Science Progress and Research

ISSN: 2635-0955

Review Article

DOI: https://doi.org/10.52152/spr/2021.111

Role of miRNAs in Urological Cancers

Shifali Gupta[1], Suresh Goyal[2*], Malika Arora[3], Deepak Gupta[4]

[1]MD Pediatrics, Senior Resident , Department of pediatrics , GGS Medical college Faridkot
[2]Assistant professor , MCh Urology, GGS Medical College Faridkot
[3]Scientist II, Multidisciplinary Research Unit , GGS Medical College Faridkot
[4]Assistant Professor, Department of Surgery,Adesh Institute of Medical Sciences and Research, Bathinda

***Corresponding author:** Dr Suresh Goyal, Assistant professor, MCh Urology, GGS Medical College Faridkot,*

Submission Date : 12/2/2021, Acceptance Date : 17/3/2021, Published Date : 04/04/2021

ABSTRACT

The robustly unfavourable prognostic effect of miR-21 has been highlighted across three urologic cancers in the primary analysis. However, the effect of miR-21 in BCa fluctuated in the further confirmation demonstrating single miRNA still lacks the stability. miRNA panel contribute to a better risk stratification and prognostic prediction which could compensate for the unreliability of individual miRNAs in estimating prognosis. However, larger studies with a standardized methodology that assess both single and multiple miRNAs will offer better insight into the prognostic value of miRNAs in urologic cancer.

Keyword: miRNA, Urological Cancers, Prognosis, Biomarker

INTRODUCTION

microRNAs (miRNAs) are small non-coding RNAs (ncRNAs) with approximately 20 nucleotides (nt) length that regulate gene expression post transcriptionally. They bind to 3' untranslated regions of gene or 5' untranslated region of mRNA to regulate gene expression either by mRNA destruction or inhibition of mRNA translation. miRNA were identified in 1993 and knowledge has been growing since then. miRNA has been extensively studied in various disease pathogenesis over the past 3 decades and they are potential candidates for novel therapies in future. It is estimated that microRNAs regulate approximately 30 % of the human protein coding genome. miRNA controls the expression of genes involved in several biological processes, including apoptosis, proliferation, differentiation and metastasis. (diagram) miRNAs are encoded in the genome as long primary transcripts (named pri -miRNAs)

that contain a cap structure at the 5' end and are poly-adenylated at the 3' end. Pri-miRNAs are processed by the cellular RNaseII endonuclease III Drosha, together with DGCR8/Pasha proteins, into a structure of 60-110 nt, called precursor-miRNA (pre-miRNA), which is then exported from the nucleus to the cytoplasm by an Exportin-5 dependent mechanism. In the cytoplasm, the pre-miRNA is cleft by the RNaseIII enzyme Dicer-1, together with TRBP/PACT proteins, producing a short imperfect double-stranded miRNA duplex. This duplex is then unwound by an helicase into a mature miRNA with approximately 20 nt length, which is then incorporate in a multicomponent complex constituted by Argonaute family protein members known as RISC. [(1)]

miRNAs' main function is to inhibit protein synthesis of protein-coding genes, either by inhibition of translation or mRNA degradation. However, the relative contribution of each mechanism to repression was unknown until recently. Besides mRNAs repression, miRNAs have been also reported to activate translation of targeted mRNAs. [(2)]

A recent report showed that miRNA could regulate gene translation in a "seed" sequence-independent manner. [(3)] Various modes of action for miRNA revealed that the miRNA has diverse functions in cell biology and disease. Dysregulation of these mechanisms have been implicated in a variety of human diseases including urological malignancies. The last two decades have distinguishably been regarded as the decades of miRNA research to explore possible weapons against various cancers. Apart from diagnostic and prognostic roles, miRNA's are being explored as potential therapeutic targets in various cancers. In this review, we highlight recent advances in the applications of small RNA as therapeutics for urological cancer.

miRNA in Prostate Cancer:

Prostate cancer (PCa) is the most common non-skin cancer in men worldwide, resulting in significant mortality and morbidity. [(4)] Depending on the grade and stage of the cancer, patients may be given radiation therapy, hormonal therapy, or chemotherapy. Prostate cancer occurrence and mortality are up to 20-fold higher in industrialized countries with respect to developing ones, thus for this purpose diet and lifestyle have been proposed as factors causing this discrepancy. Nutrition and exercise modify serum factors that slow down the growth and induce apoptosis in androgen-dependent PCa cells, while high levels of body mass index, blood pressure and several metabolic factors were correlated with high risk of prostate cancer death. Serum PSA levels and digital rectal examination are the mainstay of diagnosis . but these have low sensitivity and specificity. Serum Prostate specific antigen levels (PSA) can be elevated in non malignant states also such as benign prostatic hyperplasia, acute prostatitis, prostatic massage during digital rectal examination, urinary catheterization, certain drugs etc. Digital Rectal examination has interobserver bias, and is subjective modality. These factors necessitate invasive modalities such as prostatic biopsy for diagnosis. There is a need of better non invasive markers for diagnosis, treatment and prognosis of prostate cancer. miRNA have been explored and are upcoming markers in relation to recent advances.

Figure 1 : Mode of Action of mi RNA

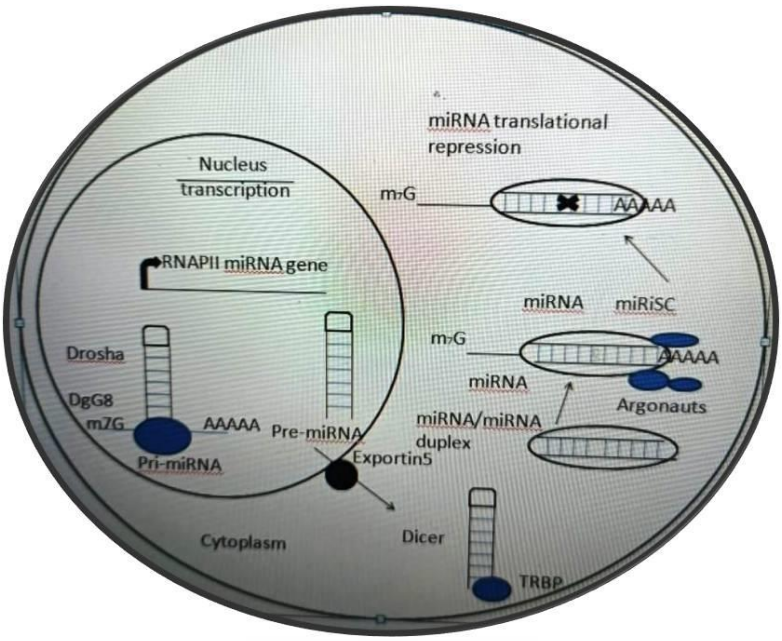

Table 1 miRNA in Prostate Cancer

Biomarker	Role in Prostate Cancer	
miR-21-5p, miR-141-3p, miR-375, and miR-574-3p	oncogenic miRNAs promoting proliferation of PCa cells, upregulated	Paiva et al. [5]
miR-205	Up and down regulation	Paiva et al. [5]
miR-203	attenuated in bone metastatic PCa	Saini et al. [6]
miR-16, miR-23, miR-99, miR-125, miR-29, and miR-30	Downregulated	Won et al. [7]
miR-32, miR-26a, miR-196a, miR-181a, miR-25, miR-93, miR-92, and let-7i	Upregulated	Fabris et al. [8]
miR-212,miR-185,miR-146a,miR-15a-16 cluster, miR-200c, miR-128	Downregulated	Razdan et al. [9]
miR-616,miR-221/222 cluster	Upregulated	Razdan et al. [9]

miRNA in Bladder Cancer

Bladder cancer is the second most common malignant tumor of the genitourinary tract and it affects >2 million patients worldwide. It was predicted that the incidence of bladder cancer may significantly increase in the near future due to an increasing exposure to risk factors and an aging population. [10] Its symptoms are nonspecific and include hematuria, discomfort during urination, and higher frequency and urgency of urination Treatment outcomes of patients with non-

metastatic bladder cancer are generally satisfactory. However, the survival of patients with metastatic bladder cancer remains poor. At present, early diagnosis and treatment are crucial for a positive prognosis. As metastatic bladder cancer has poor outcome and prognosis, early identification of this malignancy with the help of potential urinary microRNA (miRNA) and protein biomarkers is highly required

Table 2: miRNAs in Bladder Cancer

Biomarker	Levels	Inference	Reference
MicroRNA-34a	downregulated	Diagnostic value, levels are lower in bladder cancer as compared to health controls	Ding et al. [11]
miR-452, miR-452, miR-21, miR-210, miR-222, miR-9, miR-182, miR-143, miR-133b, miR-518c*, miR-129, miR-155, miR-145, and miR-152	upregulated	High levels Associated with poor prognosis	Ding et al. [11]
miR-100, miR-387, miR-31, miR-141, miR-205, miR-101, miR-26a, miR-203, miR-424, miR-214, miR-29c, miR-27a, miR-27b, miR-203, and miR-34a	downregulated	Low levels associated with poor prognosis	Xie et al. [12]
miR-139-5p and miR-143-5p	downregulated	Diagnostic and prognostic value	Braicu et al. [13]
miR-141b, miR-200 s or miR-205	upregulated	Diagnostic and prognostic value	Braicu et al. [13]
hsa-let-7c, mir-143, mir-944, mir-192, mir-590, mir-490, mir-141, mir-93, mir-1-2, mir-200c, mir-133a-1, mir-1-1, mir-133b, mir-20a, mir-185, mir-19a, mir-19b-2, mir-19b-1, mir-17, mir-15a, and mir-133a-2	related to proliferation, invasion, metastasis differentiation, epithelial-to-mesenchymal transition (EMT) and angiogenesis of tumors.	Signature miRNA for prognosis of bladder cancer	Yin et al. [14]
let-7c, miR-100, and miR-145	Helps in scoring of patient and provide insight into targeted immunotherapy	Prognostic marker for muscle invasive bladder cancer	Feng et al. [15]

miRNA in Renal Cancer

Renal cancer is one of the most lethal urological cancers.[16] In the past, patients with renal cell carcinoma (RCC) were usually presented at an advanced stage with renal mass, pain and/or hematuria. With the widespread availability of imaging, RCC is diagnosed incidentally during evaluation of another disease. These cancers are radio and chemo-resistant. The surgery is the only curative modality available in the management of RCC. Localised and locally advanced RCC, if treated by radical surgery, has

good prognosis. The metastatic RCC has a very poor prognosis.[17] The discovery of miRNAs in RCC can pave the way for early diagnosis, treatment and prognosis of the advanced and metastatic disease.

Table 3 miRNA in Renal Cancer

Biomarker	Levels in Renal Cancer	Remarks	
miR-27, -28, -185, let-7f-2)	Over expressed	As compared to healthy controls	Gottardo et al. [18]
microRNA-141 and microRNA -200c	downregulated		Nakada et al. [19]
miR-21	overexpressed	differentiation between ccRCC, pRCC, chRCC and oncocytoma	Faragalla et al. [20]
miR-210 and miR-378	Over expressed	Diminish after radical surgery	Fedorko et al. [21]
miRNA-15a in the urine	upregulated	Normal in benign disease and healthy controls	Mytsyk et al. (22)
Serum microRNA-183	upregulated	Poor responsiveness to NK cells	Zhang et al. [23]
microRNA-124-3	higher relative methylation	Higher chances of recurrence of RCC	Gebauer et al. [24]
miR-203	Downregulated	Low miR-203 expression in ccRCC specimens was associated with advanced clinical features and poorer prognosis , mir203 potentiators via FGF2 may have targeted immunotherapy treatment options.	Xu et al. [25]

CONCLUSION

With the advances in molecular biology, efforts are being made to identify sensitive and specific miRNAs for early diagnosis, treatment and prognosis of various urological malignancies. This research can pave the way for improved lifespan and Quality of life of the patients with cancer.

REFERENCES

1. Siomi H, Siomi MC. Posttranscriptional regulation of microRNA biogenesis in animals. Mol Cell 2010;38(3):323-32.
2. Fabian MR, Sonenberg N, Filipowicz W. Regulation of mRNA translation and stability by microRNAs. Annu Rev Biochem 2010;79:351-79.
3. Santos AS, Cunha Neto E, Fukui RT, Ferreira LRP, Silva MER. Increased Expression of Circulating microRNA 101-3p in Type 1 Diabetes Patients: New Insights Into miRNA-Regulated Pathophysiological Pathways for Type 1 Diabetes. Front Immunol 2019;23;10:1637.
4. Rawla P. Epidemiology of Prostate Cancer. World J Oncol 2019;10(2):63-89.
5. Paiva RM, Zauli DAG, Neto, BS. et al. Urinary microRNAs expression in prostate cancer diagnosis: a systematic review. Clin Transl Oncol 2020;22:2061–2073.

6. Saini S, Majid S, Yamamura S, Tabatabai L, Suh SO, Shahryari V, Chen Y, Deng G, Tanaka Y, Dahiya R. Regulatory Role of mir-203 in Prostate Cancer Progression and Metastasis. Clin Cancer Res 2011;17(16):5287-98.
7. Kim WT, Kim W. MicroRNAs in prostate cancer. Prostate International, Volume 2013;1(1): 3-9
8. Fabris L, Ceder Y, Chinnaiyan AM, Jenster GW, Sorensen KD, Tomlins S, Visakorpi T, Calin GA. The Potential of MicroRNAs as Prostate Cancer Biomarkers. Eur Urol 2016;70(2):312-22.
9. Razdan A, de Souza P, Roberts TL. Role of MicroRNAs in Treatment Response in Prostate Cancer. Curr Cancer Drug Targets. 2018;18(10):929-944. doi:10.2174/1568009618666180315160125
10. Ploeg M, Aben KK, Kiemeney LA.The present and future burden of urinary bladder cancer in the world. World J Urol. 2009;27:289–293.
11. Ding Z, He Y, Deng Y, Peng P, Wang J, Chen X, Zhao P and Zhou X: MicroRNA-34a inhibits bladder cancer cell migration and invasion, and upregulates PTEN expression. Oncol Lett 18:5549-5554, 2019.
12. Xie Y, Ma X, Chen L, Li H, Gu L, Gao Y, Zhang Y, Li X, Fan Y, Chen J, Zhang X. MicroRNAs with prognostic significance in bladder cancer: a systematic review and meta-analysis. Sci Rep 2017;17;7(1):5619.
13. Braicu C, Buiga R. Cojocneanu, R. et al. Connecting the dots between different networks: miRNAs associated with bladder cancer risk and progression. J Exp Clin Cancer Res 2019;38,433.
14. Yin XH, Jin YH, Cao Y, Wong Y, Weng H, Sun C, Deng JH, Zeng XT. Development of a 21-miRNA Signature Associated With the Prognosis of Patients With Bladder Cancer. Front Oncol 2019;7;9:729.
15. Feng Y, Feng Q, Xu L, Jiang Y, Meng F, Shu X. A Novel Biomarker Based on miRNA to Predict the Prognosis of Muscle-Invasive Bladder Urothelial Carcinoma. J Oncol 2019;6:2019:2654296.
16. Rossi, S.H., Klatte, T., Usher-Smith, J. et al. Epidemiology and screening for renal cancer. World J Urol 2018; 36, 1341–1353.
17. American Cancer Society: Cancer Facts and Figures 2021. Atlanta, Ga: American Cancer Society, 2021. Available onlineExit Disclaimer. Last accessed January 12, 2021.
18. Gottardo F, Liu CG, Ferracin M, Calin GA, Fassan M, Bassi P, Sevignani C, Byrne D, Negrini M, Pagano F, Gomella LG, Croce CM, Baffa R. Micro-RNA profiling in kidney and bladder cancers. Urol Oncol 2007;25(5):387-92.
19. Nakada C, Matsuura K, Tsukamoto Y, Tanigawa M, Yoshimoto T, Narimatsu T, Nguyen LT, Hijiya N, Uchida T, Sato F, Mimata H, Seto M, Moriyama M. Genome-wide microRNA expression profiling in renal cell carcinoma: significant down-regulation of miR-141 and miR-200c. J Pathol 2008;216(4):418-27.
20. Faragalla H, Youssef YM, Scorilas A, Khalil B, White NM, Mejia-Guerrero S, Khella H, Jewett MA, Evans A, Lichner Z, Bjarnason G, Sugar L, Attalah MI, Yousef GM. The clinical utility of miR-21 as a diagnostic and prognostic marker for renal cell carcinoma. J Mol Diagn 2012;14(4):385-92.
21. Fedorko M, Stanik M, Iliev R, Redova-Lojova M, Machackova T, Svoboda M, Pacik D, Dolezel J, Slaby O. Combination of MiR-378 and MiR-210 Serum Levels Enables Sensitive Detection of Renal Cell Carcinoma. Int J Mol Sci 2015;29; 16(10):23382-9.
22. Mytsyk Yu, Dosenko V, Borys Yu, et al. The Possibility of Application of Detected in Urine MicroRNA-15a for Diagnostics of Renal Cell Carcinoma. Exp Clin Physiol Biochem 2017;1:49–53.
23. Zhang Q, Di W, Dong Y, Lu G, Yu J, Li J, Li P. High serum miR-183 level is associated with poor responsiveness of renal cancer to natural killer cells. Tumour Biol 2015; 36(12):9245-9.
24. Gebauer K, Peters I, Dubrowinskaja N, et al. Hsa-Mir-124-3 CpG Island Methylation Is Associated with Advanced Tumours and Disease Recurrence of Patients with Clear Cell Renal Cell Carcinoma. B J Cancer 2013;108:131–138.

25. Xu M, Gu M, Zhang K, Zhou J, Wang Z, Da J. miR-203 inhibition of renal cancer cell proliferation, migration and invasion by targeting of FGF2. Diagn Pathol 2015;9:10:24.