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MIRNAS AND GENES PARTICIPATING IN THE DEVELOPMENT OF ESOPHAGEAL CANCER

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The asymptomatic nature of esophageal cancer (EC) on early stage show the late clinical presentation leads to poor prognosis and limited success of therapeutic methods. Efforts to identify diagnostic/prognostic markers have been unsuccessful for clinics. Consequently, there is an urgent need for establishment of new non-invasive biomarkers for early diagnosis of EC [1]. The miRNAs are differentially expressed in normal and tumor cells of different subtypes of tumor tissues. Some miRNAs can be found in various biological fluids of the human body: blood, lymph, urine, etc. [2]. The level of circulating miRNAs can serve as an effective biomarker for early diagnosis of EC. The present study is aimed to identify miRNA binding sites in mRNA of genes involved in the development of EC and the clusters of miRNA binding sites in mRNA and their properties. Further, research of these miRNAs would provide a diagnostic strategy based on prevention or treatment of esophageal cancer.

Materials and Methods. The information about the role and function of genes participating in the development of esophageal cancer were taken from GeneBank databases and publications. The mRNA nucleotide sequences of the human genes were derived from GeneBank (http://www.ncbi.nlm.nih.gov). The nucleotide sequences of miRNAs were taken from the article of Londin E. et al. [3]. Searching of miRNA's target genes was performed by MirTarget program, created in our laboratory. This program defines the beginning of miRNA and mRNA binding sites; localization of binding sites in 5'-untranslated region (5'UTR), protein coding region (CDS), and 3'-untranslated region (3'UTR); free energy of interaction of miRNA with nucleotide sequence mRNA (ΔG, kJ/mole) and scheme of miRNA-mRNA nucleotides interaction.

Results. From the 68 candidate genes, participating in the development of esophageal cancer, only 54 genes were targets for miRNAs. The average free energy of binding of all miRNAs with mRNAs of all candidate genes in the 5'UTR region was equal -126 kJ/mole. The number of miRNA associations with mRNA having free energy of interaction greater than -125 kJ/mole is 16 from 87 associations of miRNA-mRNA in the 5'UTR. The miR-20-45152-5p, miR-2-3313-3p, miR-22-46979-5p and miR-1-155-3p form a cluster in mRNA of *PTPRJ* gene from 162 nt to 190 nt with a length 29 nt and average ΔG value equal to -132 kJ/mole. The whole length of all four binding sites was equal to 96 nt, that is three times more than the length of a cluster. The formation of a cluster of four binding sites in the 5'UTR of *PTPRJ* gene shows the ability of a given gene to compaction, which serves as the emergence of given miRNAs competition for the binding site. That is, from here it can be concluded that miR-2-3313-3p with a free energy of interaction equal -138 kJ/mole will occupy this binding site and will not allow other miRNAs to interact with this mRNA. Each miRNA has targets with various affinities and expression levels that essentially work as the competitive inhibitors reducing free miRNA [4]. The mRNAs of *CDC16, HNF4A* and *IHH* genes have binding sites with miR-5-15733-3p, mir-9-26042-5p and miR-7-21068-3p, respectively. The mRNA of *PLEC* gene has three binding sites in the 5'UTR that form a cluster from 27 nt to 58 nt with average ΔG value equal -124 kJ/mole 31 binding sites located from 438 nt to 482 nt with a whole length 45 nt and average ΔG = -131 kJ/mole in mRNA *NFE2L2* gene were identified. In the site with length of 45 nt there are binding sites for fourteen miRNAs: miR-1-155-3p, mir-1-2121-3p, miR-10-13655-3p, miR-11-28656-5p, miR-15-32047-5p, miR-19-21199-3p, miR-19-33623-3p, miR-2-3313-3p, miR-2-4453-3p, miR-22-46979-5p, miR-3-8100-5p, miR-5-8853-5p, miR-6-19010-3p and miR-9-28523-5p. The mRNAs of *DICER1, DNMT3A, DRD2, ETS1* and *SFRP1* genes have only one binding site of miRNA in the 5'UTR at ΔG value higher than -125 kJ/mole. The analogous binding sites were identified in the CDS. The average free energy of interaction of all miRNAs with mRNAs in the CDS was equal -121 kJ/mole. The number of miRNA associations with mRNA having free energy of interaction greater than -125 kJ/mole is 13. In the CDS of mRNA of *BBC3* gene identified a cluster of binding sites from 455 nt to 482 nt with average ΔG value equal to -136 kJ/mole. miR-19-41910-5p, miR-13-32613-3p and miR-5-15548-3p have a cluster of binding sites in mRNA of *PLEC* gene in position from 7013 nt to 7058 nt with a length 46 nt and average ΔG = -129 kJ/mole. The whole

