Prediction of osa-miRNA binding sites in human mRNA genes

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miRNAs are class of small non-coding RNA proteins that are important regulators of gene expression. miRNAs in the human body is circulated in the blood in the composition of the exosomes. Exogenous miRNAs (xeno-miRNAs) that are part of the consumed food can be added to endogenous miRNAs [1]. It was found that plant miRNAs enter the blood and tissues from the gastrointestinal tract during food digestion. These exogenous miRNAs can affect the expression of human genes, affecting various physiological processes [2]. Xeno-miRNAs are the fundamentally new factor in the influence of human food on metabolic processes [3]. Studies have shown that exogenous plant miRNAs of corn, rice, barley, soybeans, grapes get into human tissues and many animals with food [4]. Research data suggests that the spectrum of xeno-miRNAs in the blood depends on the food consumed and plant miRNAs are able to get from the blood into the cells and influence the processes occurring in the body, as well as endogenous miRNAs. In this regard, it is necessary to study the possible effect of xeno-miRNA plants on the expression of human genes. As objects of study, we used rice miRNAs (osa-miRNAs), since rice contains the highest amount of miRNAs and rice is the most common nutrition of the planet's population.

The nucleotide sequences of the mRNA 17508 human genes were obtained from GenBank (https://www.ncbi.nlm.nih.gov/genbank/). 738 miRNAs *Oryza sativa* were borrowed from miRBAse (http://www.mirbase.org/). The search for miRNA target genes were determined using the MirTarget program [5, 6]. The program defines the start of miRNA binding sites with mRNAs, the location of sites in the 5'-untranslated region (5'UTR), the protein-coding region (CDS) and the 3'-untranslated region (3'UTR) of mRNAs, the free energy of interaction (ΔG, kJ/mole) and schemes of miRNA nucleotides interaction with mRNA.

As a result of the search for binding sites, it was found that with the selection criteria for ΔG/ΔGm of 96% or more, 26 genes that are targets for 20 miRNAs were identified (Table 1). Detected binding sites were located at 3'UTR, CDS and 5'UTR mRNA target genes. For

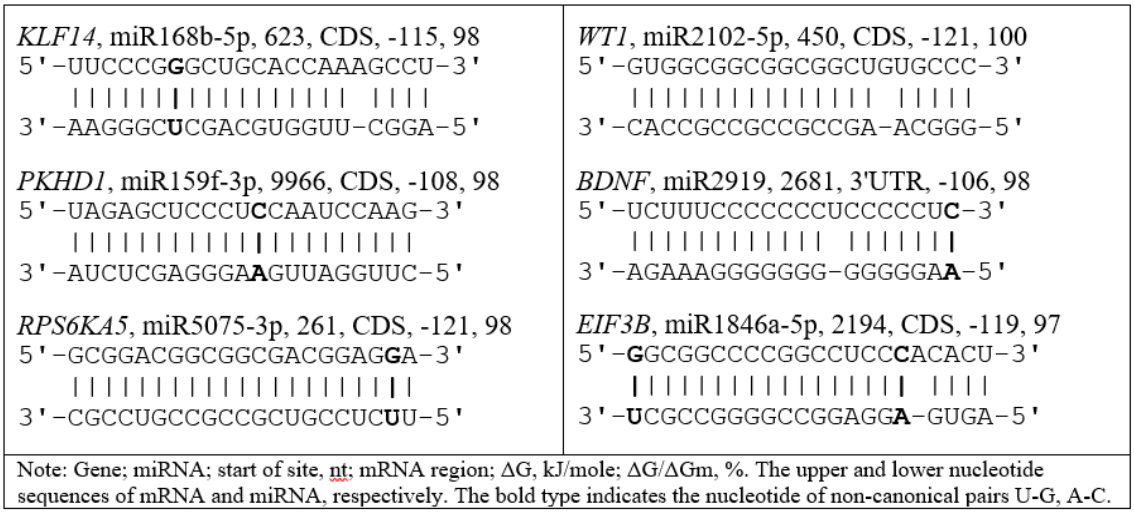
miR2102-5p, there were five target genes (*WT1, KATNAL1, NR1D2, CHSY1, DIRC2*) with a ΔG/ΔGm value of 96-100% (Table 1). The miR2102-5p binding site with the mRNA of the *WT1* gene had a maximum ΔG/ΔGm value of 100%, that is, all the nucleotides of this miRNA form hydrogen bonds with the mRNA of the *WT1* gene. miR2919 had binding sites in mRNA of four genes *KIAA1161, BDNF, GPBP1L1, ADAMTS5* with a ΔG/ΔGm value of 96% and 98%. Each of the remaining miRNAs had one of target gene. The ΔG/ΔGm value for these miRNAs varied from 96 to 98%.

