

Original Research Article

The potential of miR-153 as aggressive prostate cancer biomarker

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ABSTRACT

Introduction: Prostate cancer (PC) is one of the most frequently diagnosed cancers in males. MiR-153, as a member of the microRNA (miRNA) family, plays an important role in PC. This study aims to explore the expression and possible molecular mechanisms of the miR-153 action.

Methods: Formalin-fixed paraffin-embedded (FFPE) tissues were collected from prostatectomy specimens of 29 metastatic and 32 initial stage PC patients. Expression levels of miR-153 were measured using real-time reverse transcription polymerase chain reaction (qRT-PCR). 2–ΔΔCT method was used for quantitative gene expression assessment. The candidate target genes for miR-153 were predicted by TargetScan. Mutations in target genes of miR-153 were identified using exome sequencing. Protein-protein interaction (PPI) networks, Kyoto Encyclopedia of Genes and Genomes (KEGG) analyses were performed to investigate the potential molecular mechanisms of miR-153 in PC.

Results: MiR-153 was significantly up-regulated in PC tissues compared to non-cancerous tissues. The analysis of correlation between the expression level of miR-153 and clinicopathological factors revealed a statistically significant correlation with the stage of the tumor process according to tumor, node, metastasis (TNM) staging system ($p = 0.0256$). ROC curve analysis was used to evaluate the predictive ability of miR-153 for metastasis development and it revealed miR-153 as a potential prognostic marker (AUC = 0.85; 95%CI 0.75–0.95; sensitivity = 0.72, specificity = 0.86). According to logistic regression model the high expression of miR-153 increased the risk of metastasis development (odds ratios = 3.14, 95% CI 1.62–8.49; p -value = 0.006). Whole exome sequencing revealed nonsynonymous somatic mutations in collagen type IV alpha 1 (COL4A1), collagen type IV alpha 3 (COL4A3), forkhead box protein O1 (FOXO1), 2-hydroxyacyl-CoA lyase 1 (HACL1), hypoxia-inducible factor 1-alpha (HIF-1A), and nidogen 2 (NID2) genes. Moreover, KEGG analysis revealed that the extracellular matrix-receptor (ECM-receptor) interaction pathway is mainly involved in PC.

Conclusion: MiR-153 is up-regulated in PC tissues and may play an important role in aggressive PC by targeting potential target genes.

1. Introduction

Prostate cancer (PC) is a commonly diagnosed condition, with an estimated 1414.3 thousand new cases of PC and 375.3 thousand deaths from the disease in 2020 [1]. In one third of PC patients the tumor progresses (perineural and stromal invasion) after initial regression in response to androgen deprivation therapy [2]. Despite current advances in surgical, chemotherapeutic and radiological methods of treatment,

the five-year survival rate in castration-resistant patients is approximately 31.0% [3]. Most PC-related deaths occur due to the inability of existing treatments to prevent tumor spread [4].

Rectal examination and prostate specific antigen (PSA) levels are used to diagnose PC. However, the medical and scientific communities have questioned routine PSA testing. PSA has high sensitivity but very low specificity for PC. It can be elevated in the presence of benign prostate disease, infection, inflammation or benign hyperplasia [5].

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Routine PSA testing leads to a high percentage of false-positive results. Moreover, PSA levels correlate poorly with the stage of the disease, leading to misdiagnoses and overtreatment of indolent forms of PC [6]. Considering all the above, there is a need for new molecular genetic markers capable of both detecting the disease at the earliest stage and predicting its course.

MicroRNAs (miRNAs) are considered to be one of the most promising markers for various diseases including PC. The discovery of miRNAs provided a conceptual breakthrough in cancer research. MiRNAs are non-coding RNAs (ncRNAs) (19–22 nucleotides) which are involved in post-transcriptional regulation of gene expression. MiRNAs are increasingly associated with the initiation, development and progression of malignancies. Aberrant miRNAs expression has been identified in a variety of malignant tumors, with recent evidence suggesting that miRNAs function as tumor suppressor genes and/or oncogenes [7]. Recent studies have various miRNAs expression profiles in PC tissues [8–11]. MiR-153 was found to be downregulated in various cancers, such as breast cancer (BC), gastric cancer (GC) and oral cancer (OC) [15]. However, there are few investigations devoted to miR-153 and its role PC [12–15].

In this study, we evaluate the expression levels of miR-153 in PC tissue specimens and adjacent normal tissue specimens, the association of miR-153 with clinical characteristics and mutations in target genes of miR-153 and identified the pathways involved in PC progression. Our study was aimed to evaluate and understand the expression level of miR-153 in malignant tumor and normal prostate tissue in patients with metastatic PC and initial stages of the disease and possible molecular mechanism of the miR-153.

2. Material and methods

2.1. Patients and samples collection

In this study, 61 PC patients (average age 60, range 41–80 years) who underwent surgical treatment between 2008 and 2020 in Bashkir State Medical University hospital were included. Ethical approval for this study was obtained from Institute of Biochemistry and Genetics Bioethics Committee. All samples investigated in this study were obtained with written informed consents of the participants. We collected formalin-fixed paraffin-embedded (FFPE) tissues from prostatectomy material including 29 metastatic and 32 localized (stages I, II) PC patients. The samples were classified using the tumor, node, metastasis (TNM) staging system from clinical stages I–IV.

2.2. Samples evaluation

After tissue section were obtained, Hematoxylin and Eosin (H&E) staining was performed and the slides were examined by two independent experienced pathologists. DNA and RNA were isolated from tumor regions and normal prostate tissue from each patient. The healthy region of the prostate without tumor cells in the selected FFPE block, was taken as a source of normal RNA and DNA. Total RNA and DNA extraction was performed using Quick-DNA/RNA™ FFPE Kits (Zymo Research) following the manufacturer's protocol. The process consisted of simple tissue deparaffinization in deparaffinization solution, proteinase K treatment followed by RNA and DNA isolation in spin columns.

2.3. Real-time reverse transcription polymerase chain reaction (qRT-PCR)

The PCR amplification for the quantification of the miR-153 and U6 RNA was performed using a TaqMan MicroRNA Reverse Transcription Kit (Applied Biosystems; Life Technologies Corp) and TaqMan Human MicroRNA Assay Kit (Applied Biosystems; Life Technologies Corp). Expression levels were measured using CFX96™ PCR detection system (BioRad). All reactions were performed three times for each sample. The

2– $\Delta\Delta$ CT method was used for quantitative gene expression assessment. The 2– $\Delta\Delta$ CT method is based on the assumption that the cycle threshold difference (Δ Ct) between target gene and reference gene is proportional to relative target gene expression. The relative expression of miR-153 was shown as fold difference relative to U6 RNA.

2.4. Whole exome sequencing

Patients with metastatic adenocarcinoma were chosen for exome sequencing to identify mutations in target genes of miR-153. Target genes were selected using TargetScan. DNA fragmentation, library preparation, and exome capture were conducted according to the manufacturer's recommendations. Selection of specific DNA fragments was conducted using the SureSelect system followed by concurrent sequencing of the obtained libraries using Illumina HiSeq 2000. All the reads were aligned with the reference genome using Burrows-Wheeler Alignment (BWA) software. We used the human genome sequence (Genome Reference Consortium Human Build 37 (GRCh37-hg19)) as a reference. Identification of the variants was conducted using the Genome Analysis Tool Kit (GATK). The identified variants were annotated by ANNOVAR software using the scripts `table_annovar.pl` and `annotate_variation.pl`, which allows to compare single nucleotide substitutions with the number of specialized databases and to annotate prognostic functional significance of the revealed alterations using six in silico software programs (SIFT, PolyPhen-2, LRT, Mutation Assessor, MutationTaster, phyloP, and GERP++) from dbNSFP v.3.0a. Additionally, we used CLINVAR and CADD (Combined Annotation Dependent Depletion) softwares. Exome sequencing procedure and bioinformatics were performed as previously described by Gilyazova et al. [16].

2.5. Network analysis

The network of mutated genes was generated using STRING-DB 9.1 [17]. Minimum required interaction scores were set to “high confidence” (0.700). The Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis was performed using online KEGG tools (<http://www.kegg.jp/>).

2.6. Statistical analysis

The obtained data was analyzed using R-studio program by calculating average values, standard deviation, and arithmetic mean error. The data are presented as means $\pm$ standard deviation. To assess the significance of differences, the Mann–Whitney *U* test was used. The predictive ability of miR-153 was determined by the receiver operating characteristic (ROC) curves. A logistic regression prediction model was applied to calculate prediction scores for individual samples. Changes were considered reliably significant at $p \leq 0.05$.

3. Results

3.1. MiR-153 expression in PC tissue

The expression level of miR-153 was analyzed in 61 samples of tumor tissue (Fig. 1) and 61 adjacent normal prostate tissue (Fig. 2) using qRT-PCR. MiR-153 expression showed to be increased in tumor tissue (mean $\pm$ SEM: 1.36 $\pm$ 0.23) over normal prostatic tissue (mean $\pm$ SEM: 0.66 $\pm$ 0.09) with p -value = 0.03 (Fig. 3).

3.2. MiR-153 expression and clinicopathological factors

Patients were divided into subgroups with high ($n = 31$) expression and low ($n = 30$) expression of miR-153. The median miR-153 expression value defined the threshold value. The analysis of correlation between miR-153 expression and clinicopathological factors (Table 1) revealed a significant correlation with the stage of the tumor process

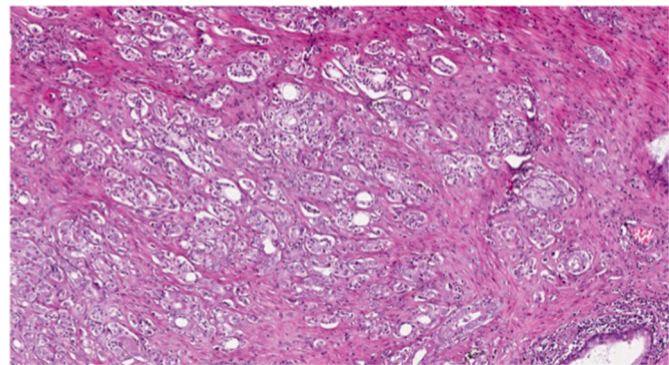


Fig. 1. Hematoxylin and Eosin (H&E) stain of prostate cancer (PC) tissue.

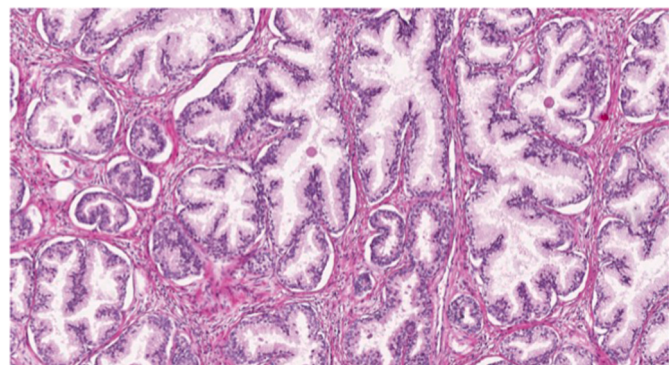


Fig. 2. Hematoxylin and Eosin (H&E) stain of normal prostate tissue.

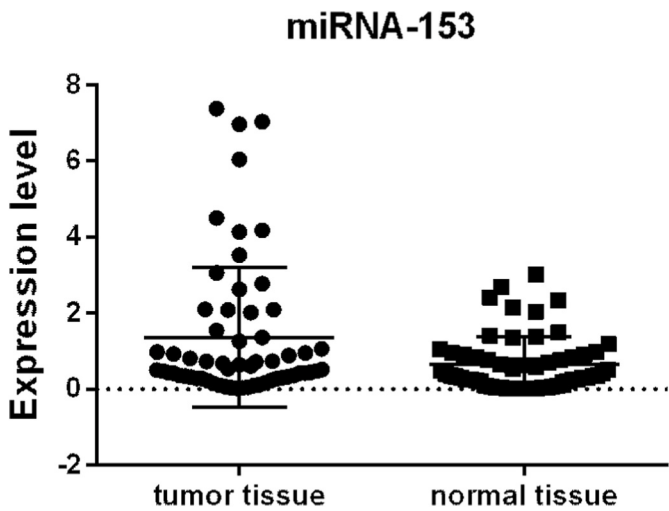


Fig. 3. MiR-153 expression level in prostate cancer (PC) tissues vs adjacent normal prostate tissues. A statistically significant increase in miR-153 expression in PC tissue compared to normal tissue was demonstrated. The significance level (p-value) is determined using the Wilcoxon T-test.

according to TNM classification ($p = 0.001$). Expression levels of miR-153 in different TNM stages of PC is presented (Fig. 4). It was shown that miR-153 expression significantly higher (mean $\pm$ SEM: 2.29 ± 0.41) in metastatic PC tumors compared to non-metastatic tumors (mean $\pm$ SEM: 0.53 ± 0.12) with $p < 0.0001$.

3.3. ROC curve of miR-153

In addition, the receiver-operating characteristic (ROC) curve was

Table 1
Association between miR-153 expression and clinical and pathological characteristics of patients with prostate cancer.

Variables	Cases (n)	MiR-153 expression		P-value
		High (n = 31)	Low (n = 30)	
Age, years				
<55	15	9	6	0.818
≥ 55	46	24	22	
Lymph node metastasis				
Yes	29	22	7	0.180
No	32	18	14	
Bone metastases				
Yes	27	18	9	0.203
No	34	16	18	
Gleason score				
<8	23	12	11	0.710
≥ 8	38	23	15	
TNM stage				
I + II	32	8	24	0.001
IV	29	23	6	

TNM, tumor, node, metastasis.

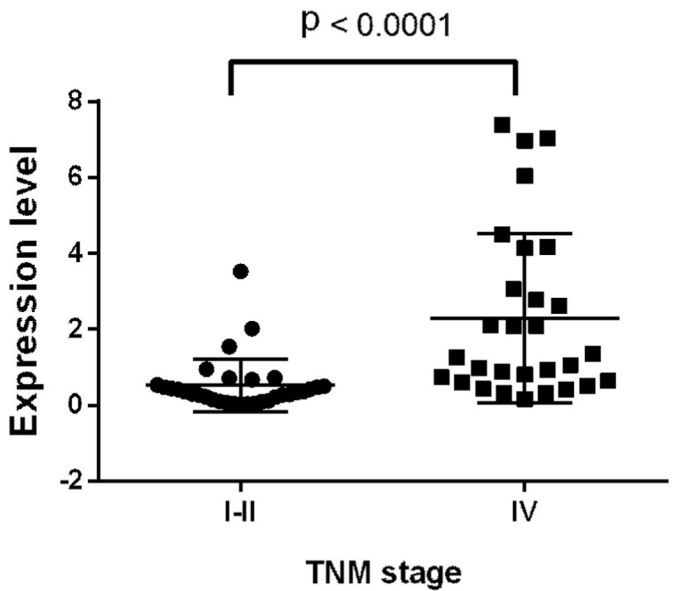


Fig. 4. Expression levels of miR-153 in different tumor, node, metastasis (TNM) staging system of prostate cancer (PC). It was demonstrated that miR-153 is upregulated in advanced PC compared to localized disease. Significance level (p-value) was determined using the Mann-Whitney U test.

drawn to further calculate the area under the curve (AUC) and authenticate the diagnostic ability of miR-153. Results revealed that miR-153 expression presented low diagnostic ability for tumor and normal prostate tissue discrimination. As shown at ROC curve of the miR-153 presented in Fig. 5, the AUC was 0.61 (95% CI 0.52–0.71; sensitivity = 0.66, specificity = 0.53). Furthermore, logistic regression analysis revealed that the miR-153 was independent predictor for PC (odds ratios = 1.57, 95% CI 1.13–2.36; $p = 0.014$).

Further the ROC curve analysis was used to evaluate the predictive ability of miR-153 for metastasis development. As shown at Fig. 6 the AUC was 0.85 (95%CI 0.75–0.95; sensitivity = 0.72, specificity = 0.86) that let suggest miR-153 as potential prognostic marker. According to logistic regression model the high expression of miR-153 increased the risk of metastasis development (odds ratios = 3.14, 95% CI 1.62–8.49; p-value = 0.006).

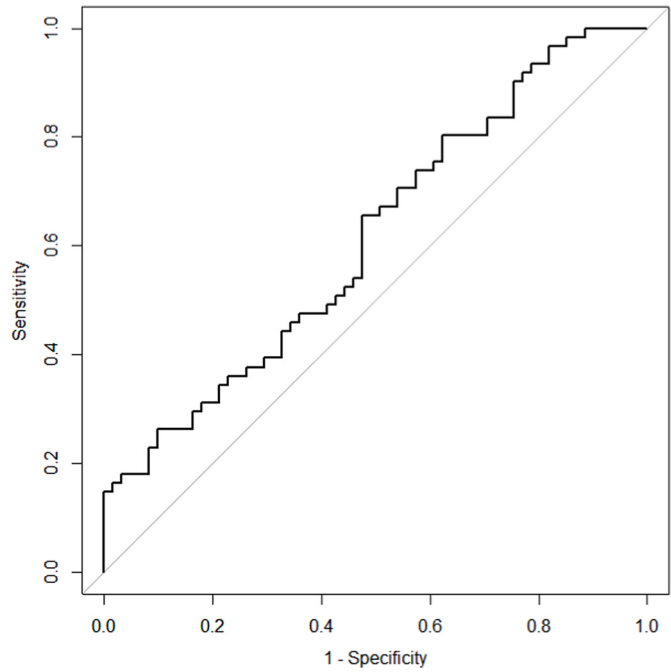


Fig. 5. Receiver operating characteristic (ROC) curve analysis of miR-153 to differentiate between prostate cancer (PC) and normal prostate tissue.

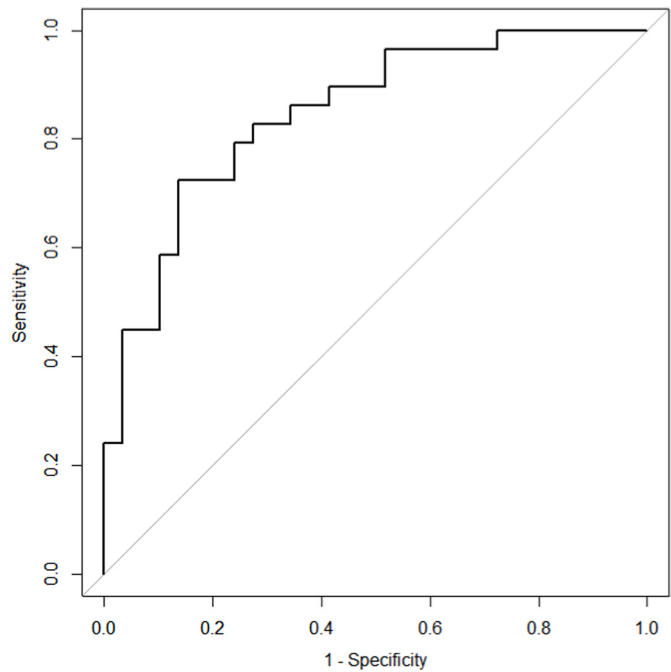


Fig. 6. Receiver operating characteristic (ROC) curve analysis of miR-153 to differentiate between metastatic prostate cancer (PC) and non-metastatic PC.

3.4. Identification of mutations in miR-153 target genes

In order to identify mutations in miR-153 target genes we performed exome sequencing in all patients with metastatic PC. We identified nonsynonymous somatic mutations in genes collagen type IV alpha 1 (COL4A1), collagen type IV alpha 3 (COL4A3), forkhead box protein O1 (FOXO1), 2-hydroxyacyl-CoA lyase 1 (HACL1), hypoxia-inducible factor 1-alpha (HIF-1A), and nidogen 2 (NID2). No pathogenic mutations were revealed in the coding regions of the phosphatase and tensin homolog

Table 2
Pathogenic mutations identified in target genes for miR-153 using exome sequencing.

ID	Gene	Chr	Pos1	Pos2	Ref	Alt	Hom/Het	SIFT_Score	SIFTpred	MutAssessor	MutTast	PolyPhen2	PhyloP
rs115324397	ABI2	chr2	204231743	204231743	A	T	het	0.005	DELETTERIOUS	2.27,0.678,M		-0.525	
	ACTB	chr7	5567477	5567477	A	G	het	0.001	DELETTERIOUS	4.95,0.911,H		2.114	
	AQR	chr15	35166090	35166090	A	G	het	0.002	DELETTERIOUS	3.54,0.789,H		2.115	
	AQR	chr15	35189132	35189132	G	T	het	0.000	DELETTERIOUS	3.94,0.823,H		2.743	
	COL4A1*	chr13	110838875	110838875	C	T	het	0.030	DELETTERIOUS	2.095,0.663,M	1,1,0,D	0.999,D	2.284
rs114015346	COL4A3*	chr2	228110691	228110691	C	A	het	0.010	DELETTERIOUS	2.61,0.708,M	1,000,1,000,D	1,0,D	2.427
	COPB3	chr17	17171261	17171261	C	A	het	0.013	DELETTERIOUS	2.805,0.725,M		2.572	
	CSTF1	chr20	54970669	54970669	C	A	het	0.000	DELETTERIOUS	2.12,0.665,M		2.618	
	EIF3A	chr10	120802249	120802249	C	A	het	0.008	DELETTERIOUS	2.175,0.670,M		2.937	
	EPH3*	chr1	220193423	220193423	T	C	het	0.020	DELETTERIOUS	3.04,0.745,M	1,1,0,D	0.998,D	1.009
rs74637339	FOXO1*	chr13	41134822	41134822	C	T	het	0.006	DELETTERIOUS	2.8,0.724,M	1,1,0,D	1,0,D	2.763
	GSP1	chr16	11980708	11980708	C	G	het	0.001	DELETTERIOUS	2.295,0.681,M		2.584	
	GTPBP4	chr10	1038459	1038459	C	A	het	0.002	DELETTERIOUS	3.535,0.788,H		2.796	
	HACL1*	chr3	15628040	15628040	T	A	het	0.004	DELETTERIOUS	2.085,0.662,M	1,1,0,D	0.998,D	2.225
	HIF1A*	chr14	62187212	62187212	G	C	het	0.008	DELETTERIOUS	2.55,0.703,M	1,000,1,000,D	0.978,D	1.423
rs61755705	ITGA1	chr5	52221259	52221259	C	T	het	0.000	DELETTERIOUS	2.095,0.663,M		2.656	
	ITGAV	chr2	187505680	187505680	C	A	het	0.003	DELETTERIOUS	3.625,0.796,H		2.712	
	LONP2	chr16	48311377	48311377	C	A	het	0.004	DELETTERIOUS	2.64,0.711,M		2.756	
	MCM4*	chr8	48883234	48883234	C	T	het	0.002	DELETTERIOUS	4.54,0.875,H	1,1,0,D	1,0,D	2.906
	NID2*	chr14	52534758	52534758	C	G	het	0.002	DELETTERIOUS	2.325,0.683,M	0.821,0.821,D	1,0,D	1.327
rs140970953	ORC1	chr1	52847394	52847394	G	T	het	0.000	DELETTERIOUS	3.795,0.811,H		2.661	
	PBRM1	chr3	52702546	52702546	G	T	het	0.012	DELETTERIOUS	3.325,0.770,M		1.449	
	SMAD3	chr15	67477139	67477139	C	A	het	0.000	DELETTERIOUS	3.065,0.747,M		2.469	
rs61734508	YTHDC2	chr5	112891819	112891819	A	T	het	0.000	DELETTERIOUS	4.2,0.846,H		0.698	

Note: SIFT: D - disease causing; MutationAssessor: H - high; M - medium; L - low pathogenicity; MutationTaster: D - disease causing, PolyPhen2: D - probably damaging (≥ 0.957); P - possibly damaging ($0.447 \leq \text{PolyPhen2} < 0.909$); PhyloP - the higher is the value, the higher the pathogenicity of the variant; *somatic mutations.

(FOXO4), and forkhead box class O 6 (FOXO6). All FOXO factors are involved in a wide range of biological processes, including cell cycle arrest, apoptosis, DNA repair, glucose metabolism, resistance to oxidative stress and longevity [32]. The biological activity of FOXO factors mainly depends on posttranslational modification of phosphorylation, acetylation or ubiquitination, thereby determining their intracellular transport [33]. Dong et al. demonstrated that FOXO1A inhibits androgen receptor (AR)-mediated gene regulation and cell proliferation in PC [34].

Another found mutation in PC cells, minichromosome maintenance complex component 4 (MCM4), belongs to the minichromosomal maintenance (MCM) protein complex which consists of six highly conserved proteins (MCM2-7) collectively interacting to promote DNA replication and DNA unwinding through replicative helicase activity disinhibition [35]. Cancers arising in different anatomic sites are also associated with minichromosome maintenance complex component 2 (MCM2), MCM4, and minichromosome maintenance complex component 6 (MCM6) overexpression, but there is not much information about the role of MCM4 in PC [35–37]. It is known that PSA may mediate MCM4 to promote the initiation and progression of PC and confirmed that PSA knockdown induce the upregulation of MCM4 [38].

Another important tumor microenvironment component is the hypoxia-inducible factor (HIF) pathway. HIF1A was also mutated in metastatic PC patient. There are some articles devoted to analysis of mutations in HIF1A and their role in PC, although ultimately its role in PC remains unknown [39,40].

KEGG analysis showed that a key signaling pathway in metastatic PC is the extracellular matrix (ECM)-receptor interaction signaling. The ECM is a non-cellular component of the stroma of tumor. ECM represent a complex network of macromolecules which undergo extensive reconstruction during tumor progression. Such remodeling of the extracellular matrix during cancer progression causes changes in its density and composition [41]. Damage to the ECM structure leads to reactive growth of tumor cells due to switching of intracellular signaling processes and cell cycle changes [42]. Proliferation increases, normal tissue architectonics is lost, local migration of tumor cells and invasion into surrounding stromal tissue occurs. One of the main factors determining the degree of tumor malignancy is the process of EMT characterized as loss of epithelial phenotype by epithelial cells and acquisition of mesenchymal phenotype associated with the ability to migrate through basal membrane. ECM is accompanied by loss of cell adhesion molecule E-cadherin, cytokeratins, increased N-cadherin, fibronectin, and vimentin [43]. ECM proteins provide biochemical signals to induce EMT. In turn, EMT becomes an inducer of metastasis, triggering various transcription factors. Thus, transformation plays an important role in tumor progression and metastasis, involving various transcription factors (TFs) and signaling processes [43,44].

5. Conclusions

Our results show that high miR-153 expression is associated with TNM stage increase in PC patients. Several potential PC related genes and pathways were identified in the study, which will improve our understanding of the molecular mechanisms which support prostate cancer progression and development. A key signaling pathway, the ECM-receptor interaction signal pathway, was identified as possibly involved in the development of PC. Further investigations are needed to perform in-depth analysis on gene ontology, browser tracks, and expression levels of miR-153 targets in metastatic PC patients.

Compliance with ethical standards

Ethical approval for this study was obtained from Institute of Biochemistry and Genetics Bioethics Committee. The study was carried out in accordance to Helsinki Declaration and local guidelines.

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Informed consent

All samples investigated in this study were obtained with written informed consents of the participants.

Availability of data and material

All supporting data and materials are available from the corresponding author upon reasonable request.

Author's contribution

Irina Gilyazova: conceptualization, writing—original draft, and project administration. Elizaveta Ivanova: writing—review and editing, investigation. Mikhail Sinelnikov: formal analysis, writing—review and editing, methodology. Ilgiz Gareev: resources and data curation. Aferin Beilerli, Ludmila Mikhaleva, and Yanchao Liang: validation and data curation. Valentin Pavlov and Elza Khushnutdinova: validation and visualization. Valentin Pavlov and Elza Khushnutdinova: supervision and funding acquisition. All authors have read and agreed to the published version of the manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ncrna.2022.10.002>.

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