RCB – Colloquium

Friday, November 3rd 2023, 1 p.m.

H 53 - Sondertermin

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"Translation of circular RNAs- regulatory mechanisms and therapeutic applications"

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 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 are 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 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 of 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.

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