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Enigmatic Translons: Animalcules of Molecular Biology?

Ribosome profiling has revealed the extensive use of multiple start codons in eukaryotic mRNAs, including in humans, reflecting a substantial, hitherto unexplored, biological phenomenon. Translation initiation at these start codons results in the synthesis of protein isoforms with alternative N-termini and also in translated regions (translons) not annotated as protein coding. Some of these unannotated translons encode microproteins and immunopeptides while many function as critical elements of translational control that sense cellular environment. This regulatory function of translons is often independent of the polypeptide products they encode.

The emerging picture of RNA translation is in striking contrast to the current data structures for annotating protein coding genes in which a sequence of an RNA molecule can have only a single protein-coding sequence (CDS). To address this limitation, we developed a new abstract representation of mRNA translation termed Ribosome Decision Graphs (RDGs). RDGs allow for a biologically realistic representation of the complexity of eukaryotic translation, focusing on locations critical for translational regulation. RDGs can be used to depict the mutual organization of translons reflecting the interplay between their translation events. RDGs can be used in the analysis of ribosome profiling data to identify critical regulatory events and model the flux of ribosomal complexes engaged with RNA as well as for the interpretation of genetic variants, enabling a mechanistic understanding of pathogenic variants occurring outside CDS regions.

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