MicroRNAs bind with mRNAs of genes involving in mitochondrial apoptosis pathway

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MicroRNAs (miRNAs) are small noncoding RNAs that promote the suppression of mRNA translation or lead to mRNA degradation. MiRNAs regulate different cell processes, including apoptosis and anti-apoptosis [1]. Changes in the mitochondrial signaling pathways may lead to human cancer, cardiovascular and other diseases [2]. Changes in miRNA concentrations in biological liquids were observed in a large number of diseases. Data on the locations of miRNA binding sites could improve understanding of the interactions between miRNAs and mRNAs. The effects of many miRNAs on gene expression remain unknown. Nucleotide sequences of genes were obtained from Genbank (http://www.ncbi.nlm.nih.gov/), and miRNAs were downloaded from the miRBase (http://www.mirbase.org/). Parameters and features of miRNA binding sites were calculated by using the RNAHybrid 2.1 program (http://bibiserv.techfak.uni-bielefeld.de/rnahybrid/) and the E-RNAhybrid 2.1 script (http://sites.google.com/site/malaheenee/software/). The ratio value of $\Delta G/\Delta G_m$ (%), where ΔG_m equals the miRNA binding energy with a perfectly complementary nucleotide sequence, was calculated. Reliable binding sites of studied mRNAs with a $\Delta G/\Delta G_m$ value greater than 80% were selected. The binding sites of 785 intergenic miRNAs, 686 intronic miRNAs, and 49 exonic miRNAs were investigated within the 5′UTRs, CDSs, and 3′UTRs of 38 mRNAs of genes participating in mitochondrial apoptosis pathway. MiRNA binding sites were located in all mRNA domains: 3′UTRs (40.4%), CDSs (39,4%), and 5′UTRs (20.2%). It was found that, 99 binding sites formed with intergenic miRNAs, 88 sites – with intronic miRNAs, and 10 sites – with exonic miRNAs. Only 18 out of these genes (*ANP32A, AVEN, BAD, BBC3, BCL2L2, BIRC7, BLK, BMF, DIABLO, HRK, HSPA1A, MADD, MOAP1, NAIP, PRPS1, SH3GLB1, TP53, XIAP*) were found to be targets for 30 intronic miRNAs (miR-1224-3p, miR-1258, miR-1273f, miR-1273g, miR-1285, miR-1294, miR-1322, miR-185-3p, miR-1913, miR-211, miR-3156-3p, miR-3176, miR-3178, miR-326, miR-3620, miR-4251, miR-

4257, miR-4258, miR-4274, miR-4292, miR-4296, miR-4306, miR-4312, miR-4326, miR-4436b-5p, miR-4486, miR-4655-3p, miR-500b, miR-5095, and miR-5096).Intronic miRNAs are often coexpressed with their host gene, therefore the expression of these marker miRNAs depend on their host genes: *ADAMTSL4*, *ANKRD30B, ANP32A, ARF1, ARFGAP1, ARRB1, BMP2K, C22orf25, C9orf86, CEMP1, CKS1B, CLCN5, CLYBL, CTBP2, GALNT10, KRIT1, MAD1L1, MALL, NAV2, PINX1, PRDM16, RPS6KA2, SCP2, SOLH, SORCS2, TRPM1, VWA5B2, VWA5B2,* and *ZNF385B*. These miRNAs provide connections between host genes and target genes via intragenic miRNAs. Alterations in host gene expression lead to changes in intronic and exonic miRNA expression, which influence the target-gene expression. The translation of *BIRC6, BIRC7, BIRC3,* and *ASRGL1* mRNAs are regulated by exonic miR-4315 (*PLEKHM1*), miR-1825 (*POFUT1*), miR-4775 (*CCNYL1*), and miR-4315 (*PLEKHM1*), respectively, where host genes are indicated in brackets. MiR-1285 is encoded in intergenic regions and intron of *KRIT1* gene, that can be undergone difficult regulation by miRNAs, because intergenic miRNAs can be expressed independently, the number of intronic miRNAs depend on splicing of their pre-mRNAs of host genes. The existence of more than one binding site may promote conservation of gene regulation, even if one of the sites has mutations.

This study has demonstrated the interaction between intragenic miRNAs and mRNA of genes involving in mitochondrial apoptosis pathway. The expression of host genes is also important as the target-genes because of intronic miRNA coexpression.

References

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