3-бөлім

МОЛЕКУЛАЛЫҚ БИОЛОГИЯ ЖӘНЕ ГЕНЕТИКА

Раздел 3

МОЛЕКУЛЯРНАЯ БИОЛОГИЯ И ГЕНЕТИКА

Section 3

MOLECULAR BIOLOGY AND GENETICS

IRSTI 34.15.25; 31.27.31; 76.03.31

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INTERACTION OF GENES AND MICRORNA RELATED TO THE DEVELOPMENT OF PROSTATE CANCER

A search for candidate genes and microRNAs associated with the development of prostate cancer was implemented. A database which includes 67 genes associated with the development of prostate cancer was created. The functions of genes was analyzed in a comparative aspect. Some genes are specific to prostate cancer, many of them are participants in various cancers. Expression of the ASAH1, AURKA, BMI1, EPHB2, GBX2 genes leads to stimulation of malignant growth of prostate cancer cells and can potentially used as therapeutic targets of this cancer. A database of microRNAs associated with the development of prostate cancer was created. Specific features of binding of genes involved in the development of prostate cancer with miRNAs, involved in the development of cancer were determined. According to the calculations, mRNAs of 67 genes involved in the development of prostate cancer are associated with nine miRNAs with a ΔG/ΔGm value more than 90%. Sites are located in CDS, 5′UTR and 3′UTR. Some miRNAs have several target genes involved in the development of prostate cancer. For miR-619-5p, miR-574-3p, miR-3960, miR-1285-3p there are multiple sites with ΔG/ΔGm greater than 90%. miR-619-5p has sites with the highest binding energy of 121 kJ/m with ΔG/ΔGm equal to 100% in mRNA of XIAP gene. It is possible binding miR-619-5p with mRNA of AURKA, BRCA1, FMN1, IL10, MYO6, UHRF1BP1 genes, responsible for the development of prostate cancer with a ΔG/ΔGm equal to 98%.

Key words: prostate cancer, gene, microRNA, mRNA, diagnostics.

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Простатаның қатерлі ісігінің дамуына қатысты гендер мен microRNA әрекеттесуі

Простатаның қатерлі ісігінің дамуына жауапты кандидатты гендер мен микроРНҚ-ға ізденіс жүргізілді. Деректер базасы құрылды, оның құрамында простатаның қатерлі ісігінің дамуына байланысты 67 гендер бар. Осы гендердің қызметтері салыстырмалы аспектісінде талданды. Кейбір гендер простатаның қатерлі ісігіне арнайы болып келеді, ал көптеген гендер түрлі онкологиялық ауруларға қатысады. ASAH1, AURKA, BMI1, EPHB2, GBX2 гендердің экспрессиясы простатаның қатерлі ісігі жасушаларының өсуіне әкеледі және ықтимал осы қатерлі ісігінің терапевтикалық нысаналары бола алады. Простатаның қатерлі ісігінің дамуына байланысты микроРНҚдың деректер базасы құрылды. Простатаның қатерлі ісігінің дамуына байланысты гендер мен miRNA байланысуының ерекшеліктері анықталды. Жүргізілген есептеулер бойынша простатаның қатерлі ісігінің дамуына байланысты 67 гендердің мРНҚ тоғыз miRNA-ды

байланыстырады, ΔG/ΔGm мәні 90% астам. Сайттар CDS, 5'UTR және 3'UTR-де орналасқан. Простатаның қатерлі ісігінің дамуына байланысты кейбір miRNA бірнеше нысана гендермен байланысады. miR-619-5p, miR-574-3p, miR-3960, miR-1285-3p үшін ΔG/ΔGm мәні 90%-дан асатын бірнеше сайттар анықталды. miR-619-5p үшін XIAP геннің мРНҚ-да ΔG/ΔGm мәні 100% тең, байланысу энергиясы 121 kJ/m тең байланысу сайттары бар. miR-619-5p простатаның қатерлі ісігінің дамуына байланысты AURKA, BRCA1, FMN1, IL10, MYO6, UHRF1BP1 гендердің мРНҚ ΔG/ΔGm мәні 98% тең жағдайда байланысады.

Түйін сөздер: простатаның қатерлі ісігі, ген, microRNA, mRNA, диагностика.

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Взаимодействие генов и microRNA, связанных с развитием рака простаты

Проведен поиск генов-кандидатов и микроРНК, связанных с развитием рака простаты. Создана база данных по генам, включающая 67 генов, связанных с развитием рака простаты. Проанализированы в сравнительном аспекте функции этих генов. Некоторые гены являются специфическими к раку простаты, многие являются участниками разных онкологических заболеваний. Экспрессия генов ASAH1, AURKA, BMI1, EPHB2, GBX2 приводит к стимуляции злокачественного роста клеток рака предстательной железы, которые потенциально могут служить терапевтическими мишенями данного онкологического заболевания. Создана база данных по микроРНК, связанных с развитием рака простаты. Определены особенности связывания генов, участвующих в развитии рака простаты с miRNA, принимающих участие в развитии рака. Согласно проведенным расчетам, mRNA 67 генов, участвующих в развитии рака простаты, связываются с девятью miRNA с высокой энергией связывания. Сайты располагаются в CDS, 5'UTR и 3'UTR. Некоторые miRNA имеют несколько генов мишеней, участвующих в развитии рака простаты. Для miR-619-5p, miR-574-3p, miR-3960, miR-1285-3p имеются множественные сайты с $\Delta G/\Delta G_m$ более 90%. miR-619-5p имеет сайты с наибольшей энергией связывания 121 kJ/m с $\Delta G/\Delta G_m$ равным 100% в mRNA гена XIAP. С $\Delta G/\Delta G_m$ равным 98% возможно связывание miR-619-5p с mRNA генов AURKA, BRCA1, FMN1, IL10, MYO6, UHRF1BP1, ответственных за развитие рака простаты.

Ключевые слова: рак простаты, ген, microRNA, mRNA, диагностика.

Introduction

Prostate cancer (PC) is the second most commonly diagnosed cancer for men all over the world (Torre 2012: 87-108). miRNAs are small endogenous non-coding RNA molecules that regulate gene expression post-translationally acting on the mRNA target. More than 60% of all protein-coding genes are controlled by miRNAs, and this makes them powerful regulators of various cellular processes involved in the pathogenesis of various cancers, including prostate cancer.

Using of miRNA as targets for anticancer therapy is based on deregulation in various cancers, including prostate cancer, and their ability to modulate the cancer phenotype, targeting multiple genes (Di Leva 2014: 287-314). Differently expressed miRNAs can play an oncogenic or tumor-suppressing role in the development and progression of cancer, making them ideal candidates for therapy (Taylor 2014: 1-13). The role of miRNAs in prostate cancer will become clearer if interactions between miRNAs and their target genes and, as a result, the effect on the carcinogenesis of the prostate were determined. It is believed that several miRNAs and their target genes are aberrantly expressed in the PC, which in turn alter the cellular growth, invasion and metastatic potential of prostate cancer cells (Pang 2010: 363-9). As a result of abnormal expression, some miRNAs can be considered as valuable biomarkers for the diagnosis, prognosis and classification of prostate cancer.

Materials and Methods

Nucleotide sequences of mRNAs of genes were downloaded from GenBank (http://www.ncbi.nlm.nih.gov). The miRNAs nucleotide sequences were downloaded from miRBase (http://mirbase.org). Binding sites for tested miRNAs were revealed using the MirTarget program (Ivashchenko 2014b: 423-7). This program defines the following features

of binding: a) beginning of miRNAs binding with mRNAs; b) localization of miRNA binding sites in the 5'-untranslated regions (5'UTRs), coding domain sequences (CDSs) and 5'-untranslated regions (3'UTRs) of mRNAs; c) free energy of hybridization (ΔG, kJ/mole); d) schemes of nucleotide interactions between miRNAs and mRNAs. The ratio ΔG/ΔGm (%) was counted for each site, where ΔGm is free energy of miRNA binding with its perfect complementary nucleotide sequence. The miRNA binding sites located on the mRNAs have ΔG/ΔGm ratios of 90% and more. We also note the position of the binding sites on the mRNA, beginning from the first nucleotide of the 5'UTR of mRNA. The MirTarget program computes the interactions between the nucleotides of miRNAs and those of target gene mRNAs. It found bonds between adenine (A) and uracil (U), guanine (G) and cytosine (C), and G and U, as well as between A and C via one hydrogen bond. In the interaction of miRNA with mRNA, the program allows one unpaired nucleotide only in mRNA, but not in miRNA, since it is bound to the RISK complex. Contrary to the hypothesis that miRNA binds with mRNA only in the 3'UTR, and interacts with mRNA only due to the «seed» of the site, the program takes into account the interaction of miRNA with mRNA over the entire length in 5'UTR, CDS and 3'UTR at the basis of physico-chemical properties of these molecules (Ivashchenko 2014b: 423-7; Ivashchenko 2016: 15-8).

Results and Discussion

A database of genes involved in prostate cancer including 67 genes was created, the information of which is given in Table 1.

Table 1 – Genes involved in prostate cancer

Gene	link to PUBMed	Gene	link to PUBMed
ALAS1	16211407, 23269617	*MSH2*	28790115, 28697982, 25255306,
AMACR	28191285, 28125866, 27271990, 26928323,26628996	*MTA1*	29024573, 28231399, 26943043, 25797255, 25447541
APC	28026816, 27726247,	*MUC1*	28930697, 27846218, 27830724, 27825118, 27165976, 25971429
ASAH1	25888580, 24091326, 23423838, 22322590, 21557271, 21116286, 19874262	*MYCBP2*	26408707, 25731699
AURKA	27207661, 26425080, 24631181, 23358695, 23333597, 21514073	*MYO6*	27431378, 26856686, 20353999, 18543251
AZGP1	28561811, 28486686, 27473574, 26383228, 21432866,	*NANOG*	29143228, 28986894, 28938627, 27956179
BAX	28345329, 28112004, 28032735	*NFKBIA*	28670959
BCL2	28396899, 27519795, 26722046, 25803782	*NRP1*	29138851, 29059172
BMI1	27703144, 27377156	*PAG1*	21092590
BRCA1	28905785, 28812325, 28448241, 27989354, 27456091	*PAOX*	26547506
BRCA2	28676659, 28623073, 28608931, 28487881, 28453706, 28410213, 28117848, 28067867	*PDLIM4*	27028812, 26628996, 29137356
CCNB1	28525372	*PLAU*	28778937
CD44	29029419, 28789597, 29104488, 29066912	*PLXNB1*	29040270, 28739743
CDC6	28228262, 24583551, 19520769, 19107233, 18541154	*PTEN*	29142193, 29141684, 29138324, 29137428, 29136769
CDCA5	27881001, 26408707	*PTTG1*	29078751, 28977903, 28827316, 28711367
CDK4	29129687	*RASSF1*	29122566, 29066912, 29039788, 28669560, 28449010
CDKN2A	27444279, 9066912, 26416059	*SAT1*	29100496, 28822858,
CFLAR	25816367, 25181458	*SMARCA4*	29102090, 29087303, 28938645

Continuation of table 1

Gene	link to PUBMed	Gene	link to PUBMed
ELOVL7	19826053, 26408707, 29059155	*SPINK1*	28994706, 28984793, 28845526
EPHB2	21603658, 19454503, 16155194, 15300251	*SSTR1*	27927191
ERG	29144945, 29129399, 29127096, 29088771, 29037514, 28872154, 28849022	*TMF1*	12368219
ETV1	26731476, 28497076	*TMPRSS2*	29144945,29129399, 29127096
EZH2	29141691, 28899973, 28832071, 28272687, 28255661	*TNF*	29150958, 29150737, 29150565,29150240
FMN1	20540360	*TOP2A*	29045811, 28915696, 28899973, 28813519, 28800016
GBX2	10690529, 9537237, 8977637	*TP53*	29147214, 29139064
GOLM1	24284362, 18953438	*TPD52*	28562687, 28436114, 27983918, 27785063
GSTP1	28653607, 28026816, 27913949, 27594734, 27511358	*UBE2I*	28817247, 28544272, 27030546
HIF1A	28415653	*UHRF1BP1*	28886272, 21326321, 19838195
HOXC6	26310814, 25725483, 24213107, 15637592	*VDR*	29146302, 29130299, 29128634, 29127362, 29113037
HPRT1	29115578, 23269617, 20067463	*VEGFA*	29146554, 29137376, 29118335
IL10	29029504, 28526808, 28073842	*VEGFB*	28925397, 28771828, 28314760, 27826041
KLK2	28216900, 27458923, 25153390	*XIAP*	29124675, 29123378, 29115633, 29109763, 29063676
KLK3	28894123, 28272245	*XPO6*	27265126, 26709895, 22127497
MKI67	28605139, 28552967, 28479874		

Some genes are specific to prostate cancer. Immunohistochemical analysis of primary prostate cancer specimens showed that higher levels of *ASAH1* (encodes a member of the acid ceramidase (AC) family of proteins) are associated with later stages of neoplasia, confirming that *ASAH1* is the therapeutic target in late and chemoresistant forms of prostate cancer and suggests that new specific AC inhibitors can act by counteracting the critical growth properties these highly aggressive tumor cells (Camacho 2013: 1207-20). Expression of *AURKA* (encodes aurora kinase A (AR)) is regulated by androgens in prostate cancer cells, which highly express AR, emphasizing its potential as a therapeutic target in patients with CRPC (Kivinummi 2017: e17978). *BMI1* is an oncogene, and its aberrant expression is associated with multiple cancers and with resistance to certain types of chemotherapy. This gene plays a central role in the repair of DNA damage (Nitu Bansal 2016: 6176-91). EPHB2 protein belongs to the Eph-receptor subgroup of EphB, is involved in various cellular processes, including mobility, division and differentiation. Allelic variants are associated with the susceptibility of the prostate (Nielson 2016: 2085–97). Expression of the *GBX2* gene leads to stimulation of malignant growth of prostate cancer cells (Gao 2000: 493-7). It was developed functional evidence for CBP and PTEN interaction in prostate cancer based on findings of their correlate expression in the human disease (Ding 2014: 2050-61).

According to the references, 206 miRNAs are involved in the development of prostate cancer (Table 2). Of these, 119 miRNAs expression rises, and 87 decreases with prostate cancer. Previously, differentiated expression of 51 individual miRNAs in benign tumors and tumors of prostatic carcinoma was demonstrated, 37 of them were decreased, and 14 were increased in carcinoma samples (Porkka 2007: 6130-5). But a change in the concentration of miRNAs does not mean that they are responsible for the disease, they can be a consequence of the disease. Therefore it is important to determine the features of interaction these miRNAs with genes involved in the development of prostate cancer.

Table 2 – Level of expression of some miRNAs in prostate cancer

miRNA	PMID	miRNA	PMID
let-7↓, miR-30↓	17891175	miR-302↑, miR-296↑	17989215
miR-34↓	18719384	miR-135↑, miR-194↑, miR-23b↓	18949015
miR-143 and miR-145↓	18955434	miR-3960↑	18975380
miR-205↓	19244118	miR-449a↓	19252524
miR-15a↓, miR-16-1↓	19498445	miR-200↓	19544444
miR-181↑, miR-17↑, miR-92↑	19585654	miR-512↓, miR-196a↓, miR-133b↓	20878953
miR-145↓	20588276	miR-15↓	20884628
miR-615↑, miR-196b↓	21255435	miR-508–5p↓, miR-100↓, miR-33a↓	21647377
miR-101↓	21368580	miR-488↑	21710544
miR-146–3p↑, miR-298↑	22052531	miR-182↓, miR-183↓, miR-200a↓, miR-429↓	19665978
miR-762↓	22154518	miR-31↓, miR-96↑, miR-181b↓, miR-18a↑	19676045
miR-29b↓	22402125	miR-21↑, miR-32↑, miR-590-5p↑, miR-152↓	22266859
miR-27a↓	22505583	let-7c↓, let-7e↓, miR-346↑, miR-1285↑, miR-940↑	22298030
miR-378b↑, miR-409–3p↓	22887127	miR-548c-3p↑	25234358
miR-224↓	23136246	miR-483–5p↑	25445383
miR-31–5p↑, miR-205–5p↑	23184537	miR-1247-5p↑	25731699
let-7b↓	23798998	miR-4516 ↑	25760964
miR-214↓, miR-182–5p↑	24167554	miR-150↑	25778313
miR-888↑	24200968	miR-187↓	25969992
miR-200b↑, miR-20b↑	24337069	miR-7↓	26172296
miR-1825↑, miR-484↓	24494028	miR-573↓	26451614
miR-345↑, miR-519c-5p↑	24893170	miR-631↓	26620225
miR-1↓	24967583	miR-340↓	26718483
miR-6090↓	26789142	miR-1184 ↑, let-7b-5p ↓, let-7c-5p↓	27265125
miR-4668-5p↓	27926529	miR-151–3p↑	3645714
miR-619-5p↑	28853076	miR-204↑	4480709
miR-203↑, miR-191, let-7i↑, miR-17-5p↑, miR-146↑, miR-196↑, miR-199↑, miR-206↑, miR-149↓, miR-218↓			16461460
miR-125b↓, miR-199a↑, miR-22↓, miR-27b↓, miR-29a↓, miR-30a↓, miR-202↑, miR-373↑, miR-302c↑, miR-210↑, miR-498↑, miR-503↑, miR-491↑, miR-320↑, miR-513↑, miR-370↑, let-7g↓, miR-23a↓, miR-497↓, let-7f↓, miR-19b↓, miR-30a-5p↓, miR-30b↓,			17616669
miR-125a↑, miR-99b↑, miR-25↑, miR-106b↑, miR-26a↑, miR-133a↓			18676839
miR-16↑, miR-636↑, miR-766↑, miR-885-5p↑, miR-328↑, miR-485- 3p↑, miR-486-5p↑, miR-574-3p↑, miR-197↑, miR-103↑, miR-92b↑, miR-92a↑, miR-34b↑, miR-640↑, miR-485-3p↑			19597549
miR-375↑, miR-148a↑, miR-200c↑, miR-223↓, miR-15b↑			20353999
miR-1207–5p↑, miR-874↑, miR-26b↓, miR-30c↓, miR-1274a↑			21098088
miR-130a↑, miR-20a↑, miR-106↑, miR-93↑, miR-27↓, miR-221↓, miR-361–3p↓, miR-19a↑, miR-222↓, miR-455↓, miR-95↑			21765474
miR-2110↑, miR-130b↑, miR-625↑, miR-432↑, miR-331-3p↑, miR-326↑, miR-301a↑, miR-181a-2↓, miR-572↓, miR-107↑, miR-574–3p↑, miR-181a-2↓			22240788
miR-96–5p↑, miR-183–5p↑, miR-145–5p↓, miR-221–5p↓			23184647
miR-1224–5p↑, miR-1249↑, miR-663↑, miR-155↓, miR-455–3P↓, miR-193a-5p↓			24191917
miR-200a↑, miR-1203↑, miR-708↑, miR-616↑, miR-551b↑, miR-375↑, miR-501–3p↑, miR-562↑, miR-184↑, miR-671-3p↑			25786615
let-7a↓, miR-451↓, miR-146a↓, miR-106a↓, miR-103↓, miR-24↓			25874774
miR-126↓, miR-34a↓, miR-195↓, miR-342–3p↑, miR-141↑, miR-622↑, miR-30d↑, miR-425↑			3123620
Note. ↑ – increased, ↓- decreased in carcinoma samples			

We have determined the features of the binding of genes involved in the development of prostate cancer with miRNAs, involved in the development of cancer. According to the calculations, mRNAs of 20 from 67 genes involving in the development of prostate cancer are associated with 17 miRNAs with a ΔG/ΔGm value more than 90% (Table 3).

For six miRNAs binding sites are located in the CDS, for tree miRNAs – in the 5'UTR, for others – in the 3'UTR. For miR-619-5p, miR-574-3p, miR-3960, miR-1285-3p there are multiple binding sites with ΔG/ΔGm value greater than 90%. Some miRNAs have several target genes involved in the development of prostate cancer.

Table 3 – Characteristics of the binding of miRNA to mRNA genes involved in the development of prostate cancer

Gene	Characteristics of binding
ALAS1	miR-3960, 134-5, 92, -115, 20
AURKA	miR-619-5p, 426-5, 98, -119, 22; miR-1285-3p, 352-5, 91, -106, 22
BRCA1	miR-619-5p, 6412-3, 98, -119, 22
BRCA2	miR-619-5p, 10746-3, 96, -117, 22
CASP8	miR-619-5p, 2488-3, 93, -113, 22
CDCA5	miR-331-3p, 1303-3, -99, 91, 21
CFLAR	miR-619-5p, 5910-3, 95, -115, 22; 1932-3, 95, -115, 22; miR-1285-5p, 5245-3, 91, -101, 21; 6149-3, 91, -101, 21
EPHB2	miR-4516, 3143-3, 94, -93, 17
FMN1	miR-619-5p, 6536-3, 98, -117, 22; miR-361-3p, 4194-3, -104, 89, 23; 4195-3, -112, 93, 23
GBX2	miR-3960, 203-C, 92, -115, 20; 204-C, 92; 206-C, 92; 207-C, 92, -115, 20
IL10	miR-619-5p, 1216-3, 98, -119, 22
MTA1	miR-6090, 2359-3, 93, -108, 19; miR-1207-5p, 2385-3, -108, 91, 21
MYO6	miR-619-5p, 7976-3, 98, -119, 22; miR-1285-5p, 8216-3, 91, -101, 21
MYCBP2	miR-133b, 995-C, -101,90, 22; mir-342-3p, 6255-C, -97, 91, 21
PAG1	miR-574-3p, 5585-3, -108, 89, 23; 5588-3, -112, 93, 23; 5590-3, -112, 93, 23; 5592-3, -110, 91, 23; 5594, -108, 89, 47
SH3GLB1	miR-497-3p, 3503-3, -97, 90, 22
SMARCA4	miR-150-3p, 830-C, -108, 90, 22; miR-497-5p, 3643-C, -99, 91, 21
TP53	miR-1285-3p, 2301-3, 95, -110, 22
UHRF1BP1	miR-619-5p, 6379-3, 98, -119, 22; miR-1224-5p, 4939-3, -93, 94, 19
VEGFA	miR-1296-3p, 590-C, -106, 90, 22
XIAP	miR-619-5p, 3541-3, -121, 95, 22; 5815-3, -121, 100, 22; 5681-3, -121, 100, 22; 5073-3, -118, 98, 22; 7675-3, -118, 98, 22; 7808-3, 95, -121, 22; miR-326, 2439-3, 93, -106, 20 ; miR-1285-5p, 5312-3, 92, -104, 21
Note. miRNA; the beginning of binding site; the miRNA region: 5 – 5'UTR, 3 – 3'UTR, C-CDS; the free energy change (ΔG, kJ/mole); the ΔG/ΔGm (%); length of miRNA (nt)	

Among miRNAs that have binding sites in mRNAs of genes responsible for the development of prostate cancer, miR-4516 has a binding site in mRNA of the *EPHB2* gene. It has been shown that among miRNAs associated with biochemical failure after post-prostatectomy, miR-4516 significantly improves the prediction of radiation therapy after biochemical insufficiency in comparison with clinico-histopathological factors, including clinically used predictive models (Bell 2015: e0118745).

miR-3960 binds with two, miR-1285-5p – with four, miR-619-5p – with mRNA of nine target genes.

miR-3960 binds with mRNA of *ALAS1* and *GBX2* genes. Multiple sites are found for miR-3960 in mRNA of *GBX2* gene, the expression of which leads to the stimulation of malignant growth of prostate cancer cells. The sites are located in the CDS mRNA of *GBX2* gene, in the 5'UTR mRNA of *ALAS1* gene. miR-3960 binding sites are located in the CDS with a displacement in one and two nucleotides (Table 3). The $\Delta G/\Delta G_m$ value for miR-3960 binding sites in mRNAs of *ALAS1* and *GBX2* genes is equal to 92%. We found earlier that miR-3960 have 1100 binding sites on 375 target mRNAs with value $\Delta G/\Delta G_m$ equal 90% and more. Approximately

half of miR-3960 binding sites are located in the protein-coding region of the mRNAs (Ivashchenko 2014b: 423-7).

miR-1285-5p binds with mRNAs of *AURKA, CFLAR, MYO6, TP53, XIAP* with ΔG/ΔGm more than 90%. Binding sites are located in the 3'UTR and 5'UTR. It is demonstrated that miR-1285-5p was upregulated in prostate cancer (including both metastasis and nonmetastasis (Chen 2012:1443-52). On the other hand, new evidence showed that miR-1285 could block the expression of p53 by binding its 3'UTR, indicating miR-1285's oncogenic function (Tian 2010: 435–439).

miR-574-3p has multiple binding sites in mRNA of *PAG1* gene. Binding sites are located in the 3'UTR. It was shown that miR-574–3p present at a higher concentration in the urine of men with prostate cancer compared to the controls, indicating their minimally invasive biomarker potential (Bryant 2012: 768–74). Several works demonstrated that miR-574-3p was upregulated in the sera of prostate cancer patients vs. healthy controls (Chiyomaru 2013: e58929-58941, Brase 2011: 608–616.).

The schemes of interaction miR-3960, miR-1285-3p with mRNAs of target genes are shown in Table 4. The interaction with mRNAs of the genes are more than 92%.

Table 4 – Schemes of miR-3960, miR-1285-3p, `miR-574-3p` binding sites with gene's mRNAs

GBX2; miR-3960; CDS; 204; -115; 92 5′ – CCGCCGCCGCCGCCGCCGCC – 3′ || ||||| |||||||||| 3′ – GGGGGCGGAGGCGGCGGCGG – 5′	*TP53*; miR-1285-3p; 3′UTR; 2301; -110; 95 5′ – GGGUCUCGCUUUGUUGCCCAGG – 3′ |||||||||||||||||||||| 3′ – UCCAGAGUGAAACAACGGGUCU – 5′
GBX2; miR-3960; CDS; 207; -115; 92 5′ – CCGCCGCCGCCGCCGCCGCC – 3′ || ||||| |||||||||| 3′ – GGGGGCGGAGGCGGCGGCGG – 5′	*PAG1;* miR-574-3p5588-3, -112, 93, 23 5′ – ACACACACACACACACACACACA – 3′ |||||| ||||||||||| || 3′ – UGUGUGAGUGUGUGUGUGUGAGU – 5′
Note. Gene; miRNA; the miRNA region; the beginning of binding site; the free energy change (ΔG, kJ/mole); the ΔG/ΔGm (%)	

miR-619-5p binds with the highest binding energy of 121 kJ/mole with ΔG/ΔGm equal to 100% (Table 3) in mRNA of *XIAP* gene. It is possible binding with ΔG/ΔGm equal to 98% to mRNA of *AURKA, BRCA1, FMN1, IL10, MYO6, UHRF1BP1* genes. miR-619-5p has a length of 22 nt, is encoded in the intron of *SSH1* gene localized on chromosome 12. We previously detected 1811 miR-619-5p binding sites on 1215 mRNAs of targets genes. Among them, 1772 miR-619-5p binding sites are located in the 3'UTR, 26 sites in the 5'UTR and 13 sites in the CDS (Ivashchenko 2014b: 1-8). It was shown that mRNAs of 201 genes are completely complementary to the miR-619-5p binding sites (Atambayeva 2017: 428).

The schemes of interaction miR-619-5p with mRNAs of target genes are shown in Table 5. The ΔG/ΔGm of interaction with mRNA of genes are more than 90%. It was shown that in all cases, miRNAs bind to mRNA without breaking the double-stranded structure.

High levels of miR-619-5p in plasma were detected in patients with PC in comparing of patients with benign prostatic hyperplasia (BPH) (Knyazev 2016: 108-11). The expression of miR-619-5p showed a 5-fold increasing in PC in comparison with BPH. These data confirm that an increasing in plasma of miR-619-5p is caused by the growth of a malignant tumor. The host gene *SSH1* encodes phosphatase activating the cofilin protein, which regulates the dynamics of actin filaments (Chang 2015: 4095-120). Presumably, a high plasma miR-619-5p level determines a high level of expression of SSH1 in the tumor, while the *SSH1* gene participates in oncogenesis. In addition, the analysis of target genes regulated by miR-619-5p showed a possible target of miR-619-5p – the Casp9 oncosuppressor (caspase participating in the initiation of apoptosis) (Kim 2015: 113-27). Thus, *SSH1* and miR-619-5p are a good example of the interrelated functions of microRNAs and the «host gene». It was shown that plasma miR-619-5p levels correlate with the growth of the prostate cancer and its spread outside the prostatic capsule. The detection of this dependence suggests that miR-619-5p is a promising oncomarker that can be used to differentiate PC stages and sheds light on some of the molecular mechanisms of oncogenesis (Shkurnikov 2017: 475-7).

Table 5 – Schemes of miR-619-5p binding sites with gene's mRNAs

AURKA; miR-619-5p; 5'UTR; 135; -119; 98 5' – GGCUCAUGCCCGUAAUCCCAGC – 3' 3' – CCGAGUACGGACAUUAGGGUCG – 5'	*BRCA1*; miR-619-5p; 3'UTR; 6412; -119; 98 5' – GGCUCACGCCUGUAAUCCCAGC – 3' 3' – CCGAGUACGGACAUUAGGGUCG – 5'
BRCA2; miR-619-5p; 3'UTR; 10746; -117; 96 5' – GGCUCAUGCCUGUAAUCCCAAC – 3' 3' – CCGAGUACGGACAUUAGGGUCG – 5'	*CASP8*; miR-619-5p; 3'UTR; 2488; -113; 93 5' – GGCUCAUGUCUAUAAUCCCAGC – 3' 3' – CCGAGUACGGACAUUAGGGUCG – 5'
CFLAR; miR-619-5p; 3'UTR; 1932; -115; 95 5' – GGCUCACACCUGUAAUCCCAGC – 3' 3' – CCGAGUACGGACAUUAGGGUCG – 5'	*CFLAR*; miR-619-5p; 3'UTR; 5910; -115; 95 5' – GGCUCACGCCUAUAAUCCCAGC – 3' 3' – CCGAGUACGGACAUUAGGGUCG – 5'
FMN1; miR-619-5p; 3'UTR; 6536; -117; 96 5' – GGCUCAUGCCUAUAAUCCCAGC – 3' 3' – CCGAGUACGGACAUUAGGGUCG – 5'	*IL10*; miR-619-5p; 3'UTR; 1351; -108; 98 5' – GGCUCACGCCUAUAAUCCCAGC – 3' 3' – CCGAGUACGGACAUUAGGGUCG – 5'
MYO6; miR-619-5p; 3'UTR; 7976; -119; 98 5' – GGCUCACGCCUGUAAUCCCAGC – 3' 3' – CCGAGUACGGACAUUAGGGUCG – 5'	*UHRF1BP1*; miR-619-5p; 3'UTR; 6378; -119; 98 5' – GGCUCACGCCUGUAAUCCCAGC – 3' 3' – CCGAGUACGGACAUUAGGGUCG – 5'
XIAP; miR-619-5p; 3'UTR; 5073; -119; 98 5' – GGCUCACGCCUGUAAUCCCAGC – 3' 3' – CCGAGUACGGACAUUAGGGUCG – 5'	*XIAP*; miR-619-5p; 3'UTR; 5681; -121; 100 5' – GGCUCACGCCUGUAAUCCCAGC – 3' 3' – CCGAGUACGGACAUUAGGGUCG – 5'
XIAP; miR-619-5p; 3'UTR; 7675; -119; 98 5' – GGCUCACGCCUGUAAUCCCAGC – 3' 3' – CCGAGUACGGACAUUAGGGUCG – 5'	*XIAP*; miR-619-5p; 3'UTR; 7807; -115; 95 5' – GGCGCAUGCCUGUAGUCCCAGC – 3' 3' – CCGAGUACGGACAUUAGGGUCG – 5'
Note. Gene; miRNA; the miRNA region; the beginning of binding site; the free energy change (ΔG, kJ/mole); the ΔG/ΔGm (%)	

Conclusion

In the present study, we performed a bioinformatic analysis of interaction of genes and microRNAs related to the development of prostate cancer. We selected a pool of 67 genes and 206 miRNAs that involved in the development of prostate cancer. We found that mRNAs of 67 genes involved in the development of prostate cancer are associated with nine miRNAs with a ΔG/ΔGm value more than 90%. Sites are located in CDS, 5'UTR and 3'UTR. miR-619-5p and miR-3960, miR-1285-3p, miR-574-3p have multiple binding sites with ΔG/ΔGm value greater than 90%.

In summary, our study provides associations of miR-619-5p, miR-3960, miR-1285-5p and miR-574-3p with mRNAs of their target genes responsible for the development of prostate cancer that can be recommended as markers of this cancer.

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