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Expanding human proteome via alternative translation: new lessons learned from circRNAs

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언어: English

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Abstract

The number of protein coding genes in human genome is surprisingly small considering its proteome complexity. This discrepancy is mainly caused by the complex regulation at the RNA level. For example, 95% of human genes undergo alternative splicing to produce multiple mRNA isoforms that code for different isoforms. However, several recent studies suggest that the regulation of mRNA translation may play important roles in expanding proteome complexity. Most human mRNAs are translated through a cap-dependent pathway, however human cells contain >10,000 circular RNAs (circRNAs) that can potentially be translated though a non-canonical cap-independent mechanism. We found that the circRNAs can be efficiently translated inside cells from either internal ribosomal entry sites (IRESs) or the short sequences containing m6A modification. In addition, we identified thousands of endogenous circRNAs that can potentially be translated. To further determine the prevalence and importance of circRNA translation, we screened a random 10-nt library using a cell-based reporter system and identified a large number of AU-rich motifs that are capable of initiating circRNA translation. These IRES-like elements are significantly enriched in circRNAs vs. linear mRNA and are sufficient to drive robust translation of circRNAs containing solely the coding sequences. Importantly, these elements are predicted to present in thousands of circRNAs with 68% of which encode a truncated isoform of host genes, and are found to bind trans-acting factors that promote circRNA translation. Using similar system, we further screened the human transcriptome for endogenous sequences that can drive cap-independent translation. Surprisingly, these cap-independent translation initiators (CiTIs) are relatively enriched in the 3'UTR and play key roles in promoting translation initiation of upstream ORFs. Collectively, our results demonstrated the prevalent cap-independent translation and the unusual complexity of translation regulation, which have important biological roles under certain stress conditions when the canonical translation is inhibited.

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