Non coding RNAs as the critical factors in chemo resistance of bladder tumor cells

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Abstract

Background: Bladder cancer (BCa) is the ninth most frequent cancer worldwide with an annual estimated 356,000 new cases and 145,000 deaths [1]. It ranks the fourth common cancer among males [2]. Many factors are involved in BCa progression such as smoking, industrial carcinogens, and familial history [3]. Approximately 10–20% of the patients who experience recurrence are prone to develop the muscle-invasive bladder cancer (MIBC) [4]. Although, surgery is the main treatment option of non-invasive bladder cancer, a noticeable ratio of these patients experience tumor relapse [3]. Non-muscle-invasive tumors can be treated by transurethral resection followed by chemotherapy or immunotherapy. Grade of tumor invasion is an important factor for the treatment management in which low-grade tumors are treated with only resection, while high-grade with relapse risk may require further resection and bacille Calmette-Guérin (BCG) therapy [5]. Chemotherapy has been considered as an effective first-line treatment for early BCa aiming to suppress cancer progression, prevent recurrences, and enhance patients’ survival [6]. However, BCa is prone for the chemo resistance and tumor relapse. Since, early detection can significantly improve the survival rate, monitoring of the drug-resistance progression can be helpful for early treatment of recurrence [7]. A combine of chemo radiation and cystectomy, offers an efficient option with long-term survival rates [8]. The methotrexate, vinblastine, doxorubicin, and cisplatin combination therapy was associated with severe side effects, while the Gemcitabine/cisplatin combination is safe and efficient in BCa patients [9]. Cisplatin-based chemotherapy is the common method, however it has not any influence on overall survival following radical cystectomy among high-risk cases [10]. Regarding the
chemotherapeutic resistance, many patients are faced with side effects without any efficient benefit. Genetic factors are associated with drug resistance through regulation of drug efflux, DNA repair, cell cycle, and apoptosis [11–13]. Non-coding RNAs (ncRNAs) are a class of RNAs including long non-coding RNAs (lncRNA), micro RNAs (miRNA), and circular RNAs (circRNA) which are involved in post transcriptional regulation. Since, the ncRNAs have an important role in drug response of tumor cells [14–16], we have summarized all of the reported ncRNAs which have been associated with chemotherapeutic resistance in BCa for the first time in the world (Table.1).

Main text
Long non coding RNAs
LncRNAs are key regulatory molecules involved in cell proliferation, development, and oncogenesis that achieve their roles through post-transcriptional regulation [54]. They have pivotal roles in transcriptional regulation through functioning as molecular signals, sponges, decoys, scaffolds, and enhancer RNAs [55, 56]. Drug resistance in various malignancies can be attributed to LncRNAs function as regulator of gene expression which results in higher rate of tumor cell proliferation and reduced apoptosis [57]. Cisplatin (DDP) has been used among the first-line chemotherapy medications for high grade and stage bladder tumor patients [58]. However, a large fraction of BCa patients are resistant to cisplatin-based chemotherapy [9, 59]. Sirtuin-1 (SIRT1) is a NAD-dependent deacetylase that diminishes the tumor suppressive effect of p53, thereby dampening the efficacy of clinical radiotherapy and chemotherapy. Therefore, SIRT1 inhibition results in tumor cells death through p53 modulation and activation [60]. It has been reported that there were significant decreased and increased levels of miR-133b and MST1P2 expressions in cisplatin-resistant bladder tumor cell lines, respectively. MiR-133b directly suppressed the SIRT1 expression. MST1P2/miR-133b axis had an important role in cisplatin-resistance of BCa through SIRT1/p53 pathway [17]. It has been shown that there was overexpression of HIF1A-AS2 in tissues and cell lines of BCa following the cisplatin treatment which makes bladder tumor cells resistance to cisplatin-triggered cell death. HIF1A-AS2 enhanced survival of tumor cells by upregulating high-mobility group A1 (HMGAI), thereby limiting the transcriptional function of p53 family. It was identified that interaction of p53 with HMGAI restricted their transcriptional activity on proapoptotic BAX protein [18]. MiR-582-5p has tumor-suppressive functions and reduces the tumor cell proliferation and migration via targeting CDKI, FOXCI, and RAB27a [61–63]. ATG7 is implicated in the two ubiquitin-like systems and is essential for autophagy [64]. It has been reported that the UCA1 was up regulated in BCa. It acts as an endogenous sponge to down regulate the miR-582-5p which resulted in ATG7 over expression. UCA1 is important for the regulation of proliferation and invasion of BCa cells through modulating UCA1-miR-582-5p-ATG7-autophagy axis. As UCA1 shRNA markedly reduced the expression level of LRP, MRP1, and GST, and significantly overexpressed TOPO-II, it is hypothesized that knockdown of UCA1 decreases chemo resistance [19]. It has been observed that there was GAS5 down regulation in bladder transitional cell carcinoma which was associated with advanced grade and stage. GAS5 also increased doxorubicin-induced apoptosis through BCL-2 suppression [20].

