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Cluster organization of miRNA binding sites in mRNA of atherosclerosis candidate genes

Dina Mukushkina
SRI of biology and biotechnology
problems
Al-Farabi Kazakh National University
Almaty, Kazakhstan
dina.mukushkina@gmail.com

Dana Aisina
SRI of biology and biotechnology
problems
Al-Farabi Kazakh National University
Almaty, Kazakhstan
dana.aisina03@gmail.com

Anatoliy Timofeevich Ivashchenko
SRI of biology and biotechnology
problems
Al-Farabi Kazakh National University
Almaty, Kazakhstan
a.iavashchenko@gmail.com

Abstract — Many candidate genes are involved in the development of atherosclerosis, which are manifested in a variety of metabolic processes, disturbances of which are observed in this disease. Many publications describe the involvement of miRNAs in the development of atherosclerosis. Therefore, it is necessary to establish which miRNAs can affect the expression of candidate genes. Quantitative characteristics of the interaction of miRNAs with mRNAs candidate genes were determined using the MirTarget program, which detects localization of miRNA binding sites in 3'UTR, 5'UTR and CDS; free energy interaction miRNA with mRNA; schemes of nucleotide interaction between miRNA and mRNA. In the mRNA of atherosclerosis genes, the binding sites of two or more miRNAs located in 3'UTR, 5'UTR and CDS are established. The organization of miRNAs binding sites with overlapping nucleotide sequences forming clusters was revealed. Such an organization of miRNAs binding sites leads to their compaction several times and causes competition among miRNAs for binding to mRNA. The features of the interaction of miRNAs with mRNA of candidate genes depending on their expression are established. Associations of miRNAs and candidate atherosclerosis genes are proposed for the early diagnosis of this disease.

Keywords — miRNA, mRNA, gene, association, marker, atherosclerosis

INTRODUCTION

Candidate genes are participated in the development of atherosclerosis, which are implicated in a variety of metabolic processes that are disturbed in this disease. It has been found that miRNAs, which are nanoscale regulatory biomolecules, are involved in many biological processes at all stages of the development of atherosclerosis, from early endothelial dysfunction to the erosion and rupture of an unstable atherosclerotic plaque. The miRNAs are able to regulate gene expression at the levels of translation binding to target mRNAs. Many publications have described the involvement of miRNAs in the development of atherosclerosis. It is necessary to establish which miRNAs affect the expression of candidate genes.

METHODS AND ALGORITHMS

The nucleotide sequences of 2565 miRNAs were downloaded from the miRBase (<http://mirbase.org>, Release 22.1) and 3707 miRNAs obtained from a report by Londin E. et al. [1]. The nucleotide sequences of mRNA genes were obtained from GenBank (<http://www.ncbi.nlm.nih.gov>). A database of 91 candidate genes including the names of the genes and publication sources (PubMed database) was compiled, confirming the associations of these genes with

atherosclerosis. A search for the target genes of miRNAs was performed using the MirTarget program [2]. This program determines the following binding characteristics: the start of the miRNA-binding site of mRNA; the locations of miRNA-binding sites (3'UTR, 5'UTR, CDS); the interaction free energy (ΔG , kJ/mole); nucleotide interaction schemes between miRNAs and mRNAs.

RESULT

Binding sites for 24 mRNAs genes with miRNAs in the 5'UTR region were identified. The binding sites of the miRNAs and mRNAs of the target genes were not uniform along the length of an mRNA. Both multiple and single binding sites were identified. The mRNA regions containing overlapping binding sites are referred to clusters [3]. The results regarding the location of miRNA-binding sites in mRNAs with overlapping nucleotide sequences in a cluster leads to the compaction and causes competition among miRNAs. The mRNA of *GAS6* gene forms a large cluster with 22 different miRNAs, half of which form two or three binding sites, while the rest represent single binding sites. The cluster size is 37 nucleotides. The total binding sites length in cluster is 858 nucleotides, where the degree of compaction is 23.2. This compaction allowed these miRNA binding sites to be located in 5'UTR with a length of 153 nucleotides. For eight associations of miRNAs with mRNA *GAS6* gene the free interaction energy of miRNAs with mRNA have been more than -130 kJ/mole, which allows us to recommend these associations as markers of atherosclerosis. The cluster of binding sites of 18 miRNAs in the *NFE2L2* gene 5'UTR.mRNA have size of 45 nucleotides (Table). The total size of all binding sites is 521 nucleotides, which means that the degree of compaction is 11.6. Nine miRNAs interacted with the mRNA of the *NFE2L2* gene with a free energy of more than -130 kJ/mole are recommended as markers of atherosclerosis. The 41 genes exhibited one binding site in CDS mRNAs for one miRNA. In CDS of *IRS2* mRNA the binding sites of 28 miRNAs were located in cluster with a length of 41 nucleotides. The total cluster size was 1147 nucleotides, while the degree of cluster compaction was 28.0. The binding sites of 12 miRNAs were located in other cluster with a length of 35 nucleotides. The *PDE4D* gene forms two clusters but smaller.

TABLE CHARACTERISTICS OF miRNA BINDING SITES IN 5'UTR AND CDS OF mRNA OF *NFE2L2* AND *PDE4D* CANDIDATE GENES

Gene	miRNA	Region of RNA	Start of site, nt	ΔG , kJ/mole	$\Delta G/\Delta G_m$, %	Length, nt
<i>NFE2L2</i>	ID00522.5p-miR	5'UTR	438	-125	89	23
	ID02187.5p-miR	5'UTR	439÷445(2)	-123	89	23
	ID03367.5p-miR	5'UTR	441÷453(2)	-115	92	20
	ID01804.3p-miR	5'UTR	442÷444(2)	-132	90	23
	ID02294.5p-miR	5'UTR	443	-132	90	24
	ID00061.3p-miR	5'UTR	444÷450(3)	-125÷-134	91÷97	22
	ID00457.3p-miR	5'UTR	444	-123	91	22
	ID01041.5p-miR	5'UTR	444÷445(2)	-129÷-134	88÷91	24
	ID01873.3p-miR	5'UTR	444÷447(2)	-121÷-123	92÷94	21
	ID00296.3p-miR	5'UTR	448	-140	89	25
	ID01641.3p-miR	5'UTR	448	-136	91	24
	ID01702.3p-miR	5'UTR	448	-138	92	24
	ID02890.3p-miR	5'UTR	458	-119	89	23
	ID02770.5p-miR	5'UTR	462	-115	92	20
	<i>PDE4D</i>	ID00061.3p-miR	CDS	391÷413(3)	-125÷-129	91÷94
ID00457.3p-miR		CDS	392	-123	91	22
ID01315.3p-miR		CDS	392	-115	92	20
ID01377.3p-miR		CDS	394	-121	95	20
ID01705.3p-miR		CDS	398	-117	92	21
ID00296.3p-miR		CDS	404÷411(4)	-140÷-142	89÷91	25
ID01641.3p-miR		CDS	407÷410(2)	-132÷-132	89	24
miR-3960		CDS	408÷415 (3)	-115÷-117	92÷93	20
ID01458.5p-miR		CDS	410	-134	91	23
ID01702.3p-miR		CDS	411	-138	92	24
ID02064.5p-miR		CDS	415	-129	90	23
ID01184.3p-miR		CDS	419	-117	93	20

CONCLUSION

What is characteristic is that miRNA ID01641.3p-miR, ID00061.3p-miR, miR-3960 and ID01702.3p-miR are found in both clusters. The first cluster consists of four single binding sites and one multiple binding site ID01702.3p-miR, cluster size is 35 nucleotides, from the position of 335 nucleotides and to 369 nucleotides. The average ΔG value is -130 kJ/mole. The second cluster consists of four multiple binding sites and six single binding sites, the cluster size is 49 nucleotides from 391 to 439 nucleotides (Table). The total cluster size is 447 nucleotides and degree of compaction was 9.1.

Clusters consisting of single miRNA-binding sites were found in the mRNA following genes: *ACE*, *ADAMTS13*, *ADRB3*, *ICAMI* and *FASLG*. In 3'UTR mRNA of 45 genes were characterized binding sites. In *ADRB3*, *CD36*, *FASLG*, *F11R*, *FLT1*, *ICAMI*, *PLA2G7*, *PPARGCIA* mRNAs the clusters of miR-466, ID00436.3p-miR, ID01030.3p-miR binding sites were established. The binding of 53 miRNAs with mRNAs of 14 candidate genes with free energy interaction more than -130 kJ/mole were established. The miR-619-5p was fully complementary to *ADAM17* and *CD36* mRNA genes, ID01593.5p-miR to *ANGPTL4* mRNA gene, ID01935.5p-miR to *NFE2L2* gene and miR-5096 to *IL18* mRNA gene.

The miRNA associations with atherosclerosis candidate genes have been established, which consist of: one gene and several miRNAs; one gene and one miRNA; one miRNA and several genes; two or more miRNAs with two or more candidate genes. sites in mRNA candidate genes contribute to a more accurate diagnosis of the participation of competing miRNAs in the development of atherosclerosis.

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630090, Новосибирск, проспект Академика Лаврентьева, 10