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Contacts
All questions, please contact the official address
of the organizing committee of the conference: bgrs2020@bionet.nsc.ru

Organizing Committee Chairman: Zubova Svetlana
Address: Lavrentieva Avenue, 10, Novosibirsk, 630090
Phone: +7 (383) 363 4977, e-mail: svetazubova@gmail.com

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Wheat and maize miRNAs are potential regulators of human genes expression

Aizhan Kazievna Rakhmetullina
SRI of biology and biotechnology problems, Al-Farabi Kazakh National University Almaty, Kazakhstan
zhanullina1994@gmail.com

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

Anna Yurevna Pyrkova
SRI of biology and biotechnology problems, Al-Farabi Kazakh National University Almaty, Kazakhstan
anna.pyrkova@kaznu.kz

Abstract — **With food, a huge variety of biological material gets into the human digestive tract, which the body uses for life support. The variety of food material entering the gastrointestinal tract, especially at the molecular level, cannot be distinguished from endogenous metabolites and these exogenous compounds can significantly alter the body's metabolism. Such compounds include plant miRNAs, which are indistinguishable from endogenous human miRNAs in physicochemical properties. It is necessary to clarify the degree of influence of exogenous plant miRNAs on the expression of human genes, since it is not known in advance what consequences can occur when plant miRNAs enters the human body. A huge amount of research does not allow experiments with all human genes and all plant miRNAs, so we have studied the effect of wheat and maize miRNAs on human genes using computer methods. As a result of studying the binding of 125 tae-miRNAs and 325 zma-miRNAs to mRNAs of 17508 human genes it was revealed that 158 genes were targets for 52 tae-miRNAs and 51 genes for 11 zma-miRNAs. Binding sites in the mRNA of human genes were located in 5'UTR, CDS, 3'UTR.**

Keywords — miRNA, mRNA, binding site, gene regulation, plant, wheat, maize, human

Introduction

Recently, publications have appeared about the ingestion of exogenous miRNAs into the human body. Plant miRNAs that enter the human body along with food are able to penetrate the tissues and affect some metabolic pathways. These extracellular miRNAs are stable and involved in intercellular interactions [1]. Wheat and maize are the most actively cultivated crops worldwide. It is imperative to learn how plant miRNAs can affect the human body and how these miRNAs can be useful or harmful. The MirTarget program used by us with high efficiency determines the quantitative characteristics of the interaction of plant miRNAs with human mRNAs.

Materials and metods

Nucleotide sequences of the mRNAs of human genes were obtained from NCBI (http://www.ncbi.nlm.nih.gov). Nucleotide sequences of wheat and maize miRNAs were downloaded from miRBase v.22 (http://www.mirbase.org/). The miRNA binding sites in mRNA of 17508 human genes were predicted using the MirTarget program, which defines the free energy of interaction miRNA and mRNA (ΔG, kJ/mole), as well as the localization of binding sites and schemes of nucleotide interactions between miRNAs and mRNAs [2, 3]. The ratio of ΔG/ΔGm (%) was determined for each binding site, where ΔGm is equal to the free energy binding of miRNA with its full complementary nucleotide sequence.

Results and discussion

We found that among 325 miRNAs of *Z. mays* only 11 miRNAs were able to bind to mRNA of human genes. These miRNAs interacted with mRNA of 51 different genes. The zma-miRNA binding sites in the mRNA of human genes were located in 5'UTR, CDS, 3'UTR. The largest number of target genes had miR529-3p. The miR529-3p interacted with mRNA of *ATP6V0A4*, *BZRAP1*, *CHD2*, *CNGA2*, *GRM4*, *HCLS1*, *HIVEP2*, *IGFN1*, *LMO7*, *LRRC73*, *LRTOMT*, *LTB4R*, *MAP7*, *MLL*, *NUDC*, *PDE4B*, *POMC*, *SOX9*, *TCEB3*, *TMEM181* genes with the value of ΔG/ΔGm from 91% to 94%. The miRNA binding sites in mRNA of 13 genes were located in CDS, four sites in 5'UTR and 3'UTR. The miR162-3p and miR11969-5p had binding sites in the mRNA of four and six target genes, respectively. The binding sites of these miRNAs were located only in CDS and 3'UTR. The rest miRNAs (miR827-3p, miR529-5p, miR162-5p, miR1432-5p, miR11970-5p, and miR11969-3p) had only one target genes, with the value of ΔG/ΔGm more than 88%. In the group of 11 miRNAs, there were four miR-3p/miR-5p pairs that belong to the same pre-miRNA (miR529-3p/5p miR482-3p/5p, miR162-3p/5p miR11969-3p/5p). The characteristics of the binding sites for miR482-5p and miR482-3p were found for eight and nine mRNA target genes, respectively. Some of the above mentioned 17 genes involved in the development of diabetic retinopathy (*ROBO4*) [4], papillary thyroid carcinoma (*CDKN1C*) [5], myeloid leukemia (*FAM168A*) [6], hypogonadotropic hypogonadism (*FGF17*) [7], pancreatic and gastric cancers (*SLC44A4*) [8], breast cancer (*ATP2A3*) [9], lung cancer (*LARP1*) [10]. The binding sites of these miRNAs were located at 5'UTR, CDS and 3'UTR, and the free binding energy was a -96 kJ/mole and -98 kJ/mole.

As a result of the studies, binding sites were established between the wheat miRNAs and the mRNA of human genes involved in the development of various diseases. Binding sites were found for 52 miRNAs with mRNAs of 158 genes with a ΔG/ΔGm value of 88% or more. The binding sites of the studied miRNAs were located at 5'UTR (9%), CDS (63%) and 3'UTR (28%) mRNA. The highest number of binding sites with high affinity was detected in CDS and 3'UTR mRNA of target genes. Data analysis showed that genes *ADARB2, ADCY6, ALPK3, ANO4, BMS2, EDEM1, ERICH1, FNIP2, KIRREL3, NGB, PAQR6, TJP3,RICH1, RLBP1, SMARCC2, UBE2K, UNG* were targets for miR408-3p, with free energy from -108 kJ/mole to -113 kJ/mole and ΔG/ΔGm value from 91% to 95%. Therefore, miR408-3p can regulate a significant number of genes and further study is required. The miR10521-5p, miR1118-5p, miR1124-3p, miR1129-5p, miR1134-3p, miR1138-3p, miR164-5p, miR5086-5p, miR9652-5p, miR9655-3p, miR9661-5p, miR9773-3p, miR9780-3p, miR9781-3p bound to mRNA of four or more target genes. The functions of the identified target genes were diverse.

The figure shows the interaction schemes of tae-mir408-3p, zma-miR529-3p, and zma-miR482-3p with different regions of mRNA (5'UTR, CDS, 3'UTR) of human genes. The interactions between miRNA and mRNA show the role of noncanonical G-U and A-C pairs in increasing the free energy of interaction between miRNA and mRNA.

Fig. 1. - Schemes of the interaction of tae-miRNA and zma-miRNA with mRNA human genes

Note: 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.

It should be noted that miRNA binding sites with mRNAs of target genes had the same ΔG (kJ/mole) and ΔG/ΔGm (%) values for each miRNA: for tae-mir408-3p and mRNA of *ADARB2*, *ANO4*, *FNIP2*, *TJP3* genes ΔG equal 110 kJ/mole, ΔG/ΔGm equal 93%; for zma-miR529 and mRNA of *ATP6VOA4*, *CHD2*, *MAP7*, *MLL*, *PDE4B* genes ΔG equal -106 kJ/mole, ΔG/ΔGm equal 94%; for zma-miR482-3p and mRNA of *ATP2A3*, *CSF1*, *LARP1*, *LMBRD2*, *PTER*, *STK32A*, *TMCO5A*, *TTC25* genes ΔG equal -96 kJ/mole, ΔG/ΔGm equal 92%.

Conclusion

Thus, the consumption of wheat and maize in food not only provides the human body with energy, but also their miRNAs are involved in the regulation of gene expression, affecting human metabolism. The miRNAs significantly affect many genes, so plant miRNAs can be regulators of human gene expression.

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