Montazer *et al.*
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REVIEW

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Role of microRNAs in regulation of WNT signaling pathway in urothelial and prostate cancers

Mehdi Montazer[1], Negin Taghehchian[2], Majid Mojarrad[3] and Meysam Moghbeli[3*]

Abstract

Background: Urothelial cancer (UC) and prostate cancer (PCa) are the most common cancers among men with a high ratio of mortality in advanced-stages. The higher risk of these malignancies among men can be associated with higher carcinogens exposure. Molecular pathology of UC and PCa is related to the specific mutations and aberrations in some signaling pathways. WNT signaling is a highly regulated pathway that has a pivotal role during urothelial and prostate development and homeostasis. This pathway also plays a vital role in adult stem cell niches to maintain a balance between stemness and differentiation. Deregulation of the WNT pathway is frequently correlated with tumor progression and metastasis in urothelial and prostate tumors. Therefore, regulatory factors of WNT pathways are being investigated as diagnostic or prognostic markers and novel therapeutic targets during urothelial and prostate tumorigenesis. MicroRNAs (miRNAs) have a pivotal role in WNT signaling regulation in which there are interactions between miRNAs and WNT signaling pathway during tumor progression. Since, the miRNAs are sensitive, specific, and noninvasive, they can be introduced as efficient biomarkers of tumor progression.

Main body: In present review, we have summarized all of the miRNAs that have been involved in regulation of WNT signaling pathway in urothelial and prostate cancers.

Conclusions: It was observed that miRNAs were mainly involved in regulation of WNT signaling in bladder cancer cells through targeting the WNT ligands and cytoplasmic WNT components such as WNT5A, WNT7A, CTNNB1, GSK3β, and AXIN. Whereas, miRNAs were mainly involved in regulation of WNT signaling in prostate tumor cells via targeting the cytoplasmic WNT components and WNT related transcription factors such as CTNNB1, GSK3β, AXIN, TCF7, and LEF1. MiRNAs mainly functioned as tumor suppressors in bladder and prostate cancers through the WNT signaling inhibition. This review paves the way of introducing a noninvasive diagnostic panel of WNT related miRNAs in urothelial and prostate tumors.

Keywords: Urothelial cancer, Metastatic bladder cancer, Metastatic prostate cancer, MicroRNA, WNT signaling pathway

Background

Urothelial cancer (UC) is the fourth most common cancer in men and the 10th cause of cancer related deaths worldwide with a high ratio of mortality in advanced-stage disease [1]. The higher risk of these malignancies among men can be associated with higher exposure to carcinogens such as smoking and occupation [2]. There are various UC environmental risk factors such as smoking, chronic inflammation of urinary tract, analgesics

*Correspondence: Meysam_moghbeli@yahoo.com; moghbelim@mums.ac.ir

[3] Department of Medical Genetics and Molecular Medicine, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
Full list of author information is available at the end of the article

abuse, arylamines, arsenic contamination, radiotherapy, and cyclophosphamide [3]. Prostate cancer (PCa) is one of the most common neoplasia in males that ranks as the fifth leading cause of cancer mortality worldwide [4]. There are significant higher rates of PCa incidence and mortality in industrialized countries compared with developing countries that can be associated with diet, age, ethnicity, genetic factors, and family history [5]. Moreover, some factors are correlated with a high risk of PCa death including body mass index and blood pressure [4, 6]. PCa is a very heterogeneous disease with different clinical manifestations that is associated with a wide range of mutations and genetic abnormalities. PCa progression involves several stages in which mutations in prostate epithelial cells result in apoptosis suppression. Finally, the PCa cells obtain the castration-resistant phenotype with poor prognosis [7]. Although, surgical resection and radiotherapy are the common therapeutic methods for localized prostate tumor, androgen inhibition is the main therapeutic method for the tumor relapse [8]. However, majority of PCa patients progress toward the metastatic castration-resistant [9]. The standard treatment method for metastatic prostate cancer (mPCa) is androgen deprivation therapy (ADT) with or without chemotherapy. Radical prostatectomy (RP) and radiation therapy (RT) can also repress the metastatic tumors and improve the survival rates in mPCa patients [10]. RP and pelvic lymphadenectomy (PLDN) are the surgical methods that are principally proposed for advanced-stage prostate tumors. PLND is the most important strategy to identify the lymph node metastases in PCa. RT is also considered as the second key therapeutic strategy for high-risk prostate tumors [11]. Molecular pathology of PCa is related to the critical mutations in some signaling pathway molecules that affect or disrupt a cross-talk along the pathways. Bladder cancer (BCa) is the 10th most frequent cancer and the 13th leading cause of death worldwide [12, 13]. About 90% of BCa are identified as urothelial carcinoma of the bladder (UCB) [14]. The main risk factors of BCa are aromatic amines exposure, smoking, genetic and hormonal conditions, *Schistosoma haematobium* infection, and arsenic contamination of drinking water [15–17]. Sex hormone receptors, including androgen receptors (AR) and estrogen receptors (ERs), have been considered as critical factors for the sex differences in BCa. Accumulating evidences revealed that steroid hormone receptor signaling plays a key role in BCa progression [18]. Androgen receptors such as estrogen receptor-α and β promote tumor growth and chemo resistance in BCa [19–21]. UCB is also known as a highly heterogeneous malignancy with different histological subtypes, including non-muscle invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC) [22, 23]. About 90% of urothelial tumors are characterized as transitional cell carcinoma [24]. Urothelial tumors have also different differentiation patterns such as squamous, micropapillary, glandular, and clear cell [25]. Squamous type is the most common type with up to 40% of urothelial cancers (UC) [26]. Micropapillary urothelial carcinoma (MPUC) is an aggressive histopathological type that accounts 2–5% of UCs [27]. A combination therapy of surgical resection and chemo radiotherapy has been suggested for the BCa; however, there is a low 5-year survival rate in advanced BC patients [28]. Endoscopic resection is a routine treatment option [29]. Although, radical cystectomy or chemo radiotherapy are also common therapeutic methods for the muscle-invasive urothelial carcinoma (MIUC) cases, half of the cases progress toward relapse [30, 31].