Table 1 - Characteristics of interaction of osa-miRNA with mRNA of human genes

Gene	miRNA	Start of site, nt	Region	ΔG, kJ/mole	ΔG/ΔGm, %	Length, nt
ADAMTS5	miR2919	471	5'UTR	-104	96	19
ANKRD27	miR1428e-3p	244	CDS	-98	96	21
BDNF	miR2919	2681	3'UTR	-106	98	19
CHSY1	miR2102-5p	348	5'UTR	-117	96	20
CMKLR1	miR396a,b-3p	3970	3'UTR	-98	96	20
COX20	miR5833-5p	396	CDS	-117	96	21
CPA3	miR1320-3p	671	CDS	-98	96	21
DIRC2	miR2102-5p	233	CDS	-117	96	20
EDN1	miR395b,d,e,g,h,i,j, k,l,m,n,p,q,r,s,y-3p	1136	3'UTR	-108	96	21
EIF3B	miR1846a,b,c-5p	2194	CDS	-119	97	21
GPBP1L1	miR2919	1015	5'UTR	-104	96	19
HK2	miR2868-5p	6645	3'UTR	-93	96	20
KATNAL1	miR2102-5p	80	5'UTR	-117	96	20
KIAA1161	miR2919	3436	3'UTR	-106	98	19
KLF14	miR168b-5p	623	CDS	-115	98	21
KLHDC10	miR1860-3p	3134	3'UTR	-108	96	22
NANOS1	miR5534a-5p	1967	3'UTR	-106	96	21
NR1D2	miR2102-5p	254	5'UTR	-117	96	20
OSTM1	miR2093-3p	848	CDS	-93	96	20
PKHD1	miR159f-3p	9966	CDS	-108	98	21
PSEN2	miR1847.1-5p	1785	3'UTR	-108	96	21
RPS6KA5	miR5075-3p	261	CDS	-121	98	21
SLC35D1	miR5339-5p	795	CDS	-102	96	21
UFSP1	miR2931-5p	960	3'UTR	-91	96	20
WT1	miR2102-5p	450	CDS	-121	100	20
ZNF442	miR2866-5p	1020	CDS	-98	96	20

The schemes of interaction of osa-miRNA with mRNA of some human genes clearly show the connections between the complementary nucleotides of these molecules (Figure 1). It can be seen from the schemes that all miRNA nucleotides form hydrogen bonds. The advantage of the MirTarget program is the incorporation of hydrogen bonds in non-canonical pairs of nucleotides U-G, A-C into the free energy of miRNA interaction with mRNA. The diagrams show the formation of three U-G pairs and three A-C pairs.

Figure 1 - Schemes of the interaction of osa-miRNA with mRNA of human genes



Note: Gene; miRNA; start of site, nt; mRNA region; ΔG, kJ/mole; ΔG/ΔGm, %. The upper and lower nucleotide sequences of mRNA and miRNA, respectively. The bold type indicates the nucleotide of non-canonical pairs U-G, A-C.

The miRNA of the miR1846a,b,c-5p family interacted with mRNA 32 genes (*EIF3B, FASN, DNAJB6, HOXD9, CDH24, FAM168A, LACC1, LYSMD2, OLIG1, BMP8A, BMP8B, C17orf72, CAB39, DEF8, DPF1, EXTL1, GMPR, HLX, IKBKAP, MEF2C, MMP11, MMP15, NR1D2, PTPRZ1, RPTOR, SLC7A6, SLC9A7, STRN4, TMEM179, WDR44, WIPF1, ZFPM1*). Members of the miR395 family (miR395b, d, e, g, h, i, j, k, l, m, n, p, q, r, s, y-3p) were associated with the mRNA of the genes *TEAD2, CD22, EDN1*. The miRNAs of the osa-miR396a,b-5p family had 22 target genes (*CMKLR1, SYVN1, SCAMP5, VPS13B, LRRC32, HSPA13, KCTD15, MIDN, CDCA7, IDI2, KLHL24, MRE11A, PPCDC, TMLHE, TUBA1A, TUBA1B, TUBA1C, SCN7A, STIL, TRAF3IP2, ABCC6, CDC14B*).

The results of the studies show the possibility of the interaction of osa-miRNA with human mRNA genes. The established associations of miRNA and their target genes allow

targeted insertion of xeno-miRNAs with food to regulate their expression of these genes. It is must be taken into account that some miRNA and miRNA families can affect the expression of many genes.

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