Drug efflux is also another mechanism of tumor drug resistance that can be regulated by different lncRNAs [65]. MALAT1 increases the expression levels of MRP1 an MDR1 through STAT3, thereby is responsible for inducing cisplatin-resistance in lung tumor cells [66]. It has been shown that MALAT1 repression caused a better response of BCa cells to chemotherapy and increased cisplatin sensitivity. MALAT1 induced chemo resistance through regulating miR-101-3p/VEGFC axis. Bladder tumor tissue had higher level of MALAT1 compared with normal margins [21]. Gastric carcinoma proliferation-enhancing transcript 1 (GHET1) is a lncRNA involved in cisplatin resistance in gastric cancer [67]. MRP1 is a member of ATP-binding cassette (ABC) superfamily which regulates the intracellular distribution of molecules and is also involved in transport of different complexes across extra-and intra-cellular membranes. Moreover, it confers resistance to chemotherapeutic treatments in cancer cells due to its ability of drugs efflux. It has been observed that there was significant GHET1 overexpression in BCa, which was positively correlated with advance tumor grade and muscle invasion. GHET1 up regulation was also associated with higher Gemcitabine-chemo resistance in BCa cells. Moreover, GHET1 up regulated the MRP1 in BCa cells, which in turn enhanced their Gemcitabine resistance [22]. Gemcitabine is a nucleotide analogue commonly used as the first line anticancer drug therapy for many solid tumors such as breast cancer, ovarian cancer, and BCa [68, 69]. FOXD2-AS1 is significantly up regulated in BCa, and via establishing a positive feedback loop with AKT and E2F1 is contributed to increased progression and aggressiveness of bladder tumor cells [70]. It has been shown that there was a dose-dependent pattern of FOXD2-AS1 overexpression in gemcitabine resistant bladder tumor cells. Repression of FOXD2-AS1 expression resulted in lower levels of ABCC3 protein, and down regulation of several genes...
Table 1: all of the ncRNAs associated with chemotherapeutic resistance in BCa

