ISSN 2570-5911
(PRINT)
ISSN 2570-5903
(ON-LINE)
DOI: 10.29256

BIOLOGICAL MARKERS IN FUNDAMENTAL AND CLINICAL MEDICINE

COLLECTION OF ABSTRACTS

VOL. 2
№ 2, 2018

CONTENTS

length of all three binding sites was equal to 71 nt. In the CDS *PDE4D* gene mRNA identified clusters of 23 binding sites of miRNAs. 10 miRNAs formed two clusters in segments from 335 nt to 369 nt with a length 35 nt and average ΔG value equal to -133 kJ/mole. The whole length of binding sites is equal to 96 nt. The second cluster of binding sites located from 391 nt to 439 nt with a length 49 nt and average ΔG = -125 kJ/mole. The average free energy of binding of miRNAs with all mRNAs in the 3'UTR was equal to -111 kJ/mole. There are no the miRNA associations with mRNA having free energy of interaction greater than -125 kJ/mole. But this does not mean that the expression of these genes could not be suppressed by miRNAs. In mRNA of *ETS1* gene it was found the interesting evidence: miR-15-36862-3p and miR-10-29282-3p have 12 and 11 multiple binding sites, respectively. They located from 3875 nt to 3931 nt. The effect of each of the miRNAs will depend on the ratio of their concentrations, and overall the expression of the *ETS1* gene will be determined by the total concentration of miR-15-36862-3p with ΔG= -108 kJ/mole and miR-10-29282-3p with ΔG= -107 kJ/mole, since they have close free energies interaction with mRNA of *ETS1* gene. The same miR-15-36862-3p and miR-10-29282-3p form a cluster of binding sites with a length 33 nt located from 5454 nt to 5487 nt in the 3'UTR of mRNA of *RUNX1* gene. Such evidence was observed in mRNA of *IGF2* gene. miR-11-27078-5p having six binding sites and miR-3-5147-5p having two binding sites, form a cluster of binding sites from 2286 nt to 2374 nt with the length equal to 89 nt. The whole length of eight binding sites was equal to 182 nt, which is two times longer than the length of a cluster. The average binding energy was equal -108 kJ/mole. The formation of a cluster of eight binding sites in *IGF2* gene in the 3'UTR shows the ability of a given gene to compaction, which serves as the emergence of given miRNAs competition for the binding site. That is, from here it can be concluded that miR-11-27078-5p with free energy of interaction equal -113 kJ/mole will take this binding site. The mRNA of *S1PR2* has seven miRNA binding sites in the 3'UTR. The binding sites of miR-2-4804-5p and miR-17-39935-3p are located in cluster from 2763 nt to 2795 nt with a length 33 nt and with average ΔG = -110 kJ/mole. The miR-19-42814-5p and miR-10-29282-3p form cluster from 3191 nt to 3218 nt with ΔG value equal -105 kJ/mole. In genes, associated with development of esophageal cancer, it is found 319 potential binding sites for 160 miRNAs that can regulate 54 of the 68 genes responsible for the development of esophageal cancer. The clustered organization of binding sites is observed in 5'UTR, CDS and 3'UTR. It was identified miRNA and mRNA associations that have a free energy of interaction equal to -125 kJ/mole or more that could serve as markers for developing methods for early diagnosis of this disease. The average free energy of binding of miRNA with mRNA of genes involved in the development of esophageal cancer is greater in 5'UTR and CDS compared to 3'UTR, which suggests preferential binding of miRNA to 5'UTR and CDS of the studied genes. It was identified the location of miRNA binding sites in clusters containing two or more binding sites with overlapped nucleotide sequences. Such a compact arrangement of binding sites in mRNA significantly reduces the proportion of binding sites in mRNA. Overlapping miRNA binding sites creates competition between miRNA per binding site, since the RISC complex interacting with mRNA with more free energy will not allow binding to another RISC with miRNA having a weaker interaction with mRNA.

References:

1. **Sharma P., Sharma R. miRNA-mRNA crosstalk in esophageal cancer: From diagnosis to therapy. Crit Rev Oncol Hematol. 2015; 96(3): 449-62.**
2. **Chen X. et al. Characterization of microRNAs in serum: a novel class of biomarkers for diagnosis of cancer and other diseases // Cell Res. 2008; 18: 997-1006.**
3. **Londin E. et al. Analysis of 13 cell types reveals evidence for the expression of numerous novel primate- and tissue-specific microRNAs. Proc Natl Acad Sci USA. 2015; 112(10): 1106-1115.**
4. **Atambayeva S. et al. The Binding Sites of miR-619-5p in the mRNAs of Human and Orthologous Genes. BMC Genomics. 2017; 18: 1-10.**

Key words: mRNA, miRNA, genes, oncological diseases, esophageal cancer.