WNT signaling is a highly regulated pathway that has a pivotal role during urothelial development and homeostasis [32]. This pathway also plays a vital role in adult stem cell niches to maintain a balance between self-renewal (undifferentiation) and differentiation [33]. WNT signaling is triggered through an interaction between WNT ligands and cysteine-rich G protein-coupled receptors (Frizzleds) and their associated co-receptors which results in activation of non-canonical and canonical pathways [34–36]. The presence of Wnt ligand leads to cytoplasmic accumulation of β-catenin that finally enters into the nucleus to regulate the WNT target genes as a transcriptional co-activator of T cell-specific factor (TCF)/lymphoid enhancer-binding factor (LEF) transcription factors [37, 38]. WNT signals are associated with epithelial-mesenchymal transition (EMT) regulators such as Snail, Twist, and Zeb [39, 40]. Deregulation of the WNT pathway is frequently correlated with tumor progression and metastasis in PCa [41, 42]. Cancer stem cells (CSCs) are known as tumor-initiating cells that are contributed with tumor metastasis [43, 44]. They have a high capacity of self-renewal and chemo-radiotherapeutic resistance by the developmental signaling pathways, EMT process, multi-drug resistance (MDR), and epigenetic changes [45, 46]. Genetic and epigenetic modifications in the regulatory components of WNT pathway result in acquiring urothelial CSC phenotype, chemo resistance, and decreased survival. Therefore, regulatory factors of WNT pathways are being investigated as diagnostic or prognostic markers and novel therapeutic targets during urothelial tumorigenesis [14]. MicroRNAs (miRNAs) are a class of non-coding RNAs which can directly interact with the 3′untranslated region (3′ UTR) of target mRNAs to induce their degradation or translation inhibition. They have a pivotal role in WNT signaling regulation. A network of miRNAs and WNT signaling pathway factors are involved in tumor

progression of brain, colorectal, breast, liver, prostate, and other types of cancers [47]. EMT is a developmental process from an epithelial to invasive mesenchymal phenotype that has key roles in primary steps of tumor metastasis [48, 49]. There are many factors and signaling pathways associated with EMT including cadherins, vimentin, TGFb, and WNT signaling pathway [50]. EMT is associated with tumor metastasis via the WNT signaling pathway and miRNAs [51]. Various miRNAs such as miR-214, miR-320, miR-101, miR-1826, miR-548b, and miR-33a have been reported to suppress the WNT pathway by regulating β-catenin in different tumors [52]. Therefore, miRNAs can be used as therapeutic agents for the targeting of canonical WNT signaling pathway in some cancer types [47]. Since, the miRNAs are sensitive, specific, and noninvasive, they can be introduced as efficient biomarkers of tumor progression. In present review, for the first time we have summarized all of the miRNAs that have been involved in regulation of WNT signaling pathway in urothelial and prostate cancers to pave the way of introducing a noninvasive diagnostic panel of WNT related miRNAs in these tumors (Table 1, Fig. 1).