| Study     | Year | Gene    | Country | Drug          | Results                                                                                     |
|-----------|------|---------|---------|---------------|--------------------------------------------------------------------------------------------|
| Chen [17] | 2020 | MST1P2, | China   | Cisplatin     | MST1P2/miR-133b axis had an important role in cisplatin-resistance of bladder cancer through SIRT1/p53 pathway. |
| Chen [18] | 2019 | HIF1A-AS2 | China   | Cisplatin     | HIF1A-AS2 enhances survival of tumor cells by upregulating HMGA1.                           |
| Wu [19]   | 2019 | UCA1    | China   | Rapamycin     | UCA1 acts as an endogenous sponge to down regulate the miR-582-5p which resulted in ATG7 over expression. |
| Zhang [20] | 2017 | GASS    | China   | Doxorubicin   | GASS increased doxorubicin-induced apoptosis through BCL-2 suppression.                     |
| Liu [21]  | 2019 | MALAT1  | China   | Cisplatin     | MALAT1 induced chemo resistance through regulating miR-101-3p/VEGFC axis.                   |
| Li [22]   | 2019 | GHET1   | China   | Gemcitabine   | GHET1 upregulated the MRp1.                                                                  |
| An [23]   | 2018 | FOXD2-AS1 | China   | Gemcitabine   | FOXD2-AS1 indirectly targets the ABCC3 through miR-143 sponging.                           |
| Wang [24] | 2017 | MiR-143 | China   | Gemcitabine   | The miR-143 attenuated gemcitabine resistance via IGF-1R suppression.                        |
| Fan [25]  | 2014 | UCA1    | China   | Cisplatin     | UCA1 overexpression was contributed to upregulation of WNT6.                                |
| Pan [26]  | 2016 | UCA1    | China   | Cisplatin, Gemcitabine | UCA1 activates miR-196a-5p via CREB which results in gemcitabine/ cisplatin resistance.   |
| Xie [27]  | 2017 | TUG1    | China   | Doxorubicin   | TUG1 knockdown decreased Dox resistance through restraining the activity of Wnt/β-catenin pathway. |
| Xie [28]  | 2018 | CDKN2B-AS | China   | Gemcitabine   | CDKN2B-AS induced Gemcitabine-resistance via sponging Let-7.                                |
| Zhuang [29] | 2017 | LET     | China   | Gemcitabine   | TGFβ1 promotes gemcitabine resistance through LncRNA-LET/NF90/miR-145 axis.                |
| Li [30]   | 2019 | DLEU1   | China   | Cisplatin     | DLEU1 upregulated the HS3ST3B1 via miR-99b suppression.                                    |
| Zhao [31] | 2019 | NEAT1.1 | China   | Cisplatin     | NEAT1.1 was downregulated following cisplatin treatment.                                   |
| Xiao [32] | 2018 | MiR-22-3p | China   | Paclitaxel, Adriamycin, Epirubicin, hydroxycamptothecin, Cisplatin, and Gemcitabine | MiR-22-3p enhanced resistance to chemotherapy in bladder tumor cells through suppressing NET1. |
| Deng [33] | 2015 | MiR-27a | China   | Paclitaxel, Adriamycin, Cisplatin | MiR-27a/RUNX-1 pathway has a key function in chemo-resistance.                            |
| Drayton [34] | 2014 | MiR-27a | UK      | Cisplatin     | MiR-27a deregulation induced cisplatin resistance in bladder cancer cells via up regulating SLC7A11. |
| Bu [35]   | 2014 | MiR-101 | China   | Cisplatin     | MiR-101 regulates cisplatin sensitivity in bladder tumor cell lines via targeting the COX-2. |
| Vyntil [36] | 2012 | MiR-34a | USA     | Cisplatin     | MiR-34a sensitized tumor cells to cisplatin by targeting SIRT-1 and CDK6.                   |
| Li [37]   | 2014 | MiR-34a | China   | Cisplatin     | MiR-34a targets CD44 after cisplatin therapy.                                              |
| Liu [38]  | 2018 | MiR-34a | China   | Epirubicin    | MiR-34a significantly reduced Epirubicin chemo resistance in bladder tumor cells through targeting TCF1 and LEP1. |
| Zhang [39] | 2017 | MiR-34a | China   | Cisplatin, Gemcitabine | MiR-34a regulation of GOLPH3 is active in bladder CSCs resistant to gemcitabine and cisplatin. |
| Tan [40]  | 2019 | MiR-34b-3p | China   | Paclitaxel, Adriamycin, Epirubicin, Cisplatin, Pirarubicin | MiR-34b-3p attenuated chemo resistance in bladder cancer through suppressing CCND2 and P2RY1. |
| Luan [41] | 2018 | MiR-98  | China   | Cisplatin, Doxorubicin | MiR-98 promotes chemo-resistance through targeting LASS2.                                |
| Li [42]   | 2019 | MiR-101-3p | China   | Cisplatin     | MiR-101-3p decreased cisplatin-resistance in bladder urothelial carcinoma through repressing EZH2 and MRp1. |
| Cao [43]  | 2018 | MiR-129-5p | China   | Gemcitabine   | MiR-129-5p inhibits resistance to gemcitabine in bladder cancer cells and promotes their apoptosis via targeting WNT5a. |
Table 1 all of the ncRNAs associated with chemotherapeutic resistance in BCa (Continued)