Accepted for printing on 20 Aug 2018

DOI: 10.29256/v.02.02.2018.escbm04

ASSOCIATION OF miRNA AND TARGET GENES OF PARKINSON'S DISEASE

Aralbayeva A.[1], Kamenova S.U.[1], Ivashchenko A.T.[2], Akimniyazova A.N.[2]
[1]Asfendiyarov Kazakh National Medical University, Kazakhstan
[2] Al-Farabi Kazakh National University, Kazakhstan

Parkinson's disease (PD) rate is the second most frequent among neurodegenerative diseases and methods of early diagnosis of this disease are actively being developed [1]. Current trends in this direction are in the search for molecular-genetic markers, which can be used in diagnosis and therapy. Among the molecular markers, miRNAs are promising that regulate the translation of multiple genes and probably the genes involved in the development of Parkinson's disease (candidate genes) [2, 3].

Materials and Methods. The search of miRNA binding site in mRNA was found using the MirTarget program which determines the start of the miRNA binding site in mRNA, the location of the site at 5'-untranslated regions (5'UTRs), coding domain sequences (CDSs), 3'-untranslated regions (3'UTRs), the free energy of interaction ΔG (kJ/mole) of the entire miRNA nucleotide sequence and the degree of complementarity of the miRNA and mRNA

nucleotides, the schemes of nucleotide interactions between miRNAs and mRNAs. The miRNA was borrowed from MirBase database and publication Londin E., et al. [4].