Prostate cancer

The WNT signaling is a critical pathway during PCa progression in which the Wnt signals induce the β-catenin nuclear accumulation resulting in up regulation of WNT target genes [53]. Normally, the destruction complex (Axin/APC/GSK-3β/CK1) maintains cytoplasmic β-catenin levels [54]. It has been reported that there were increased levels of miR-182 expressions in PCa tissues compared with normal margins that promoted cell proliferation and invasion. MiR-182 promoted WNT pathway through the targeting of WNT destruction complex components including APC, Axin, CK1, and GSK-3β [55].

Frizzled7 (FZD7) as a co-receptor of Wnt signaling is associated with tumor cell proliferation, metastasis, and EMT [56]. It is coupled with the canonical WNT/b-catenin pathway, which results in disheveled activation, GSK-3 suppression, and nuclear accumulation of b-catenin. It has been reported that there was an inverse correlation between FZD7 and miR-613 expressions in PCa samples. FZD7 functions as a receptor for the WNT ligands that can be targeted by miR-613 in PCa cells. Therefore, miR-613 up regulation inhibited the PCa cell proliferation and invasion by FZD7/WNT signaling suppression [57]. It has been shown that there was a significant SNHG7 over expression in PCa tissues and cell lines which promoted PCa invasion through miR-324-3p sponging to regulate the WNT2B expression [58]. There was significant reduced levels of miR-26a expression in PCa tissues compared with normal margins. It also inhibited PCa progression and in vivo growth through WNT5a suppression [59].

Astrocyte elevated gene-1 (AEG-1) is a regulator of cell proliferation, angiogenesis, and drug resistance in different cancers [60]. AEG-1 is a scaffold protein that activates various signaling pathways such as MEK/ERK, PI3K/Akt, and WNT [61]. It induces the b-catenin nuclear transport that results in EMT through E-cadherin down regulation and Vimentin over expression [62]. It has been shown that there was significant miR-1297 down regulation in PCa tissues which suppressed PCa cell proliferation and invasion through AEG-1 targeting [63]. DIXDC1 is a positive regulator of the WNT signaling pathway which has an important function in formation of Disheveled, Axin, and b-catenin complex in Wnt pathway [64]. It activates the WNT3A signaling via DVL2. It has been reported that there was DIXDC1 up regulation in PCa cell lines. The miR-1271 also suppressed tumor cell proliferation and invasion through DIXDC1 targeting [65].

N-myc downstream-regulated gene 2 (NDRG2) is involved in cell proliferation and apoptosis by regulation of WNT, MAPK, TGFβ, and AKT signaling pathways [66–68]. It inhibits the WNT-mediated transcriptional activation of CCND1. It has been reported that there was miR-454 up regulation in PCa tissues and cell lines. There was also a significant inverse correlation between NDRG2 and miR-454 expressions in PCa tissues. Moreover, miR-454 down regulation inhibited the WNT signaling [69]. DKK3 is an inhibitor of WNT signaling through suppression of LRP5/6 interaction with WNT that induces internalization of LRP5/6. DKK3 and SMAD4 up regulations reduced the tumorigenicity of PCa cells through WNT signaling. There were significant increased levels of miR-183 expressions in PCa tissues in comparison with normal margins which were directly correlated with prostate-specific antigen (PSA) and pT stage, while inversely associated with overall survival. MiR-183 activated the WNT pathway via DKK3 and SMAD4 targeting in PCa cells [70]. NKD1 is another negative regulator of WNT signaling via β-catenin suppression [71]. It has been reported that there were increased levels of miR-744 expressions in castration-resistant prostate cancer (CRPC) compared with androgen-dependent prostate cancer (ADPC) samples which was inversely correlated with CRPC patients survival. MiR-744 promoted cell proliferation and migration through down regulation of WNT signaling inhibitors such as SFRP1, GSK3β, and NDK1 in CRPC cells [72].

Cancer stem cells (CSCs) are a subpopulation of tumor cells with self-renewal ability and chemo radio therapeutic resistance that are one of the main reasons of tumor relapse [73, 74]. Therefore, a combination therapy including chemotherapy, radiotherapy, and surgical resection

