MicroRNAs as the critical regulators of protein kinases in prostate and bladder cancers

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Abstract

Background: Bladder cancer (BCa) and prostate cancer (PCa) are frequent urothelial and genital malignancies with a high ratio of morbidity and mortality which are more common among males. Since BCa and PCa cases are mainly diagnosed in advanced stages with clinical complications, it is required to introduce the efficient early detection markers. Protein kinases are critical factors involved in various cellular processes such as cell growth, motility, differentiation, and metabolism. Deregulation of protein kinases can be frequently observed through the neoplastic transformation and tumor progression. Therefore, kinases are required to be regulated via different genetic and epigenetic processes. MicroRNAs (miRNAs) are among the critical factors involved in epigenetic regulation of protein kinases. Since miRNAs are noninvasive and more stable factors in serum and tissues compared with mRNAs, they can be used as efficient diagnostic markers for the early detection of PCa and BCa.

Main body: In present review, we have summarized all of the reported miRNAs that have been associated with regulation of protein kinases in bladder and prostate cancers.

Conclusions: For the first time, this review highlights the miRNAs as critical factors in regulation of protein kinases during prostate and bladder cancers which paves the way of introducing a noninvasive kinase-specific panel of miRNAs for the early detection of these malignancies. It was observed that the class VIII receptors of tyrosine kinases and non-receptor tyrosine kinases were the most frequent targets for the miRNAs in bladder and prostate cancers, respectively.

Keywords: Bladder cancer, Prostate cancer, MicroRNA, Kinase, Diagnosis

Background

High frequencies of double primary bladder and prostate cancers have been reported in several studies in which there were up to 70% of prostate cancers in bladder cancer patients [1]. Bladder cancer (BCa) is the 12th most frequently diagnosed malignancy globally [2], with a global age-standardized rate of 10.1 and 2.5 per 100,000 for males and females, respectively [3]. A total of 81,190 newly diagnosed BCa cases and 17,240 deaths were recorded in 2018 in the USA [4]. BCa is the fourth most frequent malignancy and the second most prevalent tumor of the urinary tract after prostate cancer (PCa) in the USA [4]. Considering tumor invasion, BCa is classified into muscle-invasive bladder cancer (MIBC) and non-muscle-invasive bladder cancer (NMIBC) [5]. Almost 25–30% of newly diagnosed BCa patients are MIBC and 15% of them show local or remote metastasis [6, 7]. Based on the histopathological features, BCa is classified into squamous cell carcinoma, adenocarcinoma, and transitional cell carcinoma (TCC). TCC or urothelial carcinoma accounts for 90% of all BCa cases [8, 9]. Intravesical chemotherapy or immunotherapy after transurethral resection is regarded as the standard
treatment options for BCa; however, the tumor recurrence within 5 years and treatment failure (which is seen in 30% of the patients) have challenged these approaches [10]. The cigarette smoking, gender, chemicals exposure, and water pollutants are some of the BCa risk factors. However, BCa is observed in a small fraction of individuals with the well-known risk factors that may refer to the contribution of various genetic and epigenetic alterations in BCa susceptibility [11, 12]. PCa is the most frequently diagnosed malignancy and the second major cause of cancer mortality among males in western countries [4, 13]. It is a highly heterogeneous malignancy in which some patients have an indolent manifestation (90% 5-year survival rate), while other patients experience an aggressive manifestation with local and distant metastases (5-year survival rate of 29%) [14]. Age, race, familial history, environmental factors, and occupational exposures are considered as the main risk factors associated with PCa progression [15, 16]. Protein kinases are a large family of proteins responsible for the phosphorylation of key proteins involved in cell proliferation, metabolism, differentiation, and apoptosis [17, 18]. Regarding the pivotal regulatory roles of protein kinases in fundamental cellular processes, these factors should be strictly regulated to maintain the normal status inside the cells [19]. Protein kinases are categorized based on their amino acid targets to the tyrosine and serine/threonine kinases which can be located in membranes or cytoplasm. Deregulation of tyrosine kinases (TKs) is frequently observed during tumor progression and metastasis [20–22]. Therefore, TKs targeting and inhibition can improve the prognosis and clinical outcomes in cancer patients [23].

MiRNAs are small single-stranded non-coding RNAs (21–24 nucleotides in length), which negatively regulate the expression of their target mRNAs through translational inhibition or mRNAs degradation [24]. They are involved in regulation of important pathophysiological mechanisms including cell proliferation, differentiation, tumorigenesis, and angiogenesis [24, 25]. MiRNAs deregulations disrupt the normal modulatory functions of several signaling pathways that leads in tumor progression and metastasis [26]. There is a correlation between the tumor cell response to radiotherapy and miRNAs functions [27]. EGFR-tyrosine kinase inhibitors (TKIs) have a pivotal role in treatment and prognosis of cancer patients with epidermal growth factor receptor (EGFR) mutations. However, drug resistance limits the efficacy of EGFR-TKI in these patients. The ability of miRNAs to regulate many oncogenic pathways provides them as the novel prognostic biomarkers. Putative roles of miRNAs have been shown in regulation of EGFR-TKI resistance in EGFR-mutated tumors [28]. Exosomes can be used to deliver the miRNAs to EGFR expressing tumor cells [29].

MiRNAs are involved in regulation of cytochrome P450 as the main EGFR-TKI metabolizing enzyme to enhance drug-mediated toxicity and reduce pharmacological side effects [30, 31]. Aberrant expression of miRNAs is associated with progression of various malignancies including PCa and BCa [32, 33]. Since miRNAs are more stable than mRNAs in paraffin-embedded tissues and serum, they can be used as efficient noninvasive diagnostic markers in early detection of cancer. Although kinase inhibitors have been widely used as efficient options in urothelial tumor therapy, many tumors acquire resistance toward the protein kinase inhibitors. Therefore, it is required to clarify the molecular mechanisms which are involved in regulation of protein kinases. MicroRNAs have been introduced as important regulators of protein kinases during tumor progression and chemoresistance [34, 35]. Therefore, in present review we have summarized all of the miRNAs which have been reported as the regulators of protein kinases during bladder and prostate cancer progressions (Table 1) (Fig. 1).

Main text

Class I receptors of tyrosine kinases

EGFR is a trans-membrane protein which belongs to the erbB family of receptors. Interaction of EGFR with its cognate EGF ligand induces intrinsic tyrosine kinase activity that subsequently activates intracellular signaling cascades [36]. EGFR is implicated in regulation of cell proliferation, angiogenesis, and tumor invasiveness [20]. It activates multiple signaling pathways including PI3K/AKT and MAPK/ERK [37]. AKT has an oncogenic function by the induction of cell proliferation and apoptosis suppression [38]. It has been reported that the miR-133a and miR-133b reduced tumor growth, cell proliferation, and migration through EGFR, p-ERK, p-AKT, and MMP-2 targeting in BCa cells [39]. There was also a significant miR-135a downregulation in metastatic PCa tumors which was associated with advanced-stage tumor, higher Gleason score, and poorer prognosis. MiR-135a suppressed PCa cell proliferation and migration via targeting EGFR [40]. E-box binding homeobox 1 (ZEB1) is a zinc-finger transcription factor involved in DNA damage response [41, 42]. ZEB1 is phosphorylated and stabilized by ATM following radiotherapeutic-related DNA damage. It induces USP7 to deubiquitinate and stabilize the CHK1. Therefore, ZEB1 increases radioresistance by promotion of homologous recombination-mediated DNA repair [43]. A significant miR-875-5p downregulation was observed in prostate tumors compared with normal margins. There was also a direct correlation between miR-875-5p and E-cadherin expressions in clinical samples. MiR-875-5p promoted radiosensitivity of PCa cells by EGFR targeting [44]. E-cadherin downregulation is
### Table 1
All of the miRNAs which have been reported to regulate the protein kinases in bladder and prostate cancers

| Gene | Target | Cancer | Sample | Results | Country | Year | Study |
|------|--------|--------|--------|---------|---------|------|-------|
| **Class I receptors of tyrosine kinases** | | | | | | | |
| miR-133a/b | EGFR | Bladder | 2 cell lines | The miR133a and miR-133b reduced tumor growth, cell proliferation, and migration | China | 2012 | Zhou [39] |
| miR-135a | EGFR | Prostate | 2 cell lines | MiR-135a suppressed cell proliferation and migration | China | 2016 | Xu [40] |
| miR-875-5p | EGFR | Prostate | 2 cell lines | The miR-875-5p promoted radiosensitivity | Italy | 2017 | Bezawy [44] |
| miR-200a | EGFR | Bladder | 3 cell lines | MiR-200a downregulation promoted of EGFR translation and enhancement of anchorage-independent tumor growth | USA | 2017 | Huang [64] |
| miR-133a/b | EGFR | Prostate | 2 cell lines | MiR-133 functions as a potent tumor suppressor agent, especially in androgen-independent PCa | China | 2012 | Tao [65] |
| miR-4319 | Her-2 | Prostate | 40 patients | Suppressed growth and chemoresistance | USA | 2018 | Lin [69] |
| miR-331-3p | MET | Bladder | 1 cell line | MiR-331-3p was associated with PCa progression | Australia | 2011 | Epis [73] |
| miR-148a-3p | ERBB3 | Bladder | 59 patients | Suppressed EMT | China | 2016 | Wang [75] |
| **Class V, VII, and VIII receptors of tyrosine kinases** | | | | | | | |
| miR-99a | FGFR3 | Prostate | 2 cell lines | Inhibited PCa cell growth, invasion, and migration | Canada | 2019 | Nam [113] |
| miR-100 | FGFR3 | Bladder | 4 cell lines | Hypoxia increased viability of tumor cells under stressful conditions through miR-100 suppression | UK | 2013 | Blick [84] |
| miR-1-3p | TrkB | Bladder | 38 patients | Inhibited the progression and invasion of BCa | China | 2018 | Gao [86] |
| miR-34C | MET | Prostate | 57 patients | There was an inverse correlation between MET and miR-34C expression levels | Sweden | 2013 | Hagman [95] |
| miR-323a | c-Met | Bladder | 20 patients | Induced apoptosis | China | 2019 | Qiu [99] |
| miR-403-3p | c-Met | Bladder | 10 patients | Inhibited BCa migration and invasion | China | 2013 | Xu [100] |
| miR-23b/27b | EGFR, c-MET | Bladder | 57 patients | Suppressed proliferation and migration of BCa cells | Japan | 2014 | Chiyomaru [101] |
| miR-101 | c-Met | Bladder | 20 patients | Repressed BCa invasion | China | 2013 | Hu [106] |
| miR-323a-3p | MET | Bladder | 9 patients | Inhibited invasion and migration of BCa cell lines | China | 2017 | Li [107] |
| miR-1 | c-Met | Prostate | 82 patients | Repressed the proliferation | China | 2019 | Gao [108] |
| **Class II and X receptors of tyrosine kinases** | | | | | | | |
| miR-139 | IGFR1, AXL | Prostate | 578 patients | Inhibited PCa cell migration, proliferation, and cell cycle | Canada | 2019 | Nam [113] |
| miR-145 | IGFR1 | Bladder | 3 cell lines | Tumor suppressor | China | 2014 | Zhu [114] |
| Let-7a | IGFR1 | Prostate | 1 cell line | Suppressed prostate tumor cell proliferation, and triggers cell cycle arrest and apoptosis | China | 2013 | Wang [118] |
| **Non-receptor tyrosine kinases** | | | | | | | |
| miR-4723 | ABL | Prostate | 57 patients | Inhibited tumor cell proliferation and invasion and induced apoptosis | USA | 2013 | Arora [121] |
| miR-20a | ABL2 | Prostate | 30 patients | Inhibited migration and invasion of PCa cells | China | 2014 | Qiang [126] |
| miR-3607 | SRC | Prostate | 100 patients | Suppressed the tumorigenicity | USA | 2014 | Saini [130] |
| miR-1 | SRC | Prostate | 139 patients | There was an inverse association between miR-1 and SRC expression levels | Taiwan/USA | 2015 | Liu [137] |
| miR-124 | SRC | Prostate | 4 cell lines | Inhibited PCa cell proliferation, increased sensitivity to enzalutamide, and triggered apoptosis | USA | 2015 | Shi [140] |
| miR-1178-3p | SRC | Bladder | 3 cell lines | The circFND3C5B upregulation suppressed BCa growth and metastasis via miR-1178-3p sponging | China | 2018 | Liu [143] |
| miR-199a | YES1 | Prostate | 74 patients | Increased chemosensitivity and apoptotic cell death | China | 2017 | Chen [146] |
Table 1 (continued)

| Gene   | Target       | Cancer | Sample                  | Results                                                                 | Country | Year  | Study          |
|--------|--------------|--------|-------------------------|------------------------------------------------------------------------|---------|-------|----------------|
| miR-631 | ZAP70        | Prostate | 43 patients 6 cell lines | Suppressed invasion and migration of prostate tumor cells             | China   | 2016  | Fu [150]       |
| miR-214 | PTK6         | Prostate | 5 cell lines           | Reduced cell proliferation and viability in PCa                      | USA     | 2019  | Cagle [154]    |
|         |              |         |                         | Serine threonine kinases                                              |         |       |                |
| miR-27a | MAP2K4       | Prostate | 17 patients 5 cell lines | Tumor suppressor                                                      | China   | 2016  | Wan [157]      |
| miR-136 | MAP2K4       | Prostate | 27 patients 5 cell lines | Suppressed proliferation and invasion of PCa cells                   | China   | 2018  | Zhu [158]      |
| miR-1826 | MEK1      | Bladder  | 19 patients 4 cell lines | Inhibited cancer cell viability and invasion, and induced apoptosis   | USA     | 2012  | Hirata [162]   |
| miR-30e | MAPK         | Prostate | 57 patients 2 cell lines | Inhibited PCa cell invasion and migration                            | China   | 2018  | Zheng [170]    |

**Fig. 1** All of the miRNAs–protein kinases interactions that are involved in prostate and bladder tumor progressions.
crucial for increased tumor cell motility and loss of tissue integrity during EMT process in which non-motile epithelial cells acquire mesenchymal feature. Many transcriptional repressors such as TWIST1, SNAI1, and ZEB2/SIP1 regulate E-cadherin expression through binding to the E-box promoter sequences [45, 46]. There were significant associations between miR-200, E-cadherin, and anti-EGFR sensitivity. MiR-200 upregulated the E-cadherin and increased sensitivity to EGFR inhibitors, whereas downregulated the ZEB-1 and ZEB-2 and suppressed cell motility [47]. EGFR activation has been reported as one of the pivotal reasons of chemoresistance [48, 49]. Targeting the EGFR signaling pathway using monoclonal antibodies to inhibit the receptor dimerization or small molecule tyrosine kinase inhibitors (TKIs) is common therapeutic strategies in EGFR-mutated cancers [50, 51]. Ras signaling pathway upregulates the EGFR ligands which constitutes an autocrine EGFR activation loop to promote cancer progression [52, 53]. The polycomb repressive complexes PRC1 and PRC2 are well-established regulators of gene expression that function in chromatin remodeling and epigenetic gene silencing in the early developmental stages [54]. The expression of Snail/Suz12 is regulated by EGFR pathways in Ras-mutated PCa cells. MiR-203 had also a key role in SUZ12 regulation in PCa cells. Moreover, Snail/Suz12 axis regulated the expression of miR-203a via a mutually inhibitory feed-forward loop in an EGF-dependent manner. EGFR signaling pathway upregulated Snail/PRCs, while suppressed the miR-203a [55]. EGFR serves as an upstream regulator of TWIST1 that is a transcription factor involved in high-grade PCa [56]. There was an association between EGFR and STAT3 to facilitate EMT process in breast cancer cells through TWIST1 upregulation [56]. It has been reported that the EGFR promoted PCa growth and bone metastasis through TWIST1 induction and miR-1 suppression. There was also an inverse correlation between TWIST1 and miR-1 expression in clinical samples [57]. X-linked inhibitor of apoptosis protein (XIAP) belongs to the inhibitors of apoptosis (IAP) family of proteins which directly suppresses apoptotic pathways. XIAP upregulation is involved in radio-chemoresistance [58, 59]. However, XIAP downregulation renders the tumor cells vulnerable toward chemotherapeutic-related apoptosis [60, 61]. XIAP enhances the colorectal cancer growth via induction of E2F1 transcriptional activity [62]. EGFR-overexpressing tumors are more responsive to the anti-IAPs antagonists indicating a possible association between XIAP and EGFR in tumor cells [63]. XIAP suppressed the expression of Rac1 by PP2A activation. The activated PP2A inhibited MAPKK/MAPK axis and c-Jun which resulted in miR-200a downregulation. Since miR-200a suppresses EGFR expression, XIAP-related miR-200a downregulation leads to the promotion of EGFR translation and increased anchorage-independent growth in bladder tumor cells [64]. MiR-133a/b significantly suppressed the proliferation, migration, and invasion of PCa cell lines through EGFR inhibition. MiR-133 functions as a potent tumor suppressor, especially in androgen-independent PCa. MMP-2 as an effector of EGFR pathway which is regulated through GSK3β/snail/E-cadherin axis was also downregulated following the miR-133a/b transfection [65]. ETS variant gene 6 (ETV6) is a member of the E26 transformation-specific family. Deletion of ETV6 has been frequently reported in PCa [66, 67]. ETV6 is a tumor suppressor that represses cell proliferation and migration in PCa. It was also observed that the EGFR induced miR-96 while inhibited ETV6 during PCa progression [68]. ERBB2 is also a class I receptor tyrosine kinase. MiR-4319 suppressed growth and chemoresistance in PCa cells through ERBB2 targeting. There were significant reduced levels of miR-4319 in PCa specimens compared with normal margins which was associated with poor prognosis and survival. MiR-4319 also upregulated the BCL-2 and CASP9 [69]. HuR belongs to the RNA-binding proteins (RBPs) involved in various physiological processes such as cell proliferation and stress responses [70]. Upregulation of HuR and/or its cytoplasmic aggregation has been reported in PCa [71, 72]. The 3’-UTR of ERBB2 is a specific site for the HuR binding in PCa cells that enhances ERBB2 levels through counteracting the repression of ERBB2 through miR-331-3p. The concomitant upregulated HuR and downregulated miR-331-3p were associated with PCa progression through increased ERBB2 levels [73]. ERBB3 as a transmembrane receptor belongs to the EGFR family that promotes cellular proliferation, survival, and migration [21]. Interaction of ERBB3 and p85 triggers the PI3K recruitment and activation [74]. ERBB3 downregulation suppressed EMT in UM-UC-3 and T24 bladder cancer cell lines through regulation of AKT2/Sna1 pathway. There were significant ERBB3 upregulation and miR-148a-3p downregulation in BCa tissues compared with normal margins. MiR-148a-3p directly targeted the ERBB3, DNMT1, and AKT2 [75].

Class V, VII, and VIII receptors of tyrosine kinases

Fibroblast growth factor receptor 3 (FGFR3) is a member of the trans-membrane tyrosine kinase family of receptors that functions as a key regulator of multiple cellular and biological processes such as cell growth, differentiation, apoptosis, migration, and tumor progression [76, 77]. Increased levels of circ0068871 were observed in BCa tissues compared with normal margins which were correlated with N-stage and T-stage. Circ0068871 enhanced BCa progression via FGFR3 upregulation and
downregulation in BCa tissues and cell lines compared with controls. MiR-101 suppressed the T24 cells invasion, whereas c-MET upregulation increased T24 cells invasion. Therefore, it was concluded that the miR-101 repressed BCa invasion through c-MET targeting [106]. It has been observed that the miR-433 suppressed EMT through regulating AKT/GSK-3β/Snail signaling pathway in BCa cells in which CREB1 and c-Met were downregulated by miR-433. There was significant miR-433 downregulation in tumor cells compared with normal margins. MiR-433-induced c-Met suppression inhibited the AKT and induced GSK-3β, which were contributed to the Snail nuclear accumulation and elevated E-cadherin expression. CREB1 downregulation inhibited AKT/GSK-3β/Snail signaling pathway in BCa cells [96]. MiR-323a-3p significantly inhibited the EMT progression of BCa cells through regulating MET/SMAD3/SNAIL signaling. MiR-323a-3p also inhibited invasion and migration of BCa cell lines through inhibiting MET to regulate EMT progression of BCa cells in which CREB1 and c-Met were downregulated by miR-433 [96]. There was significant miR-433 downregulation in tumor cells compared with normal margins. It functioned as a tumor suppressor that repressed the proliferation of prostate tumor cells through targeting the c-MET/AKT/mTOR axis [108].

Class II and X receptors of tyrosine kinases
IGF1R is a tyrosine kinase receptor involved in important biological and physiological processes such as cellular differentiation, proliferation, migration, and tissue homeostasis [109, 110]. IGF1R activation has been identified to be correlated with poorer prognosis of PCa [110]. AXL is a trans-membrane receptor tyrosine kinase which constitutes the TAM family of receptor tyrosine kinases along with TYRO3 and MER [111]. AXL regulates PCa invasion and proliferation [112]. It has been reported that the miR-139 suppressed the AXL and IGF1R in PCa cells. The patients without tumor recurrence had higher expression levels of miR-139 compared with metastatic cases. There were significant associations between miR-139 downregulation and poor prognostic indicators such as high tumor stage/grade, lymph node involvement, and recurrence. MiR-139 inhibited PCa cell migration, proliferation, and cell cycle via targeting AXL and IGF1R which leads to downstream effects on the PI3K/AKT axis and cyclin D1 downregulation [113]. MiR-145 was introduced as a tumor suppressor via IGF-IR suppression in bladder tumor cells [114]. IGF1R is upregulated in metastatic and hormone-resistant PCa [115–117]. Let-7a1 suppressed prostate tumor cell proliferation, while triggered cell cycle arrest and apoptosis via IGF1R, c-FOS, and ELK1 inhibition [118].
Non-receptor tyrosine kinases

The Abelson (ABL) family of non-receptor protein tyrosine kinases is implicated in cell differentiation, proliferation, adhesion, and motility [119]. Integrin alpha3 (ITGA3) is a cell adhesion molecule involved in tumor cell proliferation and migration [120]. It has been reported that there was a significant decreased levels of miR-4723 expressions in PCa tissues which was associated with poorer prognosis. MiR-4723 inhibited tumor cell proliferation and invasion and induced apoptosis through ABL kinases and ITGA3 targeting [121]. ABL1 and ABL2 are distinct members of ABL family which are ubiquitously expressed and function as key regulators of multiple oncogenic signaling cascades promoting cell proliferation, survival, adhesion, and migration through the actin remodeling [122]. ABL kinases are involved in the actin cytoskeleton reorganization mediated by adaptor proteins such as CRKL and CRK [123]. ABL2 inhibits RhoA by depolymerization of F-actin which results in cytoskeleton collapse and cell migration suppression [124, 125]. MiR-20a upregulation was observed in PCa tissues compared with normal margin which was correlated with poorer prognosis. The inhibitory function of miR-20a on migration and invasion of PCa cells was achieved through ABL2 targeting [126]. SRC kinase family is a family of non-receptor tyrosine kinases that are implicated in key signaling pathways responsible for cell growth, differentiation, migration, and apoptosis [127, 128]. Overexpression of SRC kinase is associated with higher risk of tumor metastasis and poor prognosis in PCa [127, 129]. It has been revealed that there were significant correlations between miR-3607 downregulation, increased tumor growth, PSA levels, and lower survival in PCa. MiR-3607 also significantly suppressed the tumorigenicity of cancer cells through SRC kinases targeting [130]. Hormone ablation therapy is used to temporarily manage metastatic PCa symptoms and tumor growth; however, tumor cells will finally become resistant to hormone therapy. Reconstitution of androgen receptor (AR)-mediated signaling is a core process that leads to castration-resistant prostate cancer (CRPC) [131, 132]. SRC interacts with multiple receptor families and is especially activated in downstream of receptor tyrosine kinases [133]. SRC is considered as an upstream signaling molecule involved in the survival of PCa cells in AR deprivation conditions [133–136]. MiR-1 was involved in inhibition of the in vivo bone metastasis. AR upregulated the miR-1 through binding to the miR-1-2 regulatory region. There was an inverse association between miR-1 and SRC expression levels. Low canonical AR signature also downregulated and upregulated the miR-1 and SRC, respectively, in PCa [137]. Enhancer of zeste homolog 2 (EZH2) is a histone-lysine N-methyltransferase that suppresses tumor-suppressor genes [138] and induces AR during PCa progression [139]. MiR-124 inhibited PCa cell proliferation, increased sensitivity to enzalutamide, and triggered apoptotic death through AR, EZH2, and SRC tyrosine kinase targeting [140]. G3BP2 belongs to the Ras-GTPase-activating protein (RasGAP) SH3 domain-binding protein (G3BP) family. G3BP2 upregulation is associated with tumor invasiveness [141]. Focal adhesion kinase (FAK) has key functions in cancer progression and invasion through interaction with steroid receptor coactivator (SRC) [142]. A significant circFNDC3B downregulation was observed in BCa tissues and cell lines which were correlated with high tumor stage and grade, lymph node involvement, and poor prognosis. CircFNDC3B suppressed BCa growth and metastasis via miR-1178-3p sponging that downregulated the G3BP2 and inhibited the SRC/FAK phosphorylation [143]. Yamaguchi sarcoma viral homolog 1 (YES1) is a proto-oncogene tyrosine–protein kinase which belongs to the SRC family involved in tumor cell proliferation and chemoresistance [144, 145]. There was a significant lower level of miR-199a in PCa tissues compared with normal margins. MiR-199a downregulation was also characteristic of paclitaxel-resistant and aggressive PCa through YES1 targeting. Increased chemosensitivity and apoptotic cell death and YES1 inhibition were observed in PCa cells with miR-199a upregulation [146]. Zeta-associated protein 70 (ZAP70) is a member of the SYK tyrosine kinases which has a pivotal role for T cell migration and T cell hybridoma invasion [147, 148]. ZAP-70 expression is also correlated with increased response to the survival and migration signals in B cell chronic lymphocytic leukemia [149]. An inverse association was reported between ZAP70 and miR-631 in PCa tissues and cell lines. MiR-631 suppressed invasion and migration of prostate tumor cells via ZAP70 inhibition [150]. Protein tyrosine kinase 6 (PTK6) is a non-receptor tyrosine kinase involved in modulation of cell growth and differentiation [151–153]. PTK6 induces EMT through AKT41 activation. MiR-214 suppressed growth and migration of PCa cell lines through PTK6 targeting. Ibrutinib (IBT) is a chemotherapeutic medication that permanently binds and irreversibly inhibits Bruton tyrosine kinase (BTK). It is conventionally used for the treatment of liquid malignancies such as mantle cell lymphoma and chronic lymphocytic leukemia. The results demonstrated that inhibiting PTK6 using miR-214 alone or in concomitant administration of miR-214 and IBT reduced cell proliferation and viability in PCa [154].
Serine threonine kinases
MAP2K4 belongs to the MAPK signaling pathway involved in regulation of cell proliferation, cell cycle, apoptosis, tumor progression, and distant metastasis [155, 156]. MAPK family members serve as an integration point for the various biochemical signals. MiR-27a exerted its tumor-suppressive function through MAP2K4 targeting and inhibiting in prostate tumors. There were reduced levels of miR-27a expressions in PCA cells. Moreover, PI3K signaling pathway suppressed the miR-27a expression in castration-resistant PCa [157]. MiR-136 downregulation was observed in PCA tissues and cell lines. It also suppressed proliferation and invasion of PCA cells through directly targeting MAP2K4 [158]. Ras/Raf/MAPK pathway is regarded as the most characterized signaling pathway among all MAPK signal transduction pathways. Following the activation of Ras, the protein kinase activity of Raf is triggered, and MEK (MEK1 and MEK2) is activated [159]. Activation of the Ras pathway was closely associated with WNT to drive bladder tumor progression [160]. Different growth factors such as VEGF have been reported to be associated with the elevated activity of Ras/Raf/MEK/ERK pathway. CTNNB1 is a core component of the WNT pathway in BCa [161]. There were inverse correlations between miR-1826, MEK1, VEGF, and CTNNB1 expressions which are the direct targets of miR-1826. MiR-1826 also suppressed the survivin expression in transfected cells. BCa cells had significant downregulated miR-1826 levels compared with normal cells. MiR-1826 inhibited cancer cell viability and invasion and induced apoptosis through MEK1, VEGF, and CTNNB1 suppressing [162]. A variety of antioxidants including curcumin, resveratrol, and isoflavone have promising efficacy in suppressing the progression and metastasis of different tumors [163]. Resveratrol is a polyphenol found in red grapes, peanuts, and berries [164, 165]. Resveratrol exerts its anticancer activity through upregulating estrogen receptor-b and suppressing the phosphorylation of IGF-1 and ERK1/2 [166]. It has been shown that the resveratrol inhibited PCA cells viability and migration through AKT-mediated miR-21 downregulation. Therefore, AKT/miR-21 pathway is an important target of resveratrol that mediates its anticancer activity in highly aggressive PCA cells. Phosphorylation of AKT and upregulation of miR-21 targeted the PDCD4 which inhibited the eukaryotic initiation factor 4A (eIF4A). PDCD4 also suppressed AP-1-dependent transcriptional activity via c-Jun inhibition that prevented its growth-stimulating function [167]. MiR-30e drives NF-kB-mediated PCA proliferation and growth through inhibition of IkBα [168]. Blockade of M3 muscarinic acetylcholine receptor (CHRM3) inhibits the castration-resistant growth of PCA cells and increases their sensitivity to androgen deprivation through CaM/CaMKK-mediated phosphorylation of AKT [169]. There were reduced and increased levels of miR-30e and CHRM3, respectively, in PCa tissues compared with normal margins. MiR-30e inhibited PCA cell invasion and migration via CHRM3 downregulation and inhibition of MAPK signaling pathway [170].

Conclusions
For the first time, this review highlights the miRNAs as the pivotal regulators of protein kinases in bladder and prostate cancers. It was observed that the class VIII receptors of tyrosine kinases and non-receptor tyrosine kinases were the most frequent targets for the miRNAs in bladder and prostate cancers, respectively. As the miRNAs are more stable and noninvasive markers compared with mRNAs, they can be efficiently introduced as kinase-specific noninvasive markers for the early detection of bladder and prostate cancers.
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