| Study  | Year | Gene        | Country   | Drug                                      | Results                                                                 |
|--------|------|-------------|-----------|-------------------------------------------|-------------------------------------------------------------------------|
| Lv [44]| 2015 | MiR-193a-3p | China     | Pirarubicin, Paclitaxel, Adriamycin,       | MiR-193a-3p mediated HOXC9 down regulation which resulted in poorer sensitivity to chemotherapeutic drugs. |
|        |      |             |           | Epirubicin Hydrochloride, and Cisplatin    |                                                                         |
| Deng   | [45] | MiR-193a-3p | China     | Pirarubicin, Paclitaxel, Adriamycin,       | PSEN1 was directly targeted by miR-193a-3p and executed its impact on     |
|        |      |             |           | Epirubicin hydrochloride, and Cisplatin    | the multi-chemo resistance.                                             |
| Lin    | [46] | MiR-193b-3p | Taiwan    | Cisplatin                                 | CEBPD/miR-193b-3p axis had key roles in cisplatin response.             |
| Deng   | [47] | MiR-193a-3p | China     | Paclitaxel, Adriamycin, Epirubicin         | MiR-193a-3p induced multi-drug resistance in bladder cancer cells        |
|        |      |             |           | Hydrochloride, and Cisplatin               | through down regulating LOXL4.                                          |
| Lv [48]| 2014 | MiR-193a-3p | China     | Pirarubicin hydrochloride, Paclitaxel,     | HIC2, SRSF2, and PLAU achieve their role in relaying miR-193a-3p’s      |
|        |      |             |           | Adriamycin, and Epirubicin hydrochloride   | effect on chemo resistance in bladder cancer through regulation of      |
| Shindo | [49] | MiR-200b    | Japan     | Cisplatin                                 | Myc/Max, NF-jB, DNA damage response, and NOTCH pathway.                |
| Zhang  | [50] | MiR-203     | China     | Cisplatin                                 | The miR-203 up regulation increased the cytotoxic effects of cisplatin  |
| Liu    | [51] | MiR-214     | China     | Cisplatin                                 | and decreased tumor cell viability through suppressing Survivin and      |
| Li     | [52] | MiR-218     | China     | Cisplatin                                 | BCL-w.                                                                  |
| Zeng   | [53] | MiR-222     | China     | Cisplatin                                 | The UCA1-dependent suppress tumor cells proliferation and migration,    |

related to inducing drug resistance including MDR1, MRP2, and LRP. Therefore, FOXD2-AS1 regulated gemcitabine-resistance in BCa cells. FOXD2-AS1 indirectly targets the ABCC3 through miR-143 sponging [23]. Insulin-like growth factor-1 receptor (IGF-1R) has pivotal role in cell survival, differentiation, proliferation, and apoptosis inhibition [71]. IGF-1R activates the PI3K/AKT signaling which is critical for cell survival [72, 73]. MiR-143 up regulation suppresses tumor cells proliferation and migration, and triggers apoptosis. It also increases the oxaliplatin sensitivity of tumor cells through targeting IGF-1R [74]. It has been reported that there was significant decreased levels of miR-143 expression in bladder tumor cell lines and tissue samples compared with normal margins. There was an inverse association between miR-143 and IGF-1R mRNA expression levels which showed that the miR-143 exerts its tumor-suppressive role through IGF-1R regulation. MiR-143 overexpression significantly inhibited the p-ERK and p-AKT levels. It also attenuated the gemcitabine resistance via IGF-1R suppression [24].