Results. The characteristics of the interaction of the 6266 miRNA with miRNA42 candidate genes of Parkinson's disease are studied. The mRNA *CCNY* candidate of the PD gene [5] has 21 binding sites for 19 miRNAs. In a region 29 nt long at 5'UTR, 10 miRNA binding sites with nucleotide sequence overlap, which we called the cluster, are located. The total length of the miRNA of these binding sites is 247 nt, which is 13 times the cluster length. The average free binding energy (ΔG) of miRNA binding to mRNA is -128 kJ/mole, which indicates a strong interaction of these miRNAs with the mRNA of *CCNY* gene. At 5'UTR, a cluster was detected from only three miRNA binding sites. In the 3'UTR mRNA of this gene, six binding sites are located with an average value ΔG of -113 kJ/mole. There are no reliable miRNA binding sites in the CDS mRNA gene. While the mRNA of the *CD5* gene and the *CETN3* gene contain miRNA binding sites only in CDS. Candidate gene PD *GSK3B* [6] can be called unique, as it contains at the 5'UTR mRNA two clusters of miRNA binding sites. The first cluster is located from 3nt to 38nt and contains 31 binding sites with a total length of 695 nt. Therefore, compacting the miRNA binding sites allows a 19-fold decrease in the nucleotide sequence at 5'UTR to maintain the dependence of *GSK3B* gene expression on these miRNAs. The average free binding energy of all miRNAs with mRNA in this cluster is -128 kJ/mole. The second cluster is located at 5'UTR mRNA *GSK3B* gene from 353 nt to 378 nt and contains six binding sites with a total length of 135 nt and an average free energy of -127 kJ/mole. In the protein coding region of the *GSK3B* gene there are no binding sites for miRNA. The third cluster of miRNA binding sites is located from 4705 nt to 4745 nt length 41 nt. The sum of the lengths of the miRNA binding sites is 344 nt and the average value of the free interaction energy is -106 kJ/mole. In this cluster there are six binding sites for miR-466, four sites for miR-15-36862-3p and three sites for miR-9-28523-5p. Consequently, these three miRNAs are more likely to contact mRNA compared to other miRNAs. The mRNA of the *LRP10* gene [7] has binding sites for nine miRNAs. Among them, miR-619-5p, miR-5096, miR-5095, miR-5585-3p and miR-1285-5p which are unique because each of them has several hundred target genes [8, 9]. For example, miR-619-5p can bind to mRNA of 1388 genes, with 221 mRNA completely complementary [9]. The average free energy of binding nine miRNA with mRNA is -110 kJ/mole, which is typical for miRNA and mRNA interactions in 3'UTR. The mRNA of the *RAB5A* gene [10] contains miRNA binding sites only at 5'UTR, including two clusters of three miRNA binding sites with an average free energy binding of -128 kJ/mole. The mRNA of the *RBBP5* gene contains 11 binding sites in only 3'UTR by an average free energy binding of -112 kJ/mole. *SETD1A* gene [11] is unique in that it is susceptible to 24 miRNA and contains 32 CDS binding sites. Naturally, with such a number of binding sites in CDS, they must be located in clusters. In the last cluster, 12 miRNAs with a total length of 282 nt interact in the CDS mRNA region of 51nt length. These most strongly binding miRNAs interact with 4877 nt at 4927 nt with an average free energy interaction of -132 kJ/mole. All binding sites of the six miRNAs are located only in the 3'UTR mRNA of the *SLC14A1* gene [12]. The average free energy of their binding is -112 kJ/mole. Only in the 3'UTR mRNA has the candidate sites of the *VSNL1* gene [12]. In the cluster, 13 miR-574-5p binding sites, 12 for miR-101-27078-5p 12 and 12 sites for 3-5147-5p. The basis for these multiple binding sites are the CA-dinucleotides and the free energy of their interaction with mRNA is -113 kJ/mole, -108kJ/mole and -100 kJ/mole. Therefore, the binding efficiency of these miRNAs will decrease in the same sequence. With a total binding site length of 839 nt, the cluster length is only 45 nt, which reduces the nucleotide sequence of the binding sites 19 times. That is, the need for compaction of binding sites is needed regardless of their location in 5'UTR, CDS and 3'UTR. At first glance, limitations are not known for the length of 3'UTR in mRNA, however, the above few examples of compaction binding sites show that 3'UTR does not need a longer length either. Another biological implication of compacting binding sites is to create a competition between miRNA for binding to mRNA. Since one miRNA in the RISC complex, by contacting mRNA, will not allow another miRNA to interact with mRNA. When setting experiments to establish the binding of a particular miRNA to mRNA, it is necessary to know that there are no competitors for this miRNA in the environment, and there are no competitors between mRNA. As a rule, such requirements are not only taken into account in the experiment, but they are not even considered. Among the studied miRNA and candidate genes for the development of Parkinson's disease, the associations of miRNA and their target genes interacting with free energy of more than -125 kJ/mole are recommended for the diagnosis of this disease. We have chosen 22 associations. In addition, the associations of genes containing mRNA clusters for the binding of many miRNAs are certainly the markers for detecting the onset of the disease. Clusters localized in 5'UTR and CDS are more efficient than clusters located in 3'UTR.

References:

1. **Li J. et al. Identification of critical genes and miRNAs associated with the development of Parkinson's disease. J MolNeurosci. 2018. doi: 10.1007/s12031-018-1129-8.**
2. **Burgos K. et al. Profiles of extracellular miRNA in cerebrospinal fluid and serum from patients with Alzheimer's and Parkinson's diseases correlate with disease status and features of pathology. PLoS One. 2014;9(5):e94839. doi: 10.1371/journal.pone.0094839. eCollection 2014.**
3. **Rostamian D.M. et al.Differential expression of miR-34a, miR-141, and miR-9 in MPP+-treated differentiated PC12 cells as a model of Parkinson's disease. Gene. 2018;662:54-65.doi: 10.1016/j.gene.2018.04.010.**
4. **Londin E., et al. Analysis of 13 cell types reveals evidence for the expression of numerous novel primate- and tissue-specific microRNAs. PNAS. 2015;112(10):1106-1115. doi: 10.1073/pnas.**
5. **Witoelar A. et al. Genome-wide pleiotropy between Parkinson disease and autoimmune diseases.JAMA Neurol. 2017; 74(7): 780–792. Jul 10. doi: 10.1001/jamaneurol.2017.0469.**
6. **Golpich M. et al.Glycogen synthase kinase-3 beta (GSK-3β) signaling: Implications for Parkinson's disease. Res. 2015;97:16-26. doi: 10.1016/j.phrs.2015.03.010.**

7. Quadri M. et al. LRP10 genetic variants in familial Parkinson's disease and dementia with Lewy bodies: a genome-wide linkage and sequencing study. Lancet Neurol. 2018;17(7):597-608. doi: 10.1016/S1474-4422(18)30179-0.

