Analysis of UTRs from nuclear-encoded mitochondrial mRNA in Metazoa reveals new insights about molecular mechanisms controlling mitochondrial biogenesis

ID - 215

D'elia Domenica[1], Germinario Lucrezia[1], Grillo Giorgio[1]

[1]Institute for Biomedical Technologies (ITB), Via Amendola n. 122/D, Bari (Italy)

Motivation

Regulated translation of mRNA controls a wide range of processes in eukaryote and is mainly mediated by mRNA untranslated regions (UTRs). The present work represents the first large scale analysis carried out on UTRs of nucleus-encoded mitochondrial mRNA in Metazoa. The analysis has been focused on the investigation of UTRs structural and functional features and has been carried out using three reference databases: MitoRes, UTRdb and UTRsite. The aim of this study was to use UTRs analysis to investigate the role of translational control in coordinated expression of nuclear and mitochondrial genomes in mitochondrial biogenesis and function. The results obtained highlight interesting and unknown features, underlining the importance of translational control in the coordination of mitochondrial biogenesis programme during cell growth, differentiation and in response to environmental stimuli.

Methods

UTRs have been extracted from the MitoRes database, an integrated resource of nuclear-encoded mitochondria sequences collecting protein, transcript and gene sequences of Metazoa, from UniProt, RefSeq and UTRef databases, respectively.

Sequences investigated were only those annotated as complete UTRs. The data set obtained has been refined to exclude all those species whose number of transcripts was too small to be considered as representative and purified for the presence of redundancies using the CleanUp program. Structural features investigated have been length distribution and average length. Statistical analyses on average length have been carried out using the non-parametric Wilcoxon test. Concerning the compositional analysis, both the CG% content of UTR sequences and of the third silent codon positions in the corresponding CDSs have been investigated in all UTRs whose length exceeds 20nt. Results from structural and compositional analyses have been compared with those obtained by Pesole G. et al., in previous years, on total cell mRNA collected in UTRdb. The investigation about number and type of functional cis-acting motifs has been carried out using a C++ program devised for this task in our laboratory. It uses the SQL queries implemented by MySQL API and the PatSearch engine to retrieve and integrate related data about transcripts extracted from MitoRes, annotations about UTRs and functional motifs from UTRef and UTRsite databases, respectively.

When necessary, the program UTRscan has been used to investigate the presence of conserved functional motifs in UTRs and UTRef database for the extraction of updated species-specific UTR sequence collections.

Results

The structural analyses of UTR sequences investigated have revealed a significant contraction of their average length when compared with values obtained on total cell mRNAs, with a much more marked effect in 5UTRs. This feature, highlighted for the first time by our study, could be due to functional constrictions correlated with a major translation efficiency requested for this particular class of genes as well as to their endosymbiotic origin. This last hypothesis would be enforced by the high percentage of associations of uORF-IRES motifs, detected in 5UTRs of examined transcripts, whose molecular mechanism of action on translational efficiency could resemble the translational attenuation mechanism common to prokaryotic operons. As well as in 5UTRs, IRES motifs have also been identified in the 3UTR sequences of respiratory genes, where they play a key role in mediating mitochondrial differentiation during development in mammals. We have found IRESs not only in the 3UTRs of respiratory genes in human and rodents, as reported in literature, but also in B. taurus, D. rerio and D. melanogaster and in the 3UTRs of mtTFA and EF-Tu mitochondrial factors, in human and others mammals. On the whole these findings suggest that the translational molecular mechanism controlling mitochondrial differentiation is common not only to mammals, but also to other taxonomic groups, and that the coordination of nucleus-mitochondrion expression during the development is mediated at the translation level by IRESs. The importance of translation control on mitochondrial biogenesis and function has been further underlined by results obtained from our analyses on transcripts that incorporate at their 5 terminus TOP motifs, able to regulate translation in a grow-dependent manner and by the identification, not reported in literature, of INS_SCE motifs in the 3UTRs of respiratory genes mRNAs. INS_SCE has a key role in the stabilization of insulin transcript, a key

modulator of insulin production. Our findings suggest a potential coordinated control of insulin secretion and mitochondrial biogenesis that could shed light on the still unknown mechanisms controlling the functional interdependence among glucose-dependent insulin secretion, mitochondrial biogenesis and insulin-mitochondria dependent myogenesis.
Email: domenica.delia@ba.itb.cnr.it