length of all three binding sites was equal to 71 nt. In the CDS *PDE4D* gene mRNA identified clusters of 23 binding sites of miRNAs. 10 miRNAs formed two clusters in segments from 335 nt to 369 nt with a length 35 nt and average ΔG value equal to -133 kJ/mole. The whole length of binding sites is equal to 96 nt. The second cluster of binding sites located from 391 nt to 439 nt with a length 49 nt and average ΔG = -125 kJ/mole. The average free energy of binding of miRNAs with all mRNAs in the 3'UTR was equal to -111 kJ/mole. There are no the miRNA associations with mRNA having free energy of interaction greater than -125 kJ/mole. But this does not mean that the expression of these genes could not be suppressed by miRNAs. In mRNA of *ETS1* gene it was found the interesting evidence: miR-15-36862-3p and miR-10-29282-3p have 12 and 11 multiple binding sites, respectively. They located from 3875 nt to 3931 nt. The effect of each of the miRNAs will depend on the ratio of their concentrations, and overall the expression of the *ETS1* gene will be determined by the total concentration of miR-15-36862-3p with ΔG= -108 kJ/mole and miR-10-29282-3p with ΔG= -107 kJ/mole, since they have close free energies interaction with mRNA of *ETS1* gene. The same miR-15-36862-3p and miR-10-29282-3p form a cluster of binding sites with a length 33 nt located from 5454 nt to 5487 nt in the 3'UTR of mRNA of *RUNX1* gene. Such evidence was observed in mRNA of *IGF2* gene. miR-11-27078-5p having six binding sites and miR-3-5147-5p having two binding sites, form a cluster of binding sites from 2286 nt to 2374 nt with the length equal to 89 nt. The whole length of eight binding sites was equal to 182 nt, which is two times longer than the length of a cluster. The average binding energy was equal -108 kJ/mole. The formation of a cluster of eight binding sites in *IGF2* gene in the 3'UTR shows the ability of a given gene to compaction, which serves as the emergence of given miRNAs competition for the binding site. That is, from here it can be concluded that miR-11-27078-5p with free energy of interaction equal -113 kJ/mole will take this binding site. The mRNA of *S1PR2* has seven miRNA binding sites in the 3'UTR. The binding sites of miR-2-4804-5p and miR-17-39935-3p are located in cluster from 2763 nt to 2795 nt with a length 33 nt and with average ΔG = -110 kJ/mole. The miR-19-42814-5p and miR-10-29282-3p form cluster from 3191 nt to 3218 nt with ΔG value equal -105 kJ/mole. In genes, associated with development of esophageal cancer, it is found 319 potential binding sites for 160 miRNAs that can regulate 54 of the 68 genes responsible for the development of esophageal cancer. The clustered organization of binding sites is observed in 5'UTR, CDS and 3'UTR. It was identified miRNA and mRNA associations that have a free energy of interaction equal to -125 kJ/mole or more that could serve as markers for developing methods for early diagnosis of this disease. The average free energy of binding of miRNA with mRNA of genes involved in the development of esophageal cancer is greater in 5'UTR and CDS compared to 3'UTR, which suggests preferential binding of miRNA to 5'UTR and CDS of the studied genes. It was identified the location of miRNA binding sites in clusters containing two or more binding sites with overlapped nucleotide sequences. Such a compact arrangement of binding sites in mRNA significantly reduces the proportion of binding sites in mRNA. Overlapping miRNA binding sites creates competition between miRNA per binding site, since the RISC complex interacting with mRNA with more free energy will not allow binding to another RISC with miRNA having a weaker interaction with mRNA.

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Key words: mRNA, miRNA, genes, oncological diseases, esophageal cancer.

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ASSOCIATION OF miRNA AND TARGET GENES OF PARKINSON'S DISEASE

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Parkinson's disease (PD) rate is the second most frequent among neurodegenerative diseases and methods of early diagnosis of this disease are actively being developed [1]. Current trends in this direction are in the search for molecular-genetic markers, which can be used in diagnosis and therapy. Among the molecular markers, miRNAs are promising that regulate the translation of multiple genes and probably the genes involved in the development of Parkinson's disease (candidate genes) [2, 3].

Materials and Methods. The search of miRNA binding site in mRNA was found using the MirTarget program which determines the start of the miRNA binding site in mRNA, the location of the site at 5'-untranslated regions (5'UTRs), coding domain sequences (CDSs), 3'-untranslated regions (3'UTRs), the free energy of interaction ΔG (kJ/mole) of the entire miRNA nucleotide sequence and the degree of complementarity of the miRNA and mRNA