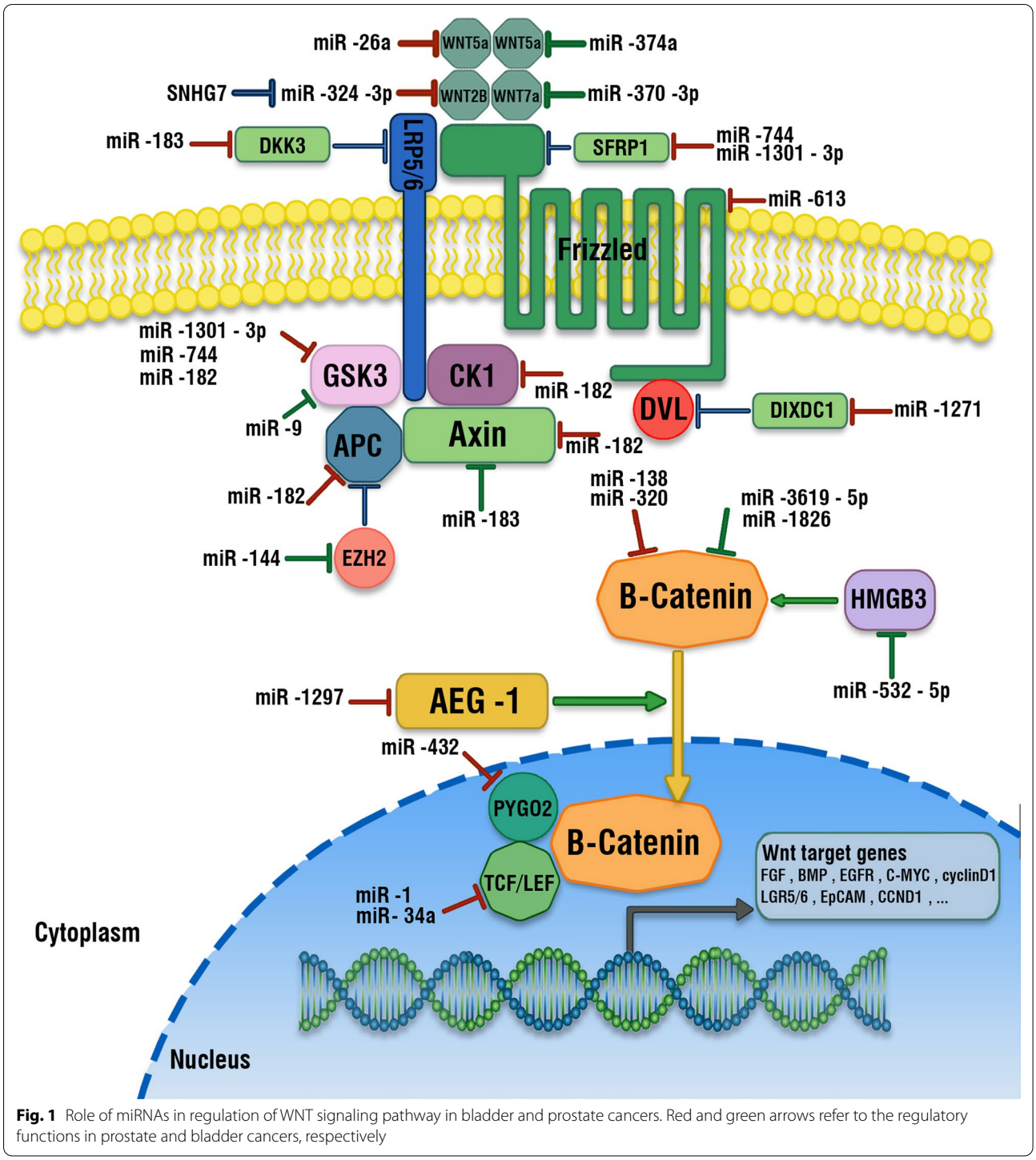

Fig. 1 Role of miRNAs in regulation of WNT signaling pathway in bladder and prostate cancers. Red and green arrows refer to the regulatory functions in prostate and bladder cancers, respectively

could be efficient for the CSCs elimination [75]. The sphere-forming CSCs have an extensive proliferation rate and resistance toward the chemotherapy that maintain tumor growth [76]. GSK3β is one of the components of destruction complex that is responsible for β-Catenin phosphorylation and ubiquitination. Since, β-Catenin degradation inactivates WNT pathway, the GSK3β inhibition promotes WNT signaling [77]. SFRP1 is also a negative regulator of WNT pathway [78]. SFRP family contains a homologous domain to the WNT-binding site of Frizzled that prevents the WNT-FZ interaction. It has been reported that there were miR-1301-3p up

Table 1 All of the microRNAs associated with regulation of WNT signaling in prostate and bladder cancers

