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Editorial

MicroRNAs an evolving prognostic, diagnostic and therapeutic target in prostate cancer

Dr. Shashank Kumar
Research Associate
Department of Biochemistry
King Georges Medical University
Lucknow, 226003
India

Shashank Kumar, PhD is perusing Post Doctoral work at Department of Biochemistry, King George's Medical University, Lucknow, India. He has expertise in areas of Free radical biology, Cancer biology, Characterization of plant products, Xenobiotic metabolism, and Microbiology. Dr. Kumar is familiar with many biochemical techniques such as Spectrophotometry, ELISA, Electrophoresis, PCR, RT-PCR, Flow Cytometry, TLC, HPLC, LC-MS, Cell culture and Microbiological techniques. He has presented his research findings in more than 30 National/International Conferences and attended about 35 Workshop at the majority of major Universities and Medical Colleges throughout the India. Recent publications include the first time reporting of hepatoprotective and oxidative stress mitigative (in vitro and in vivo) effects of E. crassipes leaf extracts as well as Cell cycle inhibitory and hepato-protective activity of Piper longum. Dr. Kumar is life time member of Italo-Latin American Society of Ethnomedicine; Indian Sciences Congress Association, India; Indian Academy of Biomedical Sciences Society, India; Member of Publication Integrity & Ethics, London; and Asian Council of Science Editors, Dubai, UAE. Dr. Kumar has been awarded Indian Council of Medical Research Senior/Research Associate, Rajiv Gandhi National Junior/Senior Research Fellowships formulated and funded by Ministry of Social Justice & Empowerment and Ministry of Tribal Affairs, and ICMR India respectively. Dr. Kumar did B.Sc. M.Sc. and PhD Biochemistry (2005-2014) from Department of Biochemistry, University of Allahabad, Allahabad, India.

MicroRNAs (miRNAs) are recently discovered class of endogenous non-coding single stranded (15–22 nucleotide long) RNAs. They have evolutionarily conserved sequences that regulate post-transcriptional gene expression by virtue of their base pairing property to complementary sequences in the 3' untranslated region (3' UTR) of target mRNAs. These modulator RNAs play vital role in cell fate as are involved in maintenance of cell homeostasis [1]. They are involved in the regulation of almost every biological pathway. Literature showed that their expression pattern is associated with several human disorders/diseases including cancer. They have ability to modulate key cellular processes by targeting tumor suppressors and oncogenes. This makes miRNAs to highly promising therapeutic targets as they have capability to define the cell phenotype by virtue of their ability to target above mentioned genes. Discoveries all around the world regarding miRNA is continuously substantiating knowledge about their role in cancer pathology and there mechanism of regulation [1]. Antagonists and mimics are the two approaches to developing miRNA based therapies which depends on miRNA function and its status in the diseased tissue. miRNA antagonists are produced to inhibit miRNAs that are involved as a gain of function in human disease. Their development includes the disease related miRNA identification and thereafter synthesis of a novel molecule having specific and inhibitory activity [2]. To ablate particular miRNA function, mostly chemically modified single stranded oligonucleotides used to pair with miRNA

complementary sequences. The modified backbone has increase affinity toward the endogenous miRNA and thereby sequesters it in a configuration that is unable to be processed by RISC (RNA Induced Silencing Complex). Anti-miRs, antagomiRs and locked nucleic acids are some examples of miRNA antagonists. On the other hand miRNAs having loss of function may be restored by using miRNA replacement therapy also known as miRNA mimics. Now days these are center of interest because they provide new therapeutic opportunity to exploit tumor suppressors [2].

Among cancer related death prostate cancer (PCa) is the second leading cause in American men. It is the most commonly diagnosed cancer in developed countries men. For the normal growth and functioning of prostate gland a hormone known as androgen is required. The interaction between hormone and its receptor (androgen receptor AR) triggers activation of different genes at transcriptional level. These gene products are essential for the growth and survival of prostate epithelial cells. In androgen deprivation therapy (ADT) which steroidal or non-steroidal inhibitors such as, cyproterone acetate, casodex or hydroxyl flutamide have been used and become the basis for advanced PCa [3]. However, prolonged androgen blockade leads to activation of various adaptive mechanisms after initial retardation of cell proliferation. ADT can accumulate mutations causing AR to become sensitive to androgen antagonists, which then act as agonists. Literature revealed that aberrant expression of miRNAs occurs in PCa during different stages of disease progression [3]. Several miRNAs, such as miR-21, miR-32 and miR-125 are directly regulated by androgens in cells and xenograft models [3]. In PCa several studies on miRNA gene expression were conducted taking different aspects in mind including that it may lead to the development of resistant PCa. However there was lack of satisfactory information regarding how androgen-sensitive prostate cancer cells changes into antiandrogen resistant cells. Inactivation of $p57^{Kip2}$ (a cyclin-dependent kinase inhibitor) is commonly observed in cancers however its mechanism has not been well studied in prostate cancer. Recently it has been reported that miR-21 is able to down regulate $p57^{Kip2}$ expression by targeting the coding region of the gene and thereby attenuate $p57^{Kip2}$ mediated functional responses. This demonstrates that $p57^{Kip2}$ is a novel target of miR-21 in PCa and reveals a novel oncogenic function of the miRNA [4]. In another study the intratumoral injection of lentivirally coded miR-15-16 led to growth arrest and considerable volume regression in xenograft prostate cancer mice model [1]. Studies showed that in response to vitamin D, tumor suppressive miR-98 is transcriptionally induced in PCa cell lines. This involves the enhanced VDR binding response element in the promoter region of miR-98 and down regulation of LIN-28 expression. Thus it may be hypothesized that the growth inhibitive miR-98 may be a potential therapeutic target for PCa [5].

As the standard PSA screening in the early diagnosis of human PCa remains a very controversial issue, novel, reliable molecular prostate cancer markers are needed. A promising marker candidate gene is the miRNA *let-7*, which was reported to be down regulated among others in human PCa. Further, the reconstitution of the *let-7* expression resulted in suppression of PCa cell proliferation. *let-7* was the second miRNA discovered and its expression has been associated with a variety of human diseases including cancer. Inflammatory microenvironment and epithelial to mesenchymal transition seems to play a substantial role in cancer etiology [6].

Literature reveals that the *let-7* miRNA together with IL6 and NFκB are actively involved in the epigenetic transition from inflammation to cell transformation. The *let-7* family miRNA negatively regulate *IL6*, *NRAS*, *c-Myc*, *HMGA1*, *HMGA2*, and *CCND2* genes. Some of these *let-7* family targets have been found to be implicated in PCa. Androgen receptor is the member of steroid receptor family and is expressed in nearly all primary human PCa. It plays a pivotal role in carcinogenesis of the prostate. Continuous androgen expression is required to maintain the normal function and glandular anatomy in adults. One of the important bypass mechanisms of *AR* up regulation is HMGB1 enrichment on the *AR* promoter resulting into its enhanced transcription. The activated AR stimulates the expression of VEGF and PSA. Out of which PSA is used as biomarker for human PCa progression. PSA constitutes a positive feedback loop stimulating *AR* expression. Lin28 is known to activate AR and thereby promote the growth of PCa. On the other hand miRNA *let-7c* negatively regulates the *AR* by suppressing its transcriptional activator c-Myc [6]. Besides several of the reviewed genes the master regulator family miRNA *let-7* is as well a promising target in PCa. Thus after deeper understanding of the molecular interactions of miRNA *let-7* with its associated genes will significantly contribute to the development of novel prognostic, diagnostic and therapeutic modalities for prostate cancer.

REFERENCES

1. Pedro M et al. MicroRNAs as Molecular Targets for Cancer Therapy: On the Modulation of MicroRNA Expression. Pharmaceut 2013; 6: 1195-1220.
2. Bader AG. Developing therapeutic microRNAs for cancer. Gene Ther. 2011; 18:1121-1126.
3. Ottman et al. MicroRNA expressions associated with progression of prostate cancer cells to antiandrogen therapy resistance. Mol Cancer. 2014; 13:1.
4. Feng Li, Mahato RI. MicroRNAs and Drug Resistance in Prostate Cancers. Mol Pharmaceutics. 2014; 11: 2539–2552.
5. Ting H et al. Identification of microRNA-98 as a Therapeutic Target Inhibiting Prostate Cancer Growth and a Biomarker Induced by Vitamin D. The J Biol Chem. 2013; 288: 1-9.
6. Wagner S. Role of mirna Let-7 and its major targets in prostate cancer. 2014; 2014: Article ID 376326.