PRESS RELEASE

Starting points for the control of protein synthesis

Bonn researchers develop a versatile toolbox for the characterization of IRESes in cells

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Bonn, March 20 - The research field of "cellular IRESes" lay dormant for decades, as there was no uniform standard of reliable methods for the clear characterization of these starting points for the ribosome-mediated control of gene expression. Researchers at the University Hospital Bonn (UKB) and the University of Bonn, in collaboration with Stanford University in California (USA), have now developed a toolbox as a new gold standard for this field. They hope to discover strong IRES elements that are directly relevant for synthetic biology and for application in emerging mRNA therapeutics. The results of their work have been published in The EMBO Journal.

Only recently has the ribosome - one of the oldest molecular machines in evolutionary terms - been recognized as an active regulator of gene expression at the level of protein biosynthesis. This is an important process for the development and function of cells, in which genetic information is converted into proteins. The final step, in which the information encoded on the messenger RNA (mRNA) is transferred, is known as translation. The "Immunobiochemistry" research group led by Prof. Kathrin Leppek at the Institute of Clinical Chemistry and Clinical Pharmacology (IKCKP) at the UKB is investigating the control of translation using the direct interaction of the ribosome with mRNAs. "As the central translation machinery that is essential for all life, the ribosome and the factors associated with it, such as proteins or RNA structures, are the focus of our research interest," says Prof. Leppek, a member of the ImmunosSensation^2 Cluster of Excellence at the University of Bonn. "There is increasing evidence that ribosome composition influences selective translation such that customized ribosomes preferentially bind and translate certain mRNAs."

Role of IRESes in gene expression

As an example of such structures, which play an important role in the initiation of translation and thus in the regulation of gene expression, the Bonn researchers have now investigated internal ribosomal entry sites (IRESes). The abbreviation IRES is short for "Internal Ribosomal Entry Sites". These are specialized, folded sequences within an RNA strand that are particularly well known in the genetic material of viruses in order to hijack the ribosomes of the host after an infection. The hepatitis C virus or the poliovirus, for example, are able to start the production of new viral proteins independently of all initiation factors thanks to their IRES elements. By recruiting ribosomes, IRES sequences enable the initiation of translation

independently of the 5' cap of the mRNA. This is a protective cap with which the host's own mRNA strands are equipped, which enable translation under normal conditions but are blocked under viral infection.

No uniform standard for the clear characterization of IRES

IRES were first described in the viral genome, which enable the replication of viruses in infected cells by recruiting host ribosomes. In recent decades, however, more and more IRESes have also been described in eukaryotic cells, which, unlike viruses, have a nucleus. "This strengthens the general view that these elements are also involved in the regulation of translation in eukaryotic cells," says first author of the paper Philipp Koch from the Leppek research group at UKB and doctoral student at the University of Bonn. His colleague and co-author Martin Haimann, also a doctoral student at the University of Bonn, adds: "However, a major challenge was the exact and reliable characterization of the newly described IRESes, especially from eukaryotic mRNAs, which was difficult due to technical hurdles and artifacts associated with existing technologies used so far."

In their current research work, the Bonn researchers have compiled and tested a number of versatile techniques that together will enable the robust characterization of IRESes in the future. One important method involves the use of circular RNA reporters, which can be used to confirm IRES-mediated activity of RNA elements. Other techniques include quantitative staining techniques of individual mRNAs in mouse embryo tissue and determination of the translation rate of individual IRES-containing mRNAs. "Such a comprehensive toolbox that can be applied in cultured cells and embryo tissue represents a new gold standard for the robust testing and characterization of IRESes," says Philipp Koch. Corresponding author Prof. Leppek adds: "Strong IRES elements are directly relevant for synthetic biology and emerging mRNA therapeutics."

Promotion:

The work was funded by the German Research Foundation (DFG) as part of the ImmunoSensation2 Cluster of Excellence, as well as by the University of Bonn as part of the "TRA: Life and Health Research Prize 2024" and the university-wide "Strengthening the Equal Opportunity Process (STEP)" program. The UKB and the University of Bonn hold a patent together with Stanford University for the development of effective non-viral IRES sequences for enhanced circular RNA translation for therapeutic and immunogenic protein production.

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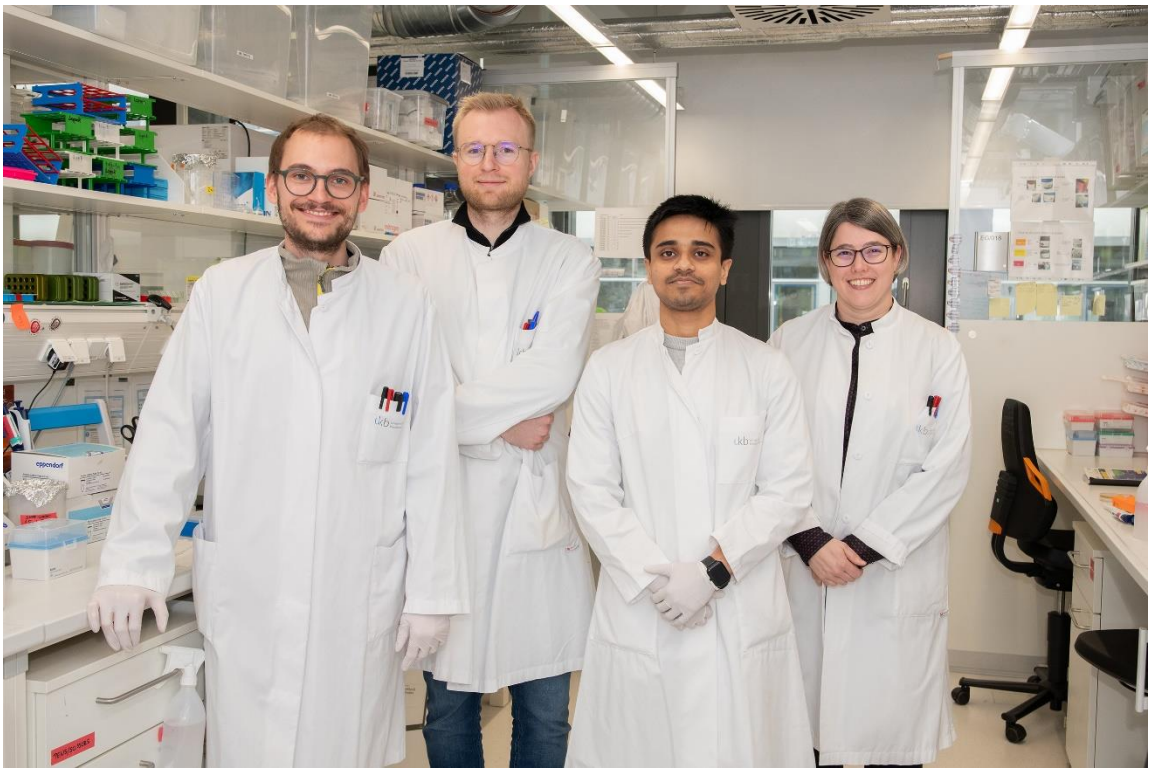

Caption: Starting points for the control of protein synthesis:
(from left) Philipp Koch, Martin Haimann, Saurabh Dey and Kathrin Leppek develop a versatile toolbox for the characterization of IRESes in cells.

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About Bonn University Hospital: The UKB treats around 500,000 patients per year, employs around 9,500 staff and has total assets of 1.8 billion euros. In addition to the 3,500 medical and dental students, 550 people are trained in numerous healthcare professions each year. The UKB is ranked first among university hospitals (UK) in NRW in the Focus Clinic List, had over 100 million third-party funds in research in 2023 and has the second highest case mix index (case severity) in Germany. The F.A.Z. Institute awarded the UKB first place among university hospitals in the category "Germany's Training Champions 2024".