8.Niyazova R. et al. miR-1322 binding sites in paralogous and orthologous genes. BioMed Research Int. 2015, 1-7, http://dx.doi.org/10.1155/2015/962637.

9. Atambayeva Sh, Niyazova R, Ivashchenko A, Pyrkova A, Pinsky I, Akimniyazova A, Labeit S. The binding sites of miR-619-5p in the mRNAs of human and orthologous genes.BMC Genomics.2017; 18:428.doi:10.1186/s12864-017-3811-6

10. Freeze B. et al. Regional expression of genes mediating trans-synaptic alpha-synuclein transfer predicts regional atrophy in Parkinson disease. NeuroimageClin. 2018;18:456-466. doi: 10.1016/j.nicl.2018.01.009. eCollection 2018.

11. Witoelar A. et al. Genome-wide pleiotropy between Parkinson disease and autoimmune diseases. JAMA Neurol.2017;74(7):780-792. doi: 10.1001/jamaneurol.2017.0469.

12. Recabarren D. et al. Gene networks in neurodegenerative disorders. Life Sci. 2017;183:83-97.doi: 10.1016/j.lfs.2017.06.009.

Keywords: biomarker, Parkinson's diseases, miRNA, binding sites cluster, target gene

Accepted for printing on 20 Aug 2018

DOI: 10.29256/v.02.02.2018.escbm05

BIOMARKERS IN CARDIAC SURGERY AND MYOCARDIAL REGENERATION AFTER CORONARY ARTERY BYPASS GRAFTING

Bunenkov N. S.[1], Komok V. V.[1], Kostevich V. A.[2], Gorbunov N. P.[2], Sokolov A. V.[2, 3], Shvetsov A. N.[1], Lukashenko V. I.[1], Siddikov A. M.[1], Kobak A. E.[1], Babeshin M. V.[1], Beliy S.A., Nemkov A. S.[1], Khubulava G. G.[1]

[1] First Saint-Petersburg Medical University, Russia

[2] Federal State Budgetary Research Institution "Institute of Experimental Medicine", Russia

[3] Almazov National Medical Research Centre, Russia

Coronary artery bypass grafting (CABG) is worldwide performed procedure for ischemic heart disease treatment. Nevertheless, there are a lot of issues. The challenge is to decrease cardiac complications namely postoperative acute myocardial infarction which occur in 4-8% cases [1]. Searching of early serum predictor of reversible intraoperative myocardial ischemic reperfusion injury may assess myocardial regeneration ability and predict outcomes of surgical procedure [2].

Aim. To assess myocardial regeneration ability with plasma protein profile and ischemic reperfusion injury after off- and on-pump CABG.

Material and methods During clinical trial Assessment of Myocardial Ischemic-Reperfusion Injury During Off- and On- Pump CABG, identifier: ClinicalTrials.gov NCT03050489 with 200 participants was performed protein profile analyses before and after off- and on-pump CABG and assessed surgical outcomes.

Results There is plasma protein profile (trpononin I, myeloperoxidase, C-reactive protein and others proteins) which shows pattern of worse surgical outcomes. Myocardial ischemic reperfusion injury was measured by speckle-tracking technique. Troponin I level elevation was higher in on-pump group whereas in off-pump group it was lower but in acceptable level. It was found that level of myeloperoxidase in plasma was higher in group with elevated level of troponin I (>9 ng/ml). Despite of higher level of troponin I in on-pump group there were no differences in mortality, inotrope dosage, hospital and intensive care unit length of stay with off-pump group. One of the important issues is to looking for early blood predictor of worse CABG outcomes which can predict regeneration ability during surgical procedure and can aid to choose optimal surgical approach.

References:

1. Moazzami K., Dolmatova E., Maher J. et al. In-Hospital Outcomes and Complications of Coronary Artery Bypass Grafting in the United States Between 2008 and 2012 // J Cardiothorac Vasc Anesth. □ 2016.10.1053/j.jvca.2016.08.008.

2. Searle J., Shih J., Muller R. et al. The role of myeloperoxidase (MPO) for prognostic evaluation in sensitive cardiac troponin I negative chest pain patients in the emergency department // Eur Heart J Acute Cardiovasc Care. □ 2013. □ T. 2, № 3. □ C. 203-10.

Keywords: markers of ischemic reperfudsion injury, predictors of outcoms of coronaroronary bypass grafting.

Accepted for printing on 21 Jun 2018