that already serve as a template for mass protein production are immune against NMD and the defective mRNAs missed by the quality control would lead to the production of large quantities of defective proteins as a result – which would have potentially fatal consequences for the organism.

However, the doctoral student was able to demonstrate that NMD also recognises older, defective mRNAs as well as newly produced ones, which improves the efficiency of the quality control. "This result also indicates that the basic mechanism of NMD in single-cell and multicellular organisms is preserved and already developed early on in the course of evolution," says Rufener.

All in all, according to the researchers, these new insights help to understand how our cells can keep the error rate relatively low during protein production despite defective genetic activity. NMD plays a key role in the clinical presentation of various genetic diseases. Consequently, the research team hopes to make a contribution towards future treatments for such diseases by improving our understanding of the molecular processes.

More information: Simone C Rufener & Oliver Mühlemann: eIF4E-bound mRNPs are substrates for nonsense-mediated mRNA decay in mammalian cells. *Nat Struct Mol Biol.*, 20:710-717 (doi:10.1038/nsmb.2576)

David Zünd, Andreas R Gruber, Mihaela Zavolan & Oliver Mühlemann: Translation-dependent displacement of UPF1 from coding sequences causes its enrichment in 3? UTRs. *Nat Struct Mol Biol.*, 7. Juli 2013, doi:10.1038/nsmb.2635

Provided by University of Bern