博士論文（要約）

Identification and characterization of TUFs having a coding potential of short peptides in human cells

(短鎖ペプチドをコードするヒト転写産物の同定と機能解析**)**

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Whole transcriptome analyses have revealed that TUFs (Transcripts with unknown function) are massively transcribed from the mammalian genome. Previous researches categorized TUFs as noncoding RNA, because most TUFs do not encode open reading frames (ORFs) with biologically significant length (>100 amino acid). However, recent studies have suggested that small ORFs (sORFs) encoding peptides shorter than 100 amino acids are an important class of functional category in mammalian genomes. Although a portion of TUFs have been studied but the biological significance of most TUFs remains elusive. Here, by using a new strategy, we identified several hundreds of ribosome-associated TUFs that are previously categorized as long noncoding RNA. Ribosome footprinting and Polysomes profiling analysis revealed that 61 of them have the potential to encode short peptides. Assessment of the RNA quality by nonsense mediated mRNA decay (NMD) identified 45 TUFs as nonNMD targets, suggesting their possible functionality in the cells. We confirmed the translation of one TUF, namely LINC00493, which harbors a putative sORF of 95 amino acids. The coding region of LINC00493 exhibited specific evolutionary conservation signatures among several species, an important indicator of a functional gene. Computational analysis predicted a transmembrane alpha helix from the peptide sequence of LINC00493. Functional proteomic analysis revealed that the peptide interacted with many mitochondrial proteins which are associated with several biological processes, most significantly in apoptosis, suggesting possible involvement of the peptide with mitochondria. Immunostaining assay confirmed the localization of the peptide into mitochondria. Furthermore, queries to the gene database NCBI-GEO revealed that the expression of LINC00493 was upregulated by several antiproliferative/apoptotic stimuli, demonstrating its possible association with mitochondria mediated apoptosis. Finally, the apoptotic assay in LINC00493 knockdown cell supported the hypothesis of its involvement with apoptosis. Here, our findings about LINC00493 collectively indicate that other candidate TUFs may also encode novel peptides and they may also have biological functions in the cell.