LnRNAs can also be associated with drug response during tumor progression through regulation of different signaling pathways [75]. Studies have confirmed the association between up regulation of IncRNA urothelial carcinoma associated 1 (UCA1) in bladder tumor tissue with cell growth, invasion, and migration [76]. UCA1 is frequently up regulated in bladder malignancies and contributed to aggressiveness of bladder tumor cells [76]. WNT signaling is an important pathway during embryogenesis and carcinogenesis [77, 78]. A significant UCA1 up regulation has been shown in bladder tumor tissues following cisplatin treatment. UCA1 overexpression was also contributed to up regulation of WNT6 and induction of WNT pathway which promotes cisplatin resistance in tumor cells [25]. The WNT6 and SRPK1 are up regulated as a result of UCA1 overexpression, which leads to cisplatin resistance [25, 79]. UCA1 promotes epithelial-mesenchymal transition (EMT) and activates mTOR and ERK pathways, and increases Gefitinib resistance in EGFR-mutant lung carcinoma [80]. It has been reported that the UCA1 activates miR-196a-5p via CREB which results in gemcitabine/cisplatin resistance. UCA1 up regulation had a significant association with diminished rate of apoptosis and higher cell survival. UCA1 promotes CREB phosphorylation through AKT pathways. Therefore, UCA1-dependent CREB activation was considered as a key step in miR-196a-5p transcriptional regulation in bladder tumor cells [26]. TUG1 is an oncogenic IncRNA in various cancers [81–86]. Doxorubicin (Dox) is an anthracycline antibiotic which induces cell cycle arrest and apoptosis through induction of the double-strand breaks [87]. It has been reported that the TUG1 knockdown decreased Dox resistance through restraining the activity of Wnt/
β-catenin pathway; whereas, TUG1 up regulation was significantly associated with Dox resistance and poor prognosis [27]. CDKN2B-AS is an oncogenic IncRNA in various cancers [88–90]. Gemcitabine is a deoxycytidine analogue with anticancer function, which is used as the first-line chemotherapeutic medication against bladder urothelial carcinoma. It is metabolized and activated by cytidine deaminase and deoxycytosine kinase, respectively. It disrupts the replication of DNA, causes cell cycle arrest at G1/S stage, and promotes apoptosis [91]. It has been reported that there was up regulation of CDKN2B-AS in bladder urothelial carcinoma tissues and cell line which was positively associated with advance tumor grade. CDKN2B-AS up regulation was also correlated with Gemcitabine chemo resistance in BCA patients. Suppression of CDKN2B-AS attenuated the Gemcitabine-resistance in 24/Gem cells through inactivation of WNT signaling pathway. Therefore, CDKN2B-AS induced Gemcitabine-resistance via sponging Let-7 for activating WNT signaling pathway [28]. Although, anti-neoplastic chemotherapeutic drugs like gemcitabine at first show beneficial effects in almost all patients, a noticeable ratio of patients experience recurrences following resistance. TGFβ1 is a cytokine involved in EMT and self-renewal [92]. NF90 is also a RNA binding protein with critical roles in RNA processing, localization, turnover, and transcriptional stability of HIF-1α, IL-2, and VEGF [93–96]. The up regulation of CSC markers such as CK14, CK5, and CD44 indicated that the BCA stemness is stimulated during chemotherapy. TGFβ1 was overexpressed following Gemcitabine treatment. Moreover, aberrant expression of IncRNA-LET/NF90/miR-145 pathway was mediated by TGFβ1 which eventually increased stemness and chemo resistance. KLF4 and HMGA2 as the miR-145 targets were responsible for miR-145 suppressive effect against the stemness of BCA cell [29].

The DLEU1 is an IncRNA associated with tumor cell aggressiveness and migration [97–100]. It has been shown that there were higher levels of DLEU1 expressions in bladder tumor tissues compared with normal margins. DLEU1 up regulation was also associated with worse prognosis in BCA patients. Moreover, up regulation of DLEU1 enhanced tumor growth and aggressiveness and induced cisplatin resistance through H53ST3B1 induction. DLEU1 up regulated the H53ST3B1 via miR-99b suppression. Overexpression of H53ST3B1 was significantly correlated with shorter survival rates in BCA patients. Furthermore, ectopic H53ST3B1 expression enhanced tumor growth, invasiveness, and cisplatin resistance [30]. NEAT1 is an oncogenic IncRNA in various cancers and promotes the cell proliferation, migration, and aggressiveness through regulation of various miRNAs. Some studies have demonstrated that NEAT1 attenuates cisplatin chemo resistance [101, 102], while other studies showed the NEAT1 as inducer of cisplatin resistance [103, 104]. It has been demonstrated that the NEAT1.1 was down regulated following cisplatin treatment in BCA cells. The p53, OCT4, and c-MYC regulated the expression level of NEAT1 through interacting with its promoter region. There were OCT4, c-MYC, and p53 up regulations in cisplatin-resistant BCA cells. The knockdown of NEAT1 suppressed the proliferation and migration of BCA cells and induced apoptosis following cisplatin treatment [31].

