PRESS RELEASE

The poly(A) detector: how cells avoid making toxic proteins

Mainz, 23 October 2019. *Researchers at the Institute of Molecular Biology (IMB) in Mainz, Germany have discovered a new route used by cells to avoid making defective proteins. In their paper published today in* Genome Biology, *the research groups led by Dr Petra Beli and Dr Julian König show how MKRN1 acts as a sensor for detecting abnormal mRNAs and blocks them from being translated into proteins. This finding identifies a crucial component of the cell's protein quality control mechanisms and gives insight into how cells avoid producing aberrant proteins that can cause neurodegenerative disease.*

Proteins are the building blocks of cells and must be constantly produced for the cell to function properly. Cells produce proteins by transcribing DNA into messenger RNA (mRNA), which is in turn translated by ribosomes into proteins. However, this multi-step process needs to be tightly controlled as there are many chances for mistakes to creep in. The last step of mRNA production is polyadenylation, when the mRNA is cleaved on the tail end and a long row of adenosines (As) is added. This structure is called a poly(A) tail and is integral to an mRNA's function.

In some cases, premature polyadenylation can occur. This is where the mRNA is mistakenly cut early in its sequence and the poly(A) tail is added to the now shortened mRNA. Premature polyadenylation is a major problem because translation of these shortened mRNAs creates truncated, non-functional proteins that can accumulate in the cell. Accumulation of toxic protein aggregates can in turn lead to cell death and contributes to neurodegenerative diseases such as amyotrophic lateral sclerosis.

To prevent this from happening, cells have an in-built quality assurance mechanism called ribosome associated quality control (RQC). Faulty mRNAs are detected during translation by various surveillance systems. Once a prematurely polyadenylated mRNA is recognised, the translating ribosome is stalled to stop it from making a non-functional protein. This is the signal for the RQC to spring into action. The stalled ribosomes are split apart and the partially synthesised protein is degraded. However, until now scientists did not know how premature poly(A) sequences are recognised and how they trigger ribosome stalling.

In a joint study, the research groups of Petra Beli and Julian König (IMB) along with Kathi Zarnack (Goethe University Frankfurt) were studying Makorin Ring Finger Protein 1 (MKRN1), an enzyme that marks other proteins for degradation by adding a small protein tag called ubiquitin. Using a specialised technique called iCLIP, they show that MKRN1 binds most strongly immediately upstream of sequences containing a string of As. Moreover, MKRN1 interacted robustly with other proteins known to bind poly(A) tails and associated with translating ribosomes. This led them to speculate that MKRN1 may be involved in detecting premature polyadenylation.

In line with this, MKRN1-deficient cells failed to halt translating ribosomes at poly(A) sequences, showing that MKRN1 plays an essential role in ribosome stalling. In addition to stopping ribosomes, the authors found that MKRN1 ubiquitylates the ribosomal protein RPS10, which may trigger ribosome stalling.

The leading author of this study, Andrea Hildebrandt, explains, "MKRN1 acts as a sensor allowing the cell to detect premature polyadenylation. Once bound to a poly(A) stretch, we think that MKRN1 blocks

ribosomes from translating and ubiquitylates ribosomal proteins to trigger ribosome stalling. The stalled ribosome then blocks other ribosomes coming up from behind, creating a ribosome 'traffic jam' that triggers the degradation of potentially harmful proteins. Thus we see MKRN1 as a first line of defence for detecting faulty mRNAs with premature poly(A) tails and stopping their translation as early as possible."

These findings explain how cells are able to avoid making toxic proteins and continue to function despite making occasional mistakes in the protein production process.

Further details

Julian König is a Group Leader at IMB, and Petra Beli is an Emmy Noether Group Leader at IMB. Further information about research in the König and Beli labs can be found here: https://www.imb.de/research/koenig/research/ and https://www.imb.de/research/beli/research/. The paper mentioned in this work can be found at: https://genomebiology.biomedcentral.com/articles/10.1186/s13059-019-1814-0.

About the Institute of Molecular Biology gGmbH

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Boehringer Ingelheim Foundation

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