CANDIDATE GENES OF CANCER AS A TARGET OF miRNA HOST GENES

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Breast cancer takes one of the first places among all cancer diseases in the world. The statistics of recent years in different countries show an intensive, steady increase in the incidence and mortality from cancer [1]. The search for connections between genes involved in the development of cancer is necessary for the diagnosis of diseases and therapy [2]. The connections of genes can pass both through the interaction of proteins synthesized by them, and mediated by connections. One of the connection ways between genes is through miRNA, which are co-expressed with its host gene and binds to the mRNA of the target gene. More than half of human miRNAs are expressed simultaneously with the host genes and the effect of these miRNAs should be considered as the effect of host genes on the miRNA target gene. This approach in studying of miRNA properties more objectively reflects its functional role - to be a binding molecule between two or more genes. Since one miRNA can act on several genes [3, 4, 5] and one gene can be targeted by several miRNA [6], these properties of miRNA should be considered as a result of the connection of many genes. Due to the location of miRNA binding sites in the form of clusters, it is realized possibility of genes competition through miRNA to influence the expression of their target genes. In this regard, it is required to establish the effect of miRNA host genes on their target genes involved in the development of cancer.

Materials and Methods. The nucleotide sequences of miRNAs of human genes were downloaded from NCBI GenBank [http://www.ncbi.nlm.nih.gov]. Nucleotide sequences of human miRNAs were downloaded from the miRBase database [http://mirbase.org]. The miRNAs binding sites in 5'-untranslated regions (5'UTRs), coding domain sequences (CDSs) and 3'-untranslated regions (3'UTRs) of several genes were predicted using the MirTarget program [7]. This program defines the following features of binding: a) the origin of initiation of miRNA binding to mRNAs; b) the localization of miRNA binding sites in 5'UTR, CDS and 3'UTR of mRNAs; c) the free energy of hybridization (ΔG, kJ/mole); and d) the schemes of nucleotide interactions between miRNAs and mRNAs. The ratio ΔG/ΔGm [%] was determined for each site (ΔGm equals the free energy of miRNA binding with its perfect complementary nucleotide sequence). Only miRNA binding sites with ΔG/ΔGm ratios of 90% or more were selected. The program identifies positions of binding sites on mRNA, beginning from the first nucleotide of mRNA’s 5’UTR. The MirTarget program found hydrogen bonds between adenine (A) and uracil (U), guanine (G) and cytosine (C), G and U, and A and C. The distances between A and C were equal to those between G and C, A and U, and G and U. The numbers of hydrogen bonds in the G-C, A-U, G-U and A-C interactions were found to be 3, 2, 1 and 1, respectively.

Results. Each of CCDC42B, FOXF2, GLYCTK, KIAA2026, PLPPR3 host genes can influence oncogenesis through encoded miR-7106-5p, miR-7106-3p, miR-6720-5p, miR-6720-3p, miR-135a-5p, miR-135a-3p, miR-4665-5p, miR-4665-3p, miR-3187-5p, miR-3187-3p. Characteristics of binding sites between five miRNA-5p and five miRNA-3p of CCDC42B, FOXF2, GLYCTK, KIAA2026, PLPPR3 host genes and 47 mRNA candidate genes involved in oncogenesis have been studied by using the MirTarget program. For miR-7106-5p and miR-7106-3p of CCDC42B host gene 27 sites have been found, that bind in 5'UTR, 3'UTR and CDS mRNAs of genes involved in breast cancer, colon cancer, esophageal squamous cell carcinoma, prostate cancer, gastric cancer, neuroblastoma, cervical cancer, osteosarcoma, ovary cancer, colorectal cancer, hepatocellular carcinoma, pancreatic cancer. miRNAs interacted with free energy from -102 kJ/mole to -115 kJ/mole. A high degree of complementarity of 94% have been found for miR-7106-5p with mRNAs of MAML1, MAPT, SBK1. Characteristics of binding sites for miR-6720-5p and miR-6720-3p of FOXF2 host gene were found for six mRNAs of target genes involved in breast cancer, colon cancer, pancreatic cancer, thyroid cancer. The binding sites of these miRNAs are located only in CDS, the free binding energy have been from -110 kJ/mole to -121 kJ/mole. The characteristics of binding sites for miR-135a-5p have been determined, and for miR-135a-3p binding sites have not been identified. For miR-135a-3p of GLYCTK host gene in CDS mRNA ILDR1 target gene, involved in the development of lymphoma, an interaction with free energy of -110 kJ/mole have been established. miR-4665-5p of KIAA2026 host gene have binding sites in 5'UTR and CDS mRNAs EFEMP1, ZFP36L2 genes involved in the development of breast cancer and pancreatic cancer. They have binding sites with same degree of complementarity equal to 91%, and identical free interaction energy equal to -123 kJ/mole. For miR-3187-5p and miR-3187-3p of PLPPR3 host gene 11 binding sites have been found with target genes involved in breast cancer, colorectal cancer, sporadic pituitary adenomas, gastric cancer, ovary cancer. The binding sites have been located in 5'UTR, 3'UTR, CDS, which interaction energy varied from -106 kJ/mole to -125 kJ/mole. Thus, the effect of miRNA CCDC42B, FOXF2, GLYCTK, KIAA2026, PLPPR3 host genes on target genes participating in various oncological diseases have been demonstrated.

Prospects for further research. As markers for diagnostics, CCDC42B, FOXF2, GLYCTK, KIAA2026, PLPPR3 host genes, their miRNAs and target genes must be considered. A hypothesis for the regulation of gene expression involving miRNA is proposed. The role of miRNA as an integrating system of gene expression in the cell and in the body is proposed.
LDL PARTICLE SIZE AND LIPID PROFILE IN CHILDREN WITH TYPE 1 DIABETES

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The role of small dense low-density lipoprotein (sLDL) subclasses in atherosclerosis has been demonstrated in many studies. Among other metabolic changes, alteration in LDL lipoprotein subclass distribution and size has been proved in diabetic adults. Because there is not enough literature data presenting LDL subclass distribution in childhood, the aim of this study was to examine LDL subclass profile in diabetic children compared with healthy control.

Materials and Methods. In this study we evaluated 130 children, 30 children with type I diabetes mellitus and 100 controls, ages 9-18 years, matched for age, sex, and BMI. Plasma LDL subclasses were analyzed using non-denaturing polyacrilamide gradient (3-31%) gel electrophoresis. Conventional plasma lipid and apoprotein parameters which are thought to affect LDL size were determined as well.

Results: The prevalence of small LDL particles (phenotype B) was in 86.7% of diabetic children, compared to control group (11%), with significant difference (c2=50.45; p<0.0001). The smallest, LDL4 subclass was not found to be dominant in control children whereas in diabetic ones it was noted in 23%. Mean LDL particle size in diabetic children (24.64 ± 0.59) was significantly smaller than in the control children (26.37± 0.68 nm; p<0.0001). The values for all measured conventional plasma lipid and apoprotein parameters in both groups were within the normal range for age of the children population. In diabetic children, LDL size was inversely correlated with plasma levels of triglycerides, and positively correlated with plasma HDL cholesterol and BMI. Overall, LDL size was not correlated with plasma concentrations of total cholesterol, LDL cholesterol, glucose, apoproteins and age in diabetic children. Although lipid and apoprotein plasma levels were within the normal range, increased frequency of LDL phenotype B confirms greater risk for atherosclerosis development in children with diabetes mellitus. LDL size measurement may potentially help to assess cardiovascular risk and adapt the treatment goals thereafter.

References: