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Chapter 4

Role of miR-2909 in Prostate Carcinogenesis

Shiekh Gazalla Ayub

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Abstract

The biggest challenge in prostate cancer treatment is to understand the signaling mechanisms controlling disease progression. In this context, microRNAs assume huge importance and have recently become an attractive area of research. MicroRNAs are naturally occurring, single-stranded, small non-coding RNAs of 19–25 nucleotides that regulate gene expression. MicroRNAs function as oncogenes or tumor-suppressor genes, and their deregulation is a common feature of human cancers including prostate cancer. Among deregulated microRNAs in prostate cancer, some microRNAs are directly under androgen receptor signaling control and function as the effectors of androgen signaling. Recent findings have shown that apoptosis antagonizing transcription factor (AATF) gene encodes a microRNA designated as miR-2909 that plays an important role in prostate cancer progression. miR-2909 is identified as an androgen-regulated microRNA acting as a novel effector of androgen/androgen receptor signaling. It enhances the proliferation potential of prostate cancer cells and assists in prostate cancer survival under reduced androgen levels by maintaining a positive feedback loop with AR. miR-2909 exerts its oncogenic effects via multiple mechanisms including attenuation of tumor-suppressive effects of TGFβ signaling by directly targeting TGFBR2 and via STAT1 pathway and upregulation of ISGylation pathway through SOCS3/STAT1 pathway.

Keywords: prostate cancer, hormone-sensitive, castration-resistant, androgen receptor, TGFβ, TGFBR2, ISG15, SOCS3, STAT1

1. Introduction

Cancer is one of the leading causes of deaths at the global level accounting for 8.2 million deaths in 2012 [1]. Among males, prostate gland is one of the five leading sites of cancer accounting for approximately 15% of cancers in men, and the incidence is expected to rise steeply by around 19% in the coming years [2, 3]. Prostate cancer (PCa) causes substantial

clinical, social and economical burden in both the developing and developed world. The prostate specific antigen (PSA), a protein mainly secreted by prostate cells, is a blood-based marker routinely used for early-stage PCa detection as well as to monitor recurrence of PCa after initial treatment [4]. Even though PSA is a valuable tool, it lacks specificity and is therefore not considered an optimal biomarker [5]. Thus, additional novel biomarkers are needed which can help to predict the exact level of disease aggressiveness, assist in clinical decision about the choice of treatment and aid in establishing more persuasive treatment for the advanced PCa. Prostate tumors are reported to display novel recurrent chromosomal translocations and aberrant expressions of certain microRNAs (miRNAs) which can be helpful for elucidating PCa biology and explored for better disease management [6]. Identification of dysregulated genes or miRNAs in PCa cannot only be promising in terms of diagnostics and therapeutics but can provide clues relevant to disease etiology and progression. miRNAs are small noncoding RNAs that finely regulate gene expression in cells. Alterations in miRNA expression have been reported to be associated with PCa development and are currently being thoroughly investigated as PCa biomarkers. Several miRNAs showing high expression levels in PCa tissues are reported as suitable diagnostic or prognostic markers [6]. Among deregulated miRNAs in PCa, some miRNAs are directly under androgen receptor (AR) signaling control and function as the effectors of androgen signaling [6]. Recent findings have shown apoptosis antagonizing transcription factor (AATF) gene encodes a miRNA designated as miR-2909 that plays an important role in immunity and cancer progression [7, 8]. AATF is known as co-activator of AR through its interaction via LXXLL motifs and therefore enhances the AR mediated transcription. AR signaling has a critical role in the development of normal prostate by triggering various events that promote epithelial cell growth, arrest and differentiation [9]. However, this pathway is modified/deregulated to promote cell survival and proliferation in PCa [10]. Keeping in view the critical role played by AR signaling in normal prostate and PCa development, human AATF genome, that holds AATF gene and its encoded miR-2909 within its fold, assumes huge importance. Exploring its role in PCa, miR-2909 was identified as an androgen-regulated miRNA acting as a novel mediator of androgen/androgen receptor signaling and exerting its oncogenic effects through multiple pathways. This chapter addresses the role played by miR-2909 in the progression of PCa and the potential signaling pathways through which it operates. The purpose of this chapter is mainly to bring into limelight the role played by one of the less known miRNAs to the readers which when combined with another set of miRNAs or specifically AR-regulated miRNAs could be exploited for therapeutic and diagnostic purposes, though further studies are demanded to obtain more definite conclusions.

2. Prostate gland structure and PCa types

Prostate is a compound tubuloalveolar exocrine gland that plays a vital role in the reproductive process by secreting a part of the seminal fluid. The average size of the prostate is about a size of a large walnut that is located close to the rectum, below the bladder at the base of the penis. The prostatic epithelium is composed of two major cell types: stromal cells and epithelial cells.

There are five types of cells present in prostate epithelium including stem cells, basal epithelial cells, transit-amplifying cells, neuroendocrine cells and secretory epithelial cells.

The stromal compartment, which normally serves as structural support, mainly consists of connective tissue, smooth muscle cells and fibroblasts. The gland can be divided into three glandular zones: the transition zone (TZ), the central zone (CZ) and the peripheral zone (PZ). The TZ consists of two lobes, accounting for 5% prostatic volume, whereas CZ is located outside the TZ and accounts for about 25% prostatic volume. Outside the CZ is the PZ which constitutes about 70% of the total prostatic volume. Most of the benign hyperplasias and 10–20% tumors arise in TZ whereas 70–75% of the prostate tumors arise in PZ. Acinar prostate carcinoma is the most common histological form whereas other subtypes only account for 5–10% of histological forms and include ductal adenocarcinoma, atrophic carcinoma, pseudo-hyperplastic carcinoma, foamy gland carcinoma, mucinous carcinoma, signet-ring carcinoma, small cell carcinoma, sarcomatoid carcinoma, urothelial carcinoma and squamous cell carcinoma.

3. MiRNAs

miRNAs are naturally occurring 18–24 nucleotides-long non-coding RNA molecules that regulate the expression of a large number of genes posttranscriptionally either through mRNA degradation or inhibition of translation [11]. miRNAs play an important role in a wide range of biological processes including cell proliferation, differentiation, development and apoptosis [12]. To date, approximately 2000 human miRNAs have been discovered and believed to regulate about 30% of human genes. miRNAs are known to regulate genes through three different mechanisms including triggering an endonucleolytic cleavage of mRNA, promoting translational repression or through accelerating the deadenylation of mRNA [11]. The endonucleolytic cleavage of target mRNAs is usually possible if the miRNA sequence is completely complementary to the target mRNA sequence although some mismatches could occur. However, translational repression occurs if there is a non-perfect match between the two sequences. Nucleotides 2–7 from the 5' end of the miRNA, called seed sequence, are essential to the binding of the miRNA to the target mRNA perfectly and all the other nucleotides of the miRNA can bind imperfectly. Though majority of data has focused on miRNAs that act via canonical pathway, there are no mechanistic requirements that restrict miRNA action to only 3'untranslated region (UTR). miRNAs have also been reported to regulate mRNA expression by targeting 5'UTR and open reading frame (ORF) binding sites. Moreover, various studies have reported miRNAs that directly bind to DNA and influence gene expression and some miRNAs are reported to even activate, rather than inhibit gene expression [13]. Altogether, these findings highlight the complexity of gene regulation by the miRNAs.

Lot of miRNAs are located in distinct regions far from protein-coding genes and expressed independently from their own promoters. However, 40% of miRNAs are located in introns of protein-coding genes and are under the control of same promoter and co-expressed with the host gene. Likewise, various miRNAs are located close to each other within 10 kb in the form of clusters. miRNAs are normally transcribed as monocistronic by polymerase II whereas

clustered miRNAs are transcribed as polycistronic RNAs. The transcribed sequences are a few hundred to a few thousand nucleotides in length and are termed as preliminary miRNAs (pri-miRNAs). Pri-miRNAs harbor a polyadenyl-tail and have a 5'7-methylguanylate cap (95) at the 5' end. The pri-miRNA synthesized is cleaved by the nuclear microprocessor complex formed by Drosha, a member of the RNase III family of enzymes, and the DiGeorge 21 critical region 8 proteins. If the seed sequence of miRNA and its target mRNA are highly complementary, mRNA degradation is induced via the RNAse III catalytic domain of the AGO proteins, which is followed by the degradation by exonuclease XRN1, the exosome and SKI complex. If the miRNA and mRNA are partially complementary, mRNA degradation is followed through different pathways. The poly(A) tail of the mRNA is deadenylated followed by degradation of the mRNA from the 3' end by the cytoplasmic exonucleases degradation mechanism or by removal of 5'cap via decapping complex proteins (DCP1 and DCP2) and CAF1-CCR4-NOT complexes and then degradation of the mRNA by XRN1 from 5' to 3' end [11].

4. MiRNAs in PCa

As miRNAs have been associated with various important physiological processes like development, differentiation, apoptosis and cell cycle regulation, thus aberrant miRNA expression can result in various pathological states, including cancer [14]. Various studies have shown that different miRNAs and their targets are aberrantly expressed in neoplastic PCa tissues compared to the normal ones, providing a significant insight into altered cellular growth, invasion and metastatic potential of PCa cells [6, 15]. These miRNAs appear to have important and unique roles with respect to apoptosis resistance, cell proliferation, epithelial-to-mesenchymal transition, invasion, metastasis and development of androgen independence. These differentially expressed miRNAs function as either oncogenes or tumor suppressor genes with oncogenic being upregulated and tumor suppressors being downregulated. Various miRNA expression profiling analytical studies have shown many miRNAs downregulated in PCa wherein their elevated levels are indicators of good prognosis [6, 15]. On the contrary, other miRNAs are promoters of carcinogenesis and their expression levels are elevated in advanced stages of some cancers, which clearly suggests these miRNAs as attractive targets for therapy [6, 15]. Although a good number of miRNAs are reported as being differentially expressed in PCa, which in turn leads to altered expression and activity of their targets, the understanding of the functional importance of only several miRNAs has been molecularly exploited. Such studies have established an intimate relationship between PCa and miRNAs with emerging data clearly suggesting miRNAs a very promising field in terms of therapeutics, although further in-depth mechanistic studies and a better understanding of the key events are desired.

5. miR-2909

miR-2909, previously known as Che-1 and encoded by AATF gene, is known to regulate crucial genes involved in host immunity, energy metabolism and oncogenic/oncostatic activities

[8, 16]. AATF/Che-1 genome has emerged like a master epigenetic switch shown to regulate cell cycle progression, checkpoint control and apoptosis [17]. A new dimension was added to AATF Genome by a finding that AATF acts as co-activator of AR through its interaction via LXXLL motifs and thus enhances the AR mediated transcription. AR signaling has a critical role in the development of normal prostate by triggering various events that promote epithelial cell growth, arrest and differentiation [9]. However, this pathway is modified/deregulated to promote cell survival and proliferation in PCa [10]. Keeping in view the critical role played by AR signaling in normal prostate and PCa development, human AATF genome, holding AATF gene and its encoded miR-2909 within its fold, assumes huge importance. Further, various studies focused to explore the role of miR-2909 in PCa were conducted and the potential signaling pathways through which miR-2909 operates were explored. A new dimensional role was added to miR-2909 by various studies that revealed miR-2909 as an androgen-regulated miRNA acting as a novel mediator of androgen/androgen receptor (AR) signaling. miR-2909 enhanced the proliferation potential of PCa cells and assisted in PCa survival under reduced androgen levels by maintaining a positive feedback loop with AR. Further, miR-2909 was shown to exert it oncogenic effects by attenuating the tumor-suppressive effects of transforming growth factor beta (TGFβ) signaling by directly targeting transforming growth factor beta receptor 2 (TGFBR2) and via signal transducer and activator of transcription 1 (STAT1) pathway and by upregulating ISGylation pathway through SOCS3/STAT1 pathway.

6. miR-2909 and AR signaling

AR signaling plays a critical role in the development of normal prostate [9]. However, this pathway is deregulated to promote cancer development and progression in PCa patients. miR-2909 is identified as an androgen-induced miRNA that functions as a novel mediator of androgen/androgen receptor signaling. Comparison of AR negative, PC3 and AR positive LNCaP PCa cell lines has shown a three-fold higher expression of miR-2909 in LNCaP cell line. Further, androgens were observed to induce an enhanced expression of miR-2909 and androgen-deprivation downregulated miR-2909 expression in androgen-dependent LNCaP cells. Moreover, the expression level of miR-2909 also increased proportionately when LNCaP cells were treated with different concentrations of DHT ranging from 0.1–15 nM. Moreover, this androgen-mediated regulation of miR-2909 was executed through AR signaling. To rule out any cross-activation of Estrogen receptor-b (ERb) signaling, it was further shown that DHT induced miR-2909 expression was significantly blocked in the presence of AR antagonists, strongly indicating the involvement of AR in androgen-mediated regulation of miR-2909 expression. It was further suggested that a positive feedback loop operates between AR and miR-2909 in prostate cells (**Figure 1**). Ectopic expression of miR-2909 in AR-positive LNCaP cells resulted in significant upregulation and inhibition of endogenous miR-2909 significantly reduced the AR and PSA expression. It is a well-established fact that the expression of AR increases in prostate tumor cells. It could therefore be speculated that the positive feedback loop between AR and miR-2909 in prostate tumors could help to maintain a steady level of AR in the absence of androgens for further progression and development.

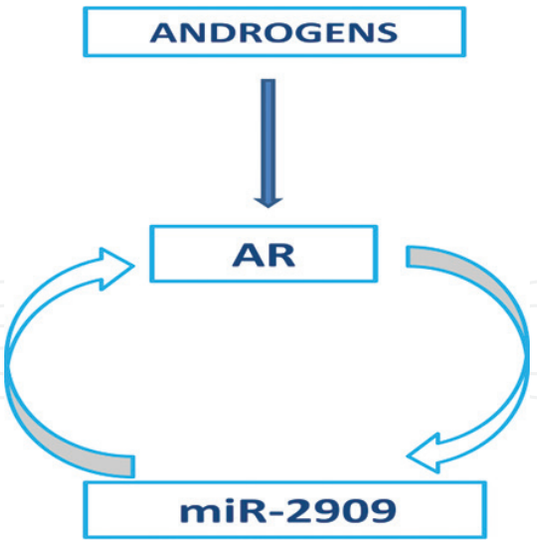

Figure 1. Feedback loop between androgen receptor and miR-2909.

7. miR-2909 stimulates androgen-dependent and androgen-independent growth

The functional analysis of miR-2909 in PCa was studied by transfecting miR-2909 into different PCa cell lines. Ectopic expression of miR-2909 enhanced the proliferation potential of both LNCaP and PC3 cells. The treatment of miR-2909-transfected LNCaP cells with an anti-androgen, bicalutamide significantly inhibited the cell proliferation rate. PCa commonly progresses from an androgen-dependent (AD) to an androgen-independent (AI) stage. Evaluating the role of miR-2909 in AI conditions, it was observed that miR-2909 overexpression significantly stimulated the growth of AD-LNCaP cells cultured in androgen-deprived medium and rescued them from androgen-ablated growth arrest. Similarly, anti-miR-2909 significantly inhibited the growth of AD LNCaP cells. Moreover, overexpression of miR-2909 significantly stimulated the growth of AR negative PC3 cells also.

8. miR-2909 and TGF beta signaling

In PCa, multiple AR mediated growth-regulatory signaling pathways are disrupted, disturbing the equilibrium between proliferation and apoptosis and tipping the balance in favor of proliferation. TGFβ signaling represents one of the important pathways AR cross talks with [18, 19]. Although various studies have shown that AR signaling blocks the TGFβ-induced inhibitory effects, however, exact molecular mechanisms are not known yet [20, 21]. We have for the first time reported in our study that miR-2909 acts as one of the central mediators of this cross talk [22]. TGFBR2, a critical signaling effector of TGFβ signaling, was shown as a novel putative target of miR-2909. TGFBR2 expression was downregulated in miR-2909 overexpressing PC3 cells and upregulated in anti-miR-2909-treated LNCaP cells. Ectopically

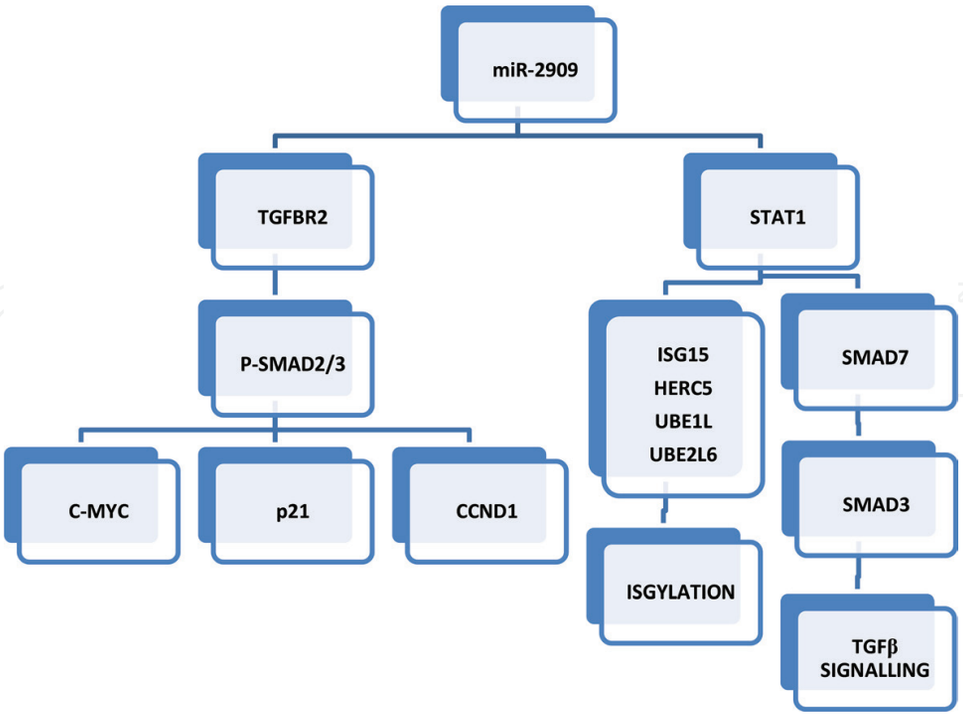

Figure 2. Schematic model summarizing the role of miR-2909 in PCa.

expressed miR-2909 decreased the basal phosphorylation of SMAD3, a downstream effector of TGFβ signaling and thus abrogating TGFβ-mediated cell growth inhibition and apoptosis in PC3 cells. Further, a significant upregulation of $p21^{CIP}$ and downregulation of c-MYC and CCND1 expression was observed in TGFβ-treated PC3 cells and miR-2909 overexpression abrogated these TGFβ-mediated effects (**Figure 2**). Thus, these results suggest a novel mechanism of escaping tumor-suppressive effects of TGFβ signaling mediated through downregulation of TGFBR2 by miR-2909 alone or AR/miR-2909 axis which could be a vital mechanism for PCa cell survival and progression. Supporting this data, various studies have shown that downregulation of TGFBR2 induces malignant transformation while TGFBR2 activation promotes the pro-apoptotic function in vitro as well as in vivo [23, 24]. The significance of TGFβ pathway in castrate-resistant prostate cancer is further supported by various studies that have reported an association between reduced TGFBR2 expression with higher Gleason score and elevated risk of relapse or decreased survival rate after androgen depletion therapy in PCa patients [25, 26].

9. miR-2909 and ISGylation

ISG15 is an interferon-induced 165-amino-acid (17 kDa) protein that belongs to a ubiquitin-like protein superfamily [27]. Like ubiquitin, ISG15 has diverse functions including ISGylation, a ubiquitin-like modification process by which ISG15 covalently conjugates to cytoplasmic and nuclear proteins through its conserved LRLRGG sequence and alters their functional properties [28]. A significant upregulation of all components of ISGylation including ISG15,

HERC5, UBE1L and UBE2L6 were observed in miR-2909 over-expressing PC3 cells (**Figure 3**). Further, it was observed that miR-2909 overexpression modulated ISGylation through STAT1 mediated via negative regulation of SOCS3. A significant upregulation of STAT1 phosphorylation and downregulation of SOCS3 was detected in miR-2909-overexpressing PC3 cells whereas miR-2909 plasmid coupled with antagomiR-2909 treatment significantly downregulated phosphorylated STAT1 and upregulated SOCS3 expression [29]. The SOCS3 is a well-documented inhibitor of JAK/STAT pathway and STAT1 phosphorylation is always reported as inversely correlated with SOCS3 expression [30]. A pro-tumorigenic activity mediated by miR-2909-induced ISGylation upregulation via STAT1 is supported by various studies reporting constitutive STAT1 activation as tumor-promoting in multiple cancer models. A positive correlation between increasing STAT1 expression and pro-proliferative gene expression with increasing disease progression from benign human papilloma virus-negative and benign human papilloma virus-positive, malignant cervical squamous carcinoma cells have been reported [31]. A similar kind of correlation between STAT1 with increasing disease progression from ductal carcinoma in situ to invasive carcinoma in breast cancer biopsies has also been reported. Likewise, the STAT1 expression in human breast cancer has been reported to be a predictive marker of poor prognosis as well as chemotherapy and radiotherapy resistance [32, 33]. Ectopic expression of miR-2909 in PC3 cells increased their proliferation rate and silencing miR-2909-induced or endogenous level of ISGylation process in PCa cells significantly reduced the cell proliferation rate. Cell cycle analysis also revealed a significant decrease in fraction of cells in S phase, clearly indicating the effect of miR-2909 on cell proliferation could be partly mediated via ISGylation.

In support of these results, interferons have been shown to upregulate AR expression, a molecule known to play a critical role in PCa development and progression. Similarly, Kiessling et al. [34] have shown that UBE1L overexpression, one of the limiting components of ISGylation

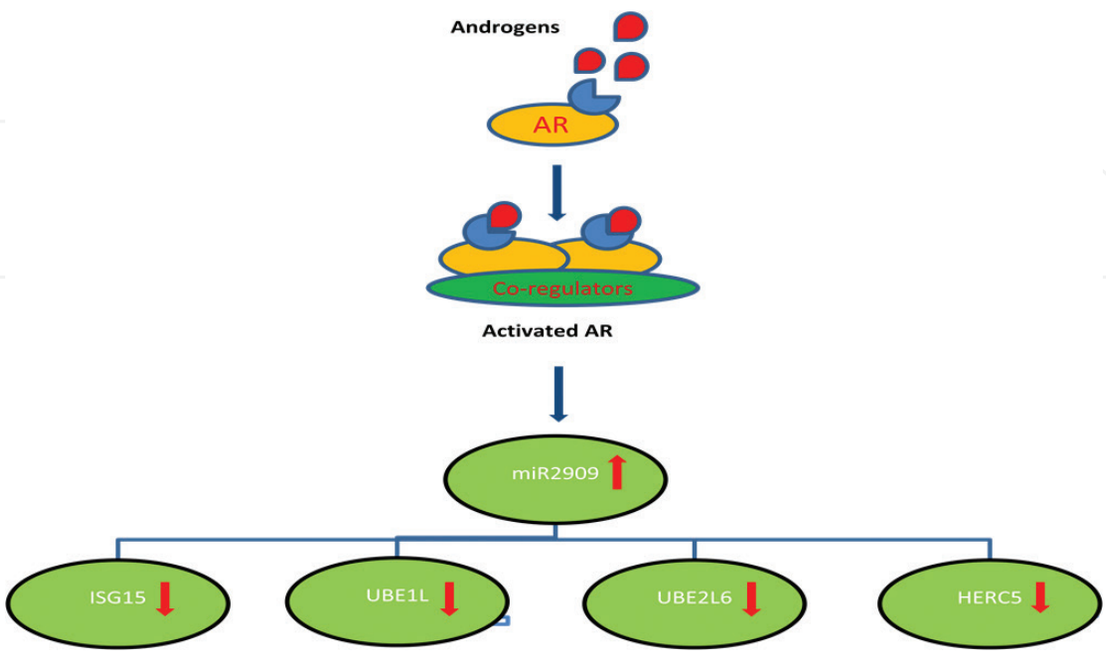

Figure 3. Downregulation of ISGylation through AR/miR-2909 axis in AR-positive LNCaP cells.

in LNCaP cells, increased AR levels in an ISG15-dependent manner. In breast cancer also, ISG15 is reported to stabilize oncogenic K-Ras protein via modifying it through ISGylation by inhibiting its targeted degradation via lysosomes [35]. All these observations clearly implicate that miR-2909 may very well play an important role in PCa progression through modulating ISGylation process.

Moreover, it is well-known that the signaling events triggered by TGF-β are negatively regulated by STAT1 through SMAD7 [36]. Phosphorylation of STAT1 induces transcription of SMAD7, which is a negative regulator for the cascade of SMAD3-mediated TGF-β signaling. miR-2909 overexpression significantly upregulated the expression of SMAD7 and decreased SMAD3 phosphorylation in PC3 cells (**Figure 2**). Moreover, the effect was reversed and the expression of SMAD3 resumed to normal levels when SMAD7 was inhibited using si-SMAD7. TGFβ is known to be a negative growth regulator that plays a critical role in PCa by controlling cell proliferation and apoptosis. An expanding body of evidence has indicated dysfunctional TGFβ signaling in various malignancies including PCa. Henceforth, all these studies suggest modulation of TGF-beta signaling by miR-2909 through multiple mechanisms. As ISGylation is known to play a pro-tumorigenic role and is also associated with poor prognosis, thus miR-2909 could serve as a potential prognostic biomarker for cancer patients. Further, the negative regulation of TGFβ signaling signifies that miR-2909 plays a pro-tumorigenic role by manipulating multiple signaling pathways. However, these studies represent the preliminary attempt and need to be further extended to human clinical PCa samples where these in vitro studies could be validated and the potential role of miR-2909 as a therapeutic biomarker could be established.

10. Urinary-exosomal miR-2909 and PCa

Exosomes are small membrane-bound vesicles of 40–100 nm in diameter found in a broad range of biological fluids. They play a critical role in cross talk between tumors and the surrounding environment. Various molecules encapsulated in these vesicles circulating in various body fluids are proteins and nucleic acids including mRNA and miRNAs [37, 38]. Various studies have reported a change in the content of freely circulating exosomal miRNAs during tumorigenesis reflecting the situation in the tumor [38]. Samina et al. [39] studied the relative urinary exosomal recruitment levels of two miRNAs, that is, mir-2909 & miR-615-3p in human subjects suffering from either bladder cancer or PCa. Urinary exosomes, derived from human subjects suffering from PCa, were found to be enriched with miR-2909 compared to those derived from either healthy control subjects or benign prostatic hyperplasia (BPH) subjects or patients with urinary bladder cancer. In contrast, miR-615-3p was significantly recruited to urinary exosomes in subjects suffering from both bladder and PCa compared to those found in either healthy-control subjects or disease-control subjects suffering from BPH. Elucidating the correlation of urinary exosomal miRNAs with PCa severity, the extent of miR-2909 recruitment to the urinary exosomes showed significant correlation with the severity of PCa based on Gleason Score within different subgroups grouped into Hormone-sensitive or Hormone-insensitive or Hormone-naive groups [39]. Further, in this study, it was reported that the serum PSA levels did not correlate with the severity of PCa either in Hormone-sensitive or Hormone-insensitive subjects. Moreover, no significant relationship between severity of PCa and age was

observed. From this study, it can be implied that urinary-exosomal miR-2909 cannot only help to differentiate bladder cancer from PCa but can also help to know the aggressiveness of PCa.

11. Clinical applications

Currently, PSA measurement is the only routinely performed test for the diagnosis of PCa. PSA is a coagulase protein secreted by prostate epithelial cells into semen. When the level of PSA goes above 4 ng/ml, the subject is asked to go for prostate biopsy for further evaluation. However, the PSA testing is non-specific as elevated PSA levels due to BPH, infection and/or chronic inflammation may sometimes lead to confounding results leading to over-diagnosis and over-treatment for insignificant tumors. Moreover, PSA measurement can also give false negative results as sometimes the patients suffering from PCa show a PSA level within normal range, thus leading to wrong diagnosis. Another important limitation of PSA testing is its lack of ability to identify aggressive and lethal forms of PCa. Thus, even though PSA is a valuable tool, it lacks specificity and is therefore not considered an optimal biomarker. Therefore, novel biomarkers are extremely desired due to the limitations of PSA.

The current research scenario gives compelling reasons to believe that miRNAs could serve as potential therapeutic tools in the form of monotherapy or in combination therapy with the available medical treatments. miRNAs alone or allied with PSA testing can serve together as potential biomarker for the accurate diagnosis of PCa [40, 41]. From the above studies, it can be implied that detection and quantification of miR-2909 alone or in combination with other miRNAs could serve as a reliable, non-invasive biofluid-based diagnostic test that can help to determine the presence and nature of a prostate malignancy as well as its response to treatment. However, it is to be insisted that a good number of investigational studies based on larger number of patients are needed to obtain more definite conclusions.

12. Conclusion

Collectively, miR-2909 is an androgen-inducible miRNA that forms a positive loop with AR and helps in prostate cancer progression. miR-2909 exerts its oncogenic effects via multiple mechanisms including attenuation of tumor-suppressive effects of TGFβ signaling and by upregulating ISGylation pathway. Moreover, it can be speculated that the recruitment of miR-2909 within the urinary exosomes in PCa patients can act as a non-invasive diagnostic marker for all the traits of PCa severity.

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