Study	Year	Gene	Country	Sample	Target	Results	Clinical application
Prostate cancer							
Wang [55]	2018	miR-182	China	25 patients 2 cell lines	GSK3β, APC, CK1, and Axin	MiR-182 promoted WNT pathway through targeting of WNT destruction complex components including APC, Axin, CK1, and GSK-3β	Diagnosis
Ren [57]	2016	miR-613	China	3 cell lines	FZD7	MiR-613 up regulation inhibited the cell proliferation and invasion by FZD7/WNT signaling suppression	Diagnosis
Liang [63]	2016	miR-1297	China	20 patients 5 cell lines	AEG1	MiR-1297 suppressed PCa cell proliferation and invasion through AEG-1 targeting	Diagnosis
Zhong [65]	2017	miR-1271	China	20 patients 5 cell lines	DIXDC1	MiR-1271 over expression suppressed tumor cell proliferation and invasion through DIXDC1 targeting	Diagnosis
Zhao [59]	2014	miR-26a	China	20 patients 6 cell lines	WNT5A	MiR-26a inhibited PCa progression and in vivo growth through WNT5a suppression	Diagnosis
Fu [69]	2018	miR-454	China	20 patients 5 cell lines	NDRG2	There was a significant inverse correlation between NDRG2 and miR-454 expressions	Diagnosis
Ueno [70]	2013	miR-183	USA	31 patients 4 cell lines	DKK3	MiR-183 activates the WNT pathway via DKK3 and SMAD4 targeting. There was an inverse correlation between the miR-183 expression and overall survival	Diagnosis and prognosis
Guan [72]	2017	miR-744	China	10 patients 3 cell lines	SFRP1, GSK3β, TLE3, and NKD1	MiR-744 promoted cell proliferation and migration through down regulation of SFRP1, GSK3β, and NDK. There was an inverse correlation between the miR-744 expression and overall survival	Diagnosis and prognosis
Song [79]	2018	miR-1301-3p	China	8 patients 6 cell lines	GSK3β and SFRP1	MiR-1301-3p promoted the PCa stem cells through GSK3β and SFRP1 targeting	Diagnosis
Hsieh [80]	2013	miR-320	Taiwan	10 patients 7 cell lines	CTNNB1	MiR-320 inhibited the β-catenin and self-renewal ability	Diagnosis
Yu [81]	2018	miR-138	China	4 cell lines	CTNNB1	MiR-138 inhibited the β-catenin to maintain PCa cell epithelial status	Diagnosis
Siu [86]	2017	miR-1	Taiwan	111 patients 6 cell lines	TCF7	AR inhibited WNT signaling via miR-1-mediated suppression of TCF7	Diagnosis
Chen [92]	2015	miR-34a	Taiwan	24 patients 2 cell lines	TCF7	MiR-34a was an inhibitor of WNT signaling through TCF7 targeting. There was a direct correlation between the miR-34a expression and overall survival	Diagnosis and prognosis
Li [93]	2017	miR-432	China	? patients 1 cell line	TRIM29 and PYGO2	MiR-432 inactivated the WNT pathway through TRIM29 and PYGO2 targeting	Diagnosis
Liang [96]	2015	miR-34a	China	5 cell lines	LEF1	MiR-34a regulated the EMT process through LEF1 targeting	Diagnosis

Table 1 (continued)

Study	Year	Gene	Country	Sample	Target	Results	Clinical application
Fu [99]	2019	miR-653-5p	China	5 cell lines	SOX30	There was an inverse correlation between SOX30 and miR-653-5p	Diagnosis
Li [102]	2016	miR-218	China	58 patients 2 cell lines	LGR4	MiR-218 suppressed PCa cell proliferation and invasion via LGR4 targeting	Diagnosis
Ren [105]	2018	miR-520b	China	25 patients 4 cell lines	CAPN4	The miR-520b inhibited the PCa cells invasion via CAPN4 targeting	Diagnosis
Cui [109]	2019	miR-15a-3p	China	35 patients 5 cell lines	SLC39A7	MiR-15a-3p inhibited the WNT signaling via SLC39A7 targeting	Diagnosis
Du [111]	2019	miR-601	China	87 patients 1 cell line	KRT5	MiR-601 down regulation inhibited the prostate cancer stem cells (PCSCs) proliferation and invasion through KRT5 induction and WNT signaling suppression	Diagnosis
Bladder cancer							
Chen [115]	2018	miR-374a	China	3 cell lines	WNT5A	MiR-374a can be introduced as an inhibitor of aggressive tumor through WNT5A targeting. There was a direct correlation between the miR-374a expression and overall survival	Diagnosis and prognosis
Cao [117]	2018	miR-129-5p	China	28 patients 2 cell lines	WNT5A	MiR-129-5p increased gemcitabine sensitivity in BCa cells through Wnt5a targeting	Diagnosis and prognosis
Huang [118]	2018	miR-370-3p	China	41 patients 4 cell lines	WNT7A	MiR-370-3p/Wnt7a axis regulated UBC invasion via canonical WNT signaling. There was an inverse correlation between the miR-370 expression and overall survival	Diagnosis and prognosis
Tian [121]	2019	miR-621	China	50 patients 3 cell lines	TRIM29	MiR-621 suppressed the BC cell proliferation and metastasis through TRIM29 targeting. There was an inverse correlation between the miR-621 expression and overall survival	Diagnosis and prognosis
Hirata [122]	2012	miR-1826	USA	19 patients 4 cell lines	CTNNB1	MiR-1826 functions as a tumor suppressor through CTNNB1	Diagnosis
Zhang [123]	2018	miR-3619-5p	China	33 patients 4 cell lines	CTNNB1	MiR-3619 had an important role during BCa progression and metastasis through β-catenin targeting. There was a direct correlation between the miR-3619 expression and overall survival	Diagnosis and prognosis
Dong [124]	2018	miR-9	China	38 patients 3 cell lines	GSK3β	There was a significant converse association between the miR-9 and GSK-3β expressions	Diagnosis
Chen [125]	2018	miR-183	China	? patients 3 cell lines	AXIN2	MiR-183 activated the WNT signaling via AXIN2 suppression	Diagnosis
Xie [129]	2019	miR-532-5p	China	35 patients 3 cell lines	HMGB3	MiR-532-5p suppressed the BCa cell proliferation and invasion through HMGB3 targeting	Diagnosis

Table 1 (continued)

Study	Year	Gene	Country	Sample	Target	Results	Clinical application
Guo (131)	2013	miR-144	China	23 patients 5 cell lines	EZH2	MiR-144 down regulation resulted in WNT signaling activation and BCa cell proliferation by EZH2 suppression	Diagnosis

regulations in PCa tissues that promoted the PCa stem cells through GSK3β and SFRP1 targeting. MiR-1301-3p up regulation also increased the sphere formation [79]. Another study reported that there were significant lower levels of miR-320 expressions in PCa tissues in comparison with normal margins. MiR-320 inhibited the β-catenin and self-renewal ability [80]. The reduced levels of miR-138 expressions have been shown in highly aggressive in comparison with less metastatic cell lines. MiR-138 also impaired cell invasion via E-cadherin up regulation and vimentin down regulation. Moreover, miR-138 inhibits the β-catenin to maintain PCa cell epithelial status [81].

Transcription factor 7 (TCF7) belongs to the TCF/LEF family that is a key effector of WNT pathway [82]. Although, Androgen deprivation therapy (ADT) is an important therapeutic method of PCa via Androgen Receptor (AR) blocking [83], castration-resistant prostate cancer (CRPC) obtains multiple mutations resulting in ADT resistance [84]. WNT signaling is one of the main alternative signaling pathways for the AR signaling in CRPC [85]. There was TCF7 up regulation in advanced PCa tumors that was inversely associated with miR-1. AR inhibited WNT signaling via miR-1-mediated suppression of TCF7 which prohibited the β-catenin–TCF7 complex formation [86]. Ras signaling is also a critical pathway during PCa metastasis [87]. It mediates its functions through induction of various pathways such as MAPK, PI3K/AKT, and WNT signaling [88, 89]. Ras and WNT cooperation is involved in invasive PCa by COX-2 and c-MYC up regulations [90, 91]. It has been shown that the Ras signaling down regulated the miR-34a which is an inhibitor of WNT signaling through TCF7 targeting [92]. PYGO2 is the main component of WNT transcriptional machinery. It has been shown that there was an inverse correlation between the levels of lncRNA625 and miR-432 expressions in the PCa tissues in comparison with normal tissues. lncRNA625 up regulation inhibited the tumor cells growth and induced apoptosis. MiR-432 inactivated the WNT pathway through TRIM29 and PYGO2 targeting. Therefore, lncRNA625 inhibited PCa cells proliferation through activation of WNT pathway by miR-432 targeting [93]. LEF1 is also one of the components of WNT transcriptional machinery that regulates the EMT through interaction with Twist1 and Snail transcription factors [94]. It mediates transcription response to the canonical WNT pathway via β-catenin interaction in which it regulates the expression of WNT target genes such as Cyclin D1 and c-MYC [95]. It has been shown that there was an inverse association between miR-34a and LEF1 expression in PCa cell lines and tissues. MiR-34a regulated the EMT process through LEF1 targeting [96]. SOX is a family of transcription factors involved in various biological processes [97]. SOX30 has a critical role in activation of post-meiotic genes during spermiogenesis. SOX30 inhibits the WNT signaling through CTNNB1 down regulation and preventing the CTNNB1-TCF7L2/TCF4 interaction [98]. It has been reported that there were significant decreased SOX30 levels in PCa cells compared with normal cells. SOX30 up regulation significantly decreased PCa cell proliferation and invasion. There was also an inverse correlation between SOX30 and miR-653-5p in which the SOX30 overexpression or miR-653-5p down regulation inhibited PCa cell proliferation through WNT signaling inactivation [99].

LGR4 is a G protein-coupled receptor (GPCR) that has pivotal roles in tissue development and tumor progression through induction of PI3K/AKT and WNT signaling pathways [100]. It activates the WNT pathway through binding with R-spondins. There is a positive correlation between the IL-6 and LGR4 expressions in tumor cells [101]. It has been reported that the miR-218 suppressed PCa cell proliferation and invasion via LGR4 targeting. MiR-218 also reduced PI3K/Akt phosphorylation and β-catenin accumulation. Moreover, it down regulated the cyclin A1 and MMP-9 via PI3K/AKT and WNT signaling pathways in PCa cells [102]. Calpains belong to the calcium-dependent cysteine proteases involved in apoptosis, cell proliferation, and invasion [103]. CAPN4 regulates the tumor cell proliferation and invasion by WNT signaling activation [104]. It has been shown that there was a high level of CAPN4 expression in PCa cell lines that promotes cell invasion by WNT activation. The miR-520b inhibited the PCa cells invasion via CAPN4 targeting [105]. Zinc is a critical element of cellular proteins involved in cell differentiation and DNA synthesis, whose homeostasis is related with zinc transporters [106]. SLC30/ZnT and SLC39/ZIP are the main zinc transporters in mammalians [107]. SLC39A7 also regulates

zinc-mediated tyrosine kinase signaling during tumor progression [108]. It is a Zinc transporter in endoplasmic reticulum/Golgi apparatus that is induced by Epidermal growth factor (EGF), Ca^{2+}, and exogenous Zn^{2+}. It has been reported that there were significant miR-15a-3p down regulations in PCa samples and cell lines. MiR-15a-3p suppressed PCa cell proliferation and invasion through WNT1, b-catenin, and c-MYC targeting. It also up regulated E-cadherin, while down regulated Vimentin via WNT signaling suppression. MiR-15a-3p inhibited the WNT signaling via SLC39A7 targeting [109]. As an intermediate filament, the Keratin 5 (KRT5) is expressed in basal layer stratified epithelial cells [110]. It has been reported that the miR-601 down regulation inhibited the prostate cancer stem cells (PCSCs) proliferation and invasion through KRT5 induction and WNT signaling suppression. The miR-601 down regulation inhibited the NANOG and OCT4 expressions. It also significantly increased the levels of Wnt1 and β-catenin expressions which showed the effect of miR-601/KRT5/WNT on PCSCs [111].

Bladder cancer

WNT5A as a non-canonical WNT is involved in β-catenin phosphorylation and canonical WNT signaling suppression [112]. WNT5A-FZD2 interaction activates STAT3 and promotes EMT process. WNT5 is also involved in GSK3b inhibition which results in b-catenin stabilization [113]. Although, WNT5A promotes non-canonical WNT pathways, it can suppress the canonical WNT pathway via β-catenin degradation [114]. It has been observed that there was a positive association between the levels of miR-374a expression and prognosis in NMIBC patients. Since the over expressed miR-374a patients had longer relapse-free survival (RFS), miR-374a can be introduced as an inhibitor of aggressive tumor through WNT5A targeting and canonical WNT signaling blockade in BCa patients [115]. Gemcitabine is an inhibitor of DNA synthesis which is an efficient neo-adjuvant chemotherapy drug to improve the survival of MIBC patients [116]. It has been reported that there was a correlation between miR-129-5p down regulation and gemcitabine resistance in BCa cells. It increased gemcitabine sensitivity in BCa cells through Wnt5a targeting [117]. Higher levels of Wnt7a expressions were observed in 5637 HMI cells compared with 5637 NMI cells. The Wnt7a up regulation was significantly correlated with UBC cell invasiveness and poor prognosis in UBC patients. MiR-370-3p/Wnt7a axis regulated UBC invasion via canonical WNT signaling in BCa [118].

The β-catenin is a pivotal positive regulator of WNT signaling pathway. TRIM29 induces the WNT signaling through β-catenin up regulation, stabilization, and decreasing its phosphorylation level [119, 120]. It has been shown that there were lower levels of miR-621 expressions in BCa tissues compared with normal margins which were negatively associated with overall survival. MiR-621 suppressed the BCa cell proliferation and metastasis through TRIM29 targeting and subsequent WNT signaling inhibition [121]. There were significant miR-1826 down regulations in BC tissues that function as a tumor suppressor through CTNNB1 and VEGFC targeting [122]. It has been shown that there were reduced levels of miR-3619 expressions in BCa cell lines and tissues. MiR-3619 had an important role during BCa progression and metastasis through CDK2 and β-catenin targeting. It also up regulated the p21 that is a key factor in BCa suppression. Moreover, miR-3619 down regulated the c-MYC via reduction in cytoplasmic β-catenin, which suggested the miR-3619 as an inhibitor of WNT pathway in BCa cells. MiR-3619 up regulated the E-cadherin and down regulated the Vimentin and N-cadherin that showed miR-3619 inhibited the EMT process in BCa [123].

GSK-3β is a suppressor of WNT signaling pathway via β-catenin phosphorylation and degradation. It has been reported that there was a significant converse association between the miR-9 and GSK-3β expressions in BCa tissues [124]. AXIN2 is one of the components of destruction complex in WNT pathway. It has been shown that there were increased levels of miR-183 expression in BCa samples that induced tumor cell proliferation. It activated the WNT signaling via AXIN2 suppression [125].

High mobility group box 3 (HMGB3) has an important role in DNA replication and transcription [126]. HMGB3 also inhibits the immune cell differentiation and regulates the hematopoietic stem cells self-renewal and differentiation. There are low levels of HMGB3 expressions in adult tissues, while there are HMGB3 up regulations during self-renewal of hematopoietic stem cells [127]. HMGB3 is a positive regulator of WNT/β-catenin signaling that induces the β-catenin expression and WNT/β-catenin activation [128]. It has been reported that there were decreased levels of miR-532-5p expressions in BCa tissues. MiR-532-5p suppressed the BCa cell proliferation and invasion through HMGB3 targeting and WNT/β-catenin signaling inhibition [129]. EZH2 is one of the components of Polycomb repressive complex 2 that suppress the gene expressions via histone H3 trimethylation at lysine 27 (H3K27me3) [130]. It has been reported that the miR-144 down regulation resulted in WNT signaling activation and BCa cell proliferation by EZH2 suppression. There were also significant lower levels of miR-144 expressions in BCa tissues and cell lines. Furthermore, EZH2 induced H3K27me3 in NKD1 and APC promoter

sequences leading to NKD1 and APC down regulations and subsequent WNT signaling activation [131].

Conclusion

WNT signaling pathway has a pivotal role during embryogenesis and tumor progression. It has been reported that the miRNAs are one of the main regulators of WNT signaling. In present review, we have summarized all of the miRNAs that have been associated with regulation of WNT signaling pathway during urothelial and prostate tumor progression and metastasis. It was observed that miRNAs mainly regulated the WNT signaling in BCa cells through targeting the WNT ligands and cytoplasmic WNT components such as WNT5A, WNT7A, CTNNB1, GSK3β, and AXIN. While, miRNAs mainly affected the WNT signaling in PCa cells via targeting the cytoplasmic WNT components and WNT related transcription factors such as CTNNB1, GSK3β, AXIN, TCF7, and LEF1. Majority of the reported miRNAs had a tumor suppressor function in bladder and prostate tumor cells by inhibition of the WNT signaling pathway. This review paves the way of introducing a noninvasive diagnostic WNT related miRNAs panel markers in UC and PCa for the first time in the world.

Abbreviations

ADT: Androgen deprivation therapy; AR: Androgen receptors; ADPC: Androgen-dependent prostate cancer; AEG-1: Astrocyte elevated gene-1; BCa: Bladder cancer; CSCs: Cancer stem cells; CRPC: Castration-resistant prostate cancer; EGF: Epidermal growth factor; EMT: Epithelial-mesenchymal transition; ERs: Estrogen receptors; Fzd7: Frizzled7; GPCR: G protein-coupled receptor; GSK-3: Glycogen synthase kinase-3; H3K27me3: Histone H3 trimethylation at lysine 27; KRT5: Keratin 5; LEF: Lymphoid enhancer-binding factor; mPCa: Metastatic prostate cancer; miRNAs: MicroRNAs; MDR: Multi-drug resistance; MIBC: Muscle-invasive bladder cancer; MIUC: Muscle-invasive urothelial carcinoma; NDRG2: N-myc downstream-regulated gene 2; NMIBC: Non-muscle invasive bladder cancer; PLDN: Pelvic lymphadenectomy; PCa: Prostate cancer; PCSCs: Prostate cancer stem cells; PSA: Prostate-specific antigen; RT: Radiation therapy; RP: Radical prostatectomy; RFS: Relapse-free survival; TCF: T cell-specific factor; TCF7: Transcription factor 7; UC: Urothelial cancer; UCB: Urothelial carcinoma of the bladder.

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Author contributions

MM, NT, and MM were involved in search strategy and drafting. MM supervised the project and revised and edited the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

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Competing interests

The authors declare that they have no competing interests.

Author details

[1]Department of Pathology, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran. [2]Medical Genetics Research Center, Mashhad University of Medical Sciences, Mashhad, Iran. [3]Department of Medical Genetics and Molecular Medicine, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.

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