**MicroRNA-22-3p and 27a**

Neuroepithelial cell transforming 1 (NET1) is a guanine nucleotide exchange factor for RhoA and is involved in regulating extracellular signal transduction. It has been observed that the miR-22-3p enhanced resistance to chemotherapy in bladder tumor cells through suppressing NET1. NET1 was also markedly up regulated in 5637 cell line compared with H-bc cell line. Moreover, there was an inverse association between NET1 and miR-22-3p expression levels. NET1 was introduced as the direct target of miR-22-3p in chemo resistance of bladder tumor cells [32]. MiR-27a down regulation in bladder tumors can be associated with reduced chemotherapeutic response [34, 105–107].

RUNX-1 is a direct target for inducing tumor chemosensitivity using miR-27a. The findings have shown a significant correlation between miR-27a overexpression and improved chemotherapeutic outcomes. The carriers of rs11671784 A allele had significantly poorer outcomes after chemotherapy compared with rs11671784 GG homozygote patients. It was also indicated that the miR-27a significantly down regulated the P-glycoprotein [108]. It has been reported that the miR-27a up regulation was significantly associated with overexpression of CASP3 and BAX, and BCL-2 down regulation. MiR-27a decreased tumor cells’ resistance to chemotherapy by increased rate of apoptosis. There was a correlation between rs11671784 G/A variation and reduced miR-27a expression which results in increased RUNX-1 expression drug resistance. RUNX-1 up regulation was significantly correlated with reduced bladder tumor drug sensitivity. Therefore, miR-27a/RUNX-1 pathway has a key function in chemo-resistance in bladder malignancies [33]. Many solid tumors display resistance towards cisplatin mainly due to sequestration, reduced uptake, and increased drug efflux. Sequestration of cisplatin is accomplished by a variety of substances such as glutathione (GSH) as an efficient electron donor involved in detoxification of xenobiotics [109]. Glutathione shows antagonistic effect against cytotoxicity of radiotherapy and chemo therapeutic medication [110]. Glutamate-cysteine ligase catalyzes the first step of GSH synthesis that is regulated by the availability of cystine at both
transcription and translation levels [111]. Heterodimeric xc-cysteine-glutamate transporter is an antiporter which simultaneously exports glutamate and imports cystine [112], and is consisted of SLC3A2 and SLC7A11. It has been observed that the miR-27a deregulation induced cisplatin resistance in BCa cells via up regulating SLC7A11, followed by increased cystine import and higher intracellular glutathione levels. The results suggested that the miR-27a/27b and SLC7A11 expression levels along with intracellular glutathione levels in BCa tissue could be considered as predictive factor for determining the probability of cisplatin-chemo resistance. Patients with down regulated SLC7A11 showed better response to therapy and had better prognosis [34]. Cyclooxygenase-2 (COX-2) is an important mediator for the synthesis of inflammatory prostaglandins and is involved in tumor invasion, angiogenesis, and drug resistance [113, 114]. There is a negative correlation between miR-101 and COX-2 expressions in which miR-101 up regulation reduces cisplatin-chemo resistance through COX-2 inhibition [115]. It has been shown that there was a significant decreased expression of miR-101 in BCa cells resistant to cisplatin. Therefore, miR-101 regulates cisplatin sensitivity in bladder tumor cell lines via targeting the COX-2 [35].

MicroRNA-34a and 98

MiR-34a is a potential tumor suppressor miRNA and its down regulation has been reported in various malignancies [116]. Dysregulated miR-34a has been associated with resistance to chemotherapeutic drugs [36, 117–120]. This might be due to the modulating impact of miR-34a on p53 signaling pathway. Ectopic expression of miR-34a caused apoptosis, cell cycle arrest, and drug resistance alteration through SIRT-1, CDK6, E2F3, and BCL-2 targeting [121–123]. CDK6 is considered as the marker of chemo-resistant bladder CSCs [124–126]. It has been reported that there was a correlation between miR-34a up regulation and cisplatin sensitivity in BCa. Moreover, miR-34a targets CDK4 after cisplatin therapy [37]. It has been reported that up regulation of miR-34a significantly reduced Epirubicin chemo resistance in bladder tumor cells through targeting TCF1 and LEF1. Therefore, miR-34a up regulation leads to the suppression of WNT signaling pathway while increasing the rate of epirubicin-induced apoptosis [38]. Golgi phosphoprotein 3 (GOLPH3) is involved in Golgi trafficking [127]. GOLPH3 deregulation is associated with poor prognosis in BCa [128]. It has been reported that there was a significant reduced miR-34a expression in gemcitabine-resistant BCa cells. MiR-34a reduced the stemness of chemo resistant BCa cells and increased gemcitabine and cisplatin responses. GOLPH3 was also significantly over expressed in BCa cells, xenograft, and sphere cells resistant to gemcitabine and cisplatin. Moreover, the up regulation of CSC biomarkers including KLF4, SOX2, and CD44 were observed in bladder tumor cells and xenograft. Therefore, miR-34a regulation of GOLPH3 is active in bladder CSCs resistant to gemcitabine and cisplatin [39]. Aberrant p53/Rb signaling pathway is correlated with increased tumor invasiveness and growth in muscle invasive BCa [129–131]. The expression levels of components of this pathway are important in predicting the clinical outcome of the chemotherapy. E2Fs as downstream effectors of Rb, and CDK6 as regulator of Rb phosphorylation are directly targeted by miR-34a. MiR-34a enhances apoptosis rate through suppressing BCL-2 expression. CDK6 interacts with CDK4 and CCND1 to form a complex which is fundamental for Rb function and G1/S transition. SIRT-1 is a NAD-dependent deacetylase which targets FOXO, SFRP1, p53, and PGC1 [132–134]. It has been reported that the miR-34a sensitized tumor cells to cisplatin by targeting SIRT-1 and CDK6. The M1-TCC patients resistant toward cisplatin chemotherapy had significantly lower levels of miR-34a expression compared with sensitive patients [36]. Cyclin is critical for the regulation of cyclin-dependent kinase (CDK) activity. Cyclin D-CDK4/6 complex has a critical role during transition from G1 to S phase [135, 136]. The P2RY1 is a member of G-protein-coupled receptors family which is a receptor for extracellular ADP [137, 138]. Binding of ADP to P2RY1 mobilizes intracellular calcium through activation of phospholipase C, which results in platelet shape change and aggregation [139, 140]. It has been reported that the miR-34b-3p attenuated chemo resistance in BCa through suppressing CCND2 and P2RY1 [40].

MiR-98 was recognized as an important agent in regulating mitochondrial activity, which increases bladder tumor cells resistance toward mitochondrial apoptosis. It was also established that miR-98 targets LASS2 tumor suppressor. There was also an inverse association between miR-98 and LASS2 mRNA levels in bladder tumors. LASS2 functions in negative regulation of mitochondrial activity and has a putative role in mediating chemo-resistance caused by miR-98. Therefore, miR-98 promotes chemo-resistance through targeting LASS2, which enhances mitochondrial fusion and disrupts mitochondrial membrane potential [41].

MicroRNA-101, 129-5p, and 193a-3p

MiR-101-3p is considered as a tumor suppressor and is down regulated in different malignancies such as BCa, colorectal cancer, and breast cancer [141–144]. EZH2 as a target of miR-101-3p is a member of the Polycomb-group family involved in transcriptional repression [145]. MRP1 is a member of ATP-binding cassette (ABC) transporters which transport different molecules across
intra- and extra-cellular membranes. It induces chemo resistance via exporting chemotherapeutic medications before they exert their antineoplastic effects [146–148]. It has been reported that there were miR-101-3p down regulations in bladder urothelial carcinoma tissues and cell lines resistant to cisplatin. MiR-101-3p overexpression also suppressed the MRP1 expression level. