Translation of circular RNAs- regulatory mechanisms and therapeutic applications

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Abstract

CircRNAs are covalently closed RNAs produced mainly by pre-mRNA back-splicing. They are widespread in eukaryotes and play diverse biological roles. Conventionally, the circRNAs were thought of as non-coding RNAs to regulate gene expression through interacting with other molecules, such as miRNA or RNA binding proteins. In 2015, we first reported that circRNAs produced in human cells *via* back-splicing can be translated by cap-independent mechanism through an IRES, suggesting that circRNA may as a new type of mRNAs. We further demonstrated that the circRNAs are enriched for N6-methyladenosine (m6A), which can serve as IRES-like elements to drive circRNA translation. Consistently, many endogenous circRNAs actually undergo translation to produce new protein isoforms. In addition, we conducted two cell-based screens of the random sequence library and a library of endogenous RNAs, resulting in the identification of many short sequence motifs or human transcript fragments with IRES-like activities. Using these sequences, we were able to use an AI approach to design and engineer new "IRESs" with improved activity and cell specificity. These results suggested that the translation of circRNA is both prevalent and robust, and thus circRNAs may serve as an alternative to linear mRNAs in mRNA therapy. To this end, we developed a self-catalyzed system that efficiently produces scarless circRNAs in a co-transcriptional fashion. This system achieved high circularization efficiency for circRNAs of various lengths, and the resulting circRNAs are highly stable and direct prolonged protein translation. Moreover, the circRNAs encapsulated in lipid nanoparticles can be efficiently delivered into mice, inducing robust protein expression that is higher than the modified linear mRNA. This study highlights the potential of circRNAs as the new generation of mRNA therapy for various applications.

Biography

Zefeng Wang received his bachelor's degree as double major in Biological Science and Computer Technology from Tsinghua University and a master degree in Molecular Biology from Institute of Biophysics, CAS. He received his PhD degree at Johns Hopkins Medical School, US, and subsequently worked as Damon Runyon fellow at the Massachusetts Institute of Technology. He became an assistant professor at the University of North Carolina at Chapel Hill in 2007 and was promoted to associate professor with tenure in 2013. In 2015, he moved to Shanghai and

became the director of the Partner Institute for Computational Biology (PICB), a partner institute jointly run by the Chinese Academy of Science and the Max-Planck society. In 2021, PICB was merged with the newly established CAS Shanghai Institute for Nutrition and Health, where he is currently working as a principal investigator and group leader of RNA system biology, and also serves as the director of CAS key lab of computational biology.

Zefeng's research focuses on the regulation of gene expression at RNA level. His lab has developed a series of genomic approaches to study RNA splicing regulation in a systematic fashion, and developed artificial proteins to specifically manipulate RNA metabolism. In addition, his recent work has also been focused on the noncanonical translation of circular RNAs (circRNAs). His work was recognized by many research awards, including RNA Society/Scaringe Young Scientist Award, Alfred Sloan Research Fellow, Beckman Young Investigator, Max-Planck Fellow, CAS pioneer hundred talents program (type A), etc. Based on the research from his lab, he also co-founded two biotech companies and served as scientific advisor on both companies. One is the CirCode BioPharm Inc that seeks to use circular RNAs as a new generation of mRNA therapy, and the other is the Enzerna Bioscience Inc that use artificial RNA endonuclease as a new type of gene therapy reagents.