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Prediction of miRNAs interaction with gastrointestinal tract cancer candidate genes

Abstract. miRNAs play an important role in regulating the expression of prevailing number of genes in the human genome. The vast majority of miRNAs are involved in the development of several diseases. Of the more than six thousand human miRNAs, only miR-619-5p has more than 200 genes with which it interacts fully complementary. These genes include several genes involved in the development of cancer of the gastrointestinal tract, which is a rare property among other miRNAs. It is required to establish the features of miR-619-5p and other miRNAs binding with candidate genes of gastrointestinal tract cancer. The location of miRNA binding sites in mRNA, the free energy of miRNA-mRNA interaction, the miRNA-mRNA nucleotide interaction scheme, and other quantitative characteristics of the miRNA-mRNA interaction were determined using the MirTarget programme. The overwhelming number of miRNAs binding sites, including miR-619-5p, are located in the 3'UTR of *CYP2W1, KIAA1456, SLC26A2, SPATA13* and *UQCRB* genes mRNA. In the mRNA of these genes, in addition to the miR-619-5p binding sites, the binding sites of seven, twenty, nine, five and four miRNAs were detected, respectively. In mRNA of these genes, clusters of miRNAs binding sites from two and three binding sites were identified. The identified miRNAs binding sites are conserved in mRNA of orthologous primates genes, which indicates the evolutionarily early emergence of a link between miRNAs and their target genes. Schemes of interaction between miRNA and mRNA nucleotides show high efficiency in determination the quantitative characteristics of this interaction. The important role of non-canonical nucleotide pairs, which increase the free energy of the interaction between miRNA and mRNA, is shown. The revealed associations of miRNA and *CYP2W1*, *KIAA1456*, *SLC26A2*, *SPATA13* and *UQCRB* target genes allow us to recommend them as markers in the development of methods for the diagnosis of the gastrointestinal tract cancer.

Key words: cancer, gene, mRNA, miRNA, miR-619-5p, target genes, associations.

Inroduction

In recent years, it has been identified that miRNAs are fully complementary to mRNA target genes [1-5]. It has been shown that such miRNAs bind to 5'UTR [3; 4; 6; 7], CDS [1; 3; 4-9] and 3'UTR [10-13]. The miRNA target genes perform many functions. It is shown that 201 target genes of miR-619-5p might serve as transcription factors, kinases, participants in metabolic processes associated with the development of various diseases, etc. [5-9]. In this work, the target genes of miR-619-5p that are involved in the development of cancer of the gastrointestinal tract are considered: *CYP2W1, KIAA1456, SLC26A2, SPATA13, UQCRB*. The *CYP2W1* gene involved in the development of stomach cancer [14; 15], small and large intestine [16-21], colorectal cancer [22-30]. The *KIAA1456* gene is associated with colorectal cancer [31]. A change in the expression of the *SLC26A2* gene in colorectal cancer was detected [32-34]. *SPATA13* [35] and *UQCRB* [36; 37] genes participate in the development of colorectal cancer. The interest in such miRNAs is determined by several factors: what function do related genes perform; whether these miRNAs can perform the function of siRNA; whether these genes are targets of other miRNAs; whether miRNAs interactions with mRNAs of orthologous genes persist, etc. A comparison of the interactions of miR-619-5p and other miRNAs with mRNAs of these genes will help to understand their participation in the development of gastrointestinal tract cancer.

Materials and methods

The nucleotide (nt) sequences of candidate genes of gastrointestinal tract cancer were downloaded from GenBank (http://www.ncbi.nlm.nih.gov). The nucleotide sequences of mRNA genes of *Chlorocebus sabaeus* (Csa), *Homo sapiens* (Hsa), *Macaca mulatta* (Mml), *Pan troglodytes* (Ptr) and *Pongo abelii* (Pab) were downloaded from NCBI (http://www.ncbi.nlm.nih.gov). The nucleotide sequences of 2,565 miRNAs were taken from miRBase, and 3,707 miRNAs from a previous study [38].

The MirTarget program (created at al-Farabi Kazakh National University by Prof. A.Yu. Pyrkova and Prof. A.T. Ivashchenko) [39] defines the following features of miRNA binding to mRNAs: (a) the start of the initiation of miRNA binding to mRNAs; (b) the localization of miRNA binding sites in 5'UTRs, CDSs and 3'UTRs of the mRNAs; (c) the free energy of interaction between miRNA and the mRNA (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 fully complementary nucleotide sequence). The MirTarget program looks for hydrogen bonds between adenine (A) and uracil (U), guanine (G) and cytosine (C), G and U, and A and C [40; 41]. The MirTarget program identifies the positions of the binding sites on the mRNA, beginning with the first nucleotide of the mRNA's 5'UTR. The characteristics of the interaction between miRNA and mRNA reflect the intermolecular interactions of their molecules and were calculated for given parameters without their variation. Consequently, the results have no statistical scatter. Other factors that may have influenced these interactions have not been studied. The subject of changing the concentration ratio of miRNA and mRNA was not incorporated into the current study, since this aspect is of independent interest. For any other pathology, other candidate genes should be used, and other miRNA binding sites should be determined. The MirTarget program determines single miRNA binding sites in mRNA, and miRNA binding sites in clusters (arranged in series with overlapping of nucleotide sequences of the same or several miRNAs) [9].

Results and discussion

Table 1 shows the quantitative characteristics of the interaction of miRNA with candidate genes mRNA of gastrointestinal tract cancer. The characteristics of the interaction of miR-619-5p with mRNA of the five candidate genes are identical. Other miRNAs were associated with the mRNAs of each gene. The mRNA of the *CYP2W1* gene had targets for seven miRNAs, with miR-4739 binds with more free energy than miR-619-5p. The binding sites of the four miRNAs formed a cluster from 2160 nt to 2219 nt with a length of 59 nt. The total length of the binding sites of these miRNAs was 88 nt, which is 1.5 times the length of the cluster. This compaction of binding sites leads to competition between miRNAs for binding in the cluster.

The mRNA of *KIAA1456* gene had 21 binding sites from which two clusters of two miRNAs and three clusters of three miRNAs were formed (Table 1). miR-5096 binds completely complementary to the mRNA of the *KIAA1456* gene. Therefore, the expression of this gene is under the strong control of miRNA.

In the mRNA of the *SLC26A2* gene, 10 miRNAs binding sites were located (Table 1). Three clusters of two binding sites significantly reduced the proportion of binding sites in the total length of mRNA. miR-1285-5p and ID01237.3p-miR had a common start of binding sites, i.e., there is a clear competition between them for binding to the *SLC26A2* gene mRNA.

The mRNA of the *SPATA13* gene had six miRNAs binding sites, of which two binds with miR-619-5p. Binding sites of ID03024.5p-miR together with miR-619-5p formed a cluster (Table 1).

The mRNA of the *UQCRB* gene also had only one cluster including the miR-619-5p binding site (Table 1). Single binding sites of another three miRNAs characterized by a ΔG/ΔGm value of 88% to 98%.

For each of the five genes, miR-619-5p binding sites were included in the cluster. In the mRNA of the *CYP2W1* gene, the cluster consisted of ID01811.5p-miR, miR-5095, miR-619-5p and ID00913.5p-miR binding sites. The cluster of ID01334.5p-miR and miR-619-5p binding sites was present in the mRNA of the *KIAA1456* gene. In the mRNA of the *SLC26A2* gene, the cluster consisted of the miR-5585-3p and miR-619-5p binding sites. The binding sites of ID03024.5p-miR and miR-619-5p formed a cluster in the mRNA of the *SPATA13* gene. In the mRNA of the *UQCRB* gene, the cluster consisted of the binding sites ID00913.5p-miR and miR-619-5p. The ability of miR-619-5p to form associations with each of the five candidate genes is hardly accidental. In addition to the ability of miR-619-5p strongly suppress the expression of these genes; this miRNA excludes other miRNAs from regulating the expression of five candidate genes. In tumor cells, miR-619-5p always

synthesized more significantly than in normal cells [42-46].

Of the 50 binding sites, 45 sites were localized in 3'UTR, four sites in the CDS and one site in the 5'UTR. Clusters from only 2-3 binding sites, while clusters of binding sites consisting of more than ten miRNAs binding sites identified in mRNA of other genes.

Table 1 – The characteristics of miRNAs interaction with mRNA of colorectal cancer genes

Gene	miRNA	Start of site, nt	Region mRNA, nt	ΔG, kJ/mole	ΔG/ΔGm,%	Length miRNA, nt
CYP2W1	ID03126.5p-miR	39	CDS	-117	93	22
	miR-7110-5p	1546	3'UTR	-108	91	21
	miR-4739	1739	3'UTR	-125	87	25
	ID01811.5p-miR	2160	3'UTR	-113	90	22
	miR-5095	2170	3'UTR	-106	91	21
	miR-619-5p	2176	3'UTR	-121	100	22
	ID00913.5p-miR	2196	3'UTR	-117	92	23
	miR-5096	2248	3'UTR	-108	96	21
KIAA1456	ID00442.5p-miR	1751	CDS	-104	91	21
	ID01334.5p-miR	2522	3'UTR	-110	90	22
	miR-619-5p	2536	3'UTR	-121	100	22
	ID02199.5p-miR	2611	3'UTR	-113	90	23
	miR-1303	2621	3'UTR	-106	91	22
	miR-1285-5p	2768	3'UTR	-102	91	21
	miR-1273a	3875	3'UTR	-121	92	25
	miR-1273c	3877	3'UTR	-113	93	22
	miR-1273g-3p	3897	3'UTR	-106	91	21
	ID01815.5p-miR	4037	3'UTR	-106	89	23
	ID01334.3p-miR	4132	3'UTR	-115	92	22
	ID02017.3p-miR	4133	3'UTR	-115	90	22
	MiR-1972	4137	3'UTR	-113	91	22
	miR-5096	5137	3'UTR	-113	100	21
	miR-619-5p	5196	3'UTR	-117	96	22
	ID01836.5p-miR	5286	3'UTR	-113	90	23
	miR-1285-5p	5302	3'UTR	-102	91	21
	ID01360.3p-miR	8419	3'UTR	-104	91	21
	ID00367.5p-miR	8422	3'UTR	-115	93	22
	miR-1273g-3p	8429	3'UTR	-106	91	21
	ID02991.3p-miR	8854	3'UTR	-89	91	21
SLC26A2	ID01697.5p-miR	124	5'UTR	-108	93	20
	ID01838.5p-miR	4438	3'UTR	-119	95	24
	miR-1285-3p	4442	3'UTR	-110	95	22
	miR-7851-3p	4495	3'UTR	-108	91	22
	miR-619-5p	5066	3'UTR	-121	100	22
	miR-619-5p	5202	3'UTR	-110	91	22
	miR-5585-3p	5209	3'UTR	-113	96	22
	ID02175.3p-miR	5257	3'UTR	-110	91	22
	miR-1285-5p	5308	3'UTR	-102	91	21
	ID01237.3p-miR	5308	3'UTR	-113	88	24
SPATA13	ID01412.5p-miR	3846	CDS	-113	91	22

Table 1 continued

Gene	miRNA	Start of site, nt	Region mRNA, nt	ΔG, kJ/mole	ΔG/ΔGm,%	Length miRNA, nt
	ID02484.3p-miR	4057	CDS	-104	91	21
	ID03024.5p-miR	5010	3'UTR	-110	91	22
	miR-619-5p	5020	3'UTR	-121	100	22
	miR-619-5p	5155	3'UTR	-117	96	22
	miR-6510-5p	5931	3'UTR	-110	90	22
UQCRB	miR-619-5p	1269	3'UTR	-121	100	22
	ID00913.5p-miR	1289	3'UTR	-115	90	23
	miR-5096	1343	3'UTR	-110	98	21
	miR-5585-3p	1412	3'UTR	-108	93	22
	ID00695.3p-miR	2233	3'UTR	-127	88	24

Particular evidence for the adequacy of the MirTarget program is in the interaction between miRNA and mRNA nucleotides. Figure 1 shows the interaction patterns of several miRNAs with mRNA nucleotides of the five studied genes. In the interaction scheme of miR-619-5p with mRNA of the *CYP2W1* gene, all nucleotides bind complementarily, which reflects the absolute affinity of miRNA and mRNA. For other miRNAs, in many cases, the interaction of miRNA with mRNA occurs with the formation of non-canonical A – C and G – U pairs. This interaction is weaker than in the case of canonical pairs; however, the nucleotide interaction stacking in each of the antiparallel RNA strands is preserved.

CYP2W1; miR-619-5p; 2176; -121; 100; 22 5'-GGCUCAUGCCUGUAAUCCCAGC-3' 3'-CCGAGUACGGACAUUAGGGUCG-5'	*CYP2W1*; ID00913.5p-miR; 2196; -117; 92; 23 5'-**G**CACUUUGGGAG**G**CCGAGGCAGG-3' 3'-**U**GUGAAACCCUC**U**CGCUCCGUCC-5'
KIAA1456; ID00367.5p-miR; 8422; -115; 93; 22 5'-UCUGUCACCCAGG**C**UGGAGGGC-3' 3'-AGACAGUGGGUCC**A**ACCUCCCC-5'	*KIAA1456*; ID01334.3p-miR; 4132; -115; 92; 22 5'-AGG**C**GUGAGCCACCGCGCCCGG-3' 3'-UCC**A**CACUCGGUGGCGCGUUCC-5'
SLC26A2; ID01237.3p-miR; 5308; -113; 88; 24 5'-**C**CUGGGUGACAGAGC**G**AGACUCC**G**-3' 3'-**A**GACCAACUGUCUCG**U**UCUGUGG**U**-5'	*SLC26A2*; ID01838.5p-miR; 4439; -113; 90; 24 5'-**G**A**G**A**G**GUCUCACUGUGUUGC**C**CA-3' 3'-**UU**U**C**C**U**CAGAGUGACACAACG**A**GU-5'
SPATA13; ID00913.5p-miR; 5040; -113; 88; 23 5'-**G**CACUUUGGGAG**G**CC**A**AGGCAGG-3' 3'-**U**GUGAAACCCUC**U**CG**C**UCCGUCC-5'	*UQCRB*; ID00913.5p-miR; 1289; -115; 90; 23 5'-**G**CACUUUGGGAG**G**CCGAGGC**G**GG-3' 3'-**U**GUGAAACCCUC**U**CGCUCCG**U**CC-5'
KIAA1456; miR-1273a; 3875; -121; 92; 25 5'-**G**AGACAGAGUCU**C**GCU**C**UGUCGCCC-3' 3'-**U**UCUUUCUCAGA**A**CGA**A**ACAGCGGG-5'	*KIAA1456*; miR-1273c; 3877; -113; 93; 22 5'-GACAG**A**GUCUCG**C**U**C**UGUCGCC-3' 3'-CUGUC**C**CAGAGC**A**A**A**ACAGCGG-5'
KIAA1456; miR-5096; 5137; -113; 100; 21 5'-GCCUGACCAACAUGGUGAAAC-3' 3'-CGGACUGGUUGUACCACUUUG-5'	*SLC26A2*; miR-5585-3p; 5209; -113; 96; 22 5'-**G**CCUGUAGUCCCAGCUA**C**UCAG-3' 3'-**U**GGACAUCAGGGUCGAU**A**AGUC-5'
UQCRB; miR-5096; 1343; -110; 98; 21 5'-GCCUG**G**CCAACAUGGUGAAAC-3' 3'-CGGAC**U**GGUUGUACCACUUUG-5'	*UQCRB*; miR-5585-3p; 1412; -108; 93; 22 5'-ACCUGUA**A**UCCCAGCUA**C**UC**G**G-3' 3'-UGGACAU**C**AGGGUCGAU**A**AGU**C**-5'
Note: Gene; miRNA; start of binding site (nt); the free energy, ΔG (kJ/mole); the ΔG/ΔGm (%); length of miRNA (nt). In bold type highlighted the non-canonical A-C and G-U pairs of nucleotide	

Figure 1 – The schemes of miRNAs interaction in 3'UTR mRNAs of candidate genes

One way of proving the stability of miRNA and target gene associations is identification of these associations in orthologous genes. We found that in the orthologous genes of *CYP2W1*, the bond between ID03126.5p-miR and orthologous genes of several primates is conservative, which is reflected in the identity of the LGLLGLWG oligopeptide in orthologous proteins of primates (Figure 2).

The oligopeptides prior to the binding site in the *Hsa* and *Ptr* are different from other primates. The oligopeptides located after the binding site are more variable in the studied objects.

The miR-619-5p binding sites in the mRNA of the five studied genes are conservative. The flanking nucleotide sequences are variable (Figure 3).

The oligonucleotides located up to the conservative binding site of mir-619-5p are very variable. With the 3'-end, after a conserved oligonucleotide, nucleotide variability is also high.

MALLLLLF**LGLLGLWG**LLCACAQD Hsa
MALLLLLF**LGLLGLWG**LLRACARD Ptr
MALLLLLL**LGLLGLWG**LLRACARD Pab
MALLLLLL**LGLLGLWG**LLRACTRD Nle
MALLLLLL**LGLLGLWG**LLRAYARD Mml
MALLLLLL**LGLLGLWG**LLRAYARD Csa

Figure 2 – Regions of orthologous *CYP2W1* proteins containing the LGLLGLWG oligopeptide encoded by ID03126.5p-miR binding sites

CTGACCCGGTGCGGT**GGCTCATGCCTGTAATCCCAGC**ACTTTGGGAGGCCGAGGCAGGCG *CYP2W1*
TAGGCTGAGCATGGT**GGCTCATGCCTGTAATCCCAGC**ACTTTGGGAGGCCAAGGCAGAAG *KIAA1456*
TCGGCCAGGTGCAGT**GGCTCATGCCTGTAATCCCAGC**ACGTTGGGAGGCCGAGGCGGGTG *SLC26A2*
AAGGCTGGGTGCTGT**GGCTCATGCCTGTAATCCCAGC**ACTTTGGGAGGCCAAGGCAGGTG *SPATA13*
TTGGCAAGGCATGGT**GGCTCATGCCTGTAATCCCAGC**ACTTTGGGAGGCCGAGGCGGGTA *UQCRB*

Figure 3 – The regions of mRNA nucleotide sequences of orthologous genes containing miR-619-5p binding sites

Conclusion

As a result of the research, the following conclusions can be drawn. The overwhelming number of miRNA binding sites, including miR-619-5p, are located in the 3'UTR. In the mRNA of *CYP2W1, KIAA1456, SLC26A2, SPATA13* and *UQCRB* target genes, in addition to the miR-619-5p binding sites, the binding sites of seven, twenty, nine, five and four miRNAs detected, respectively. In the mRNA *CYP2W1, KIAA1456, SLC26A2, SPATA13* and *UQCRB* target genes, there are clusters of miRNA binding sites from only two or three binding sites. Established miRNA binding sites conserved in mRNA of orthologous primates' genes. Schemes of interaction between miRNA and mRNA nucleotides show the important role of non-canonical A-C and G-U pairs that were not previously taken into account by other researchers, but they increase the free energy of interaction of miRNA and mRNA. The revealed associations of miRNA and *CYP2W1, KIAA1456, SLC26A2, SPATA13* and *UQCRB* target genes allow us to recommend them as markers in the development of methods for the diagnosis of the gastrointestinal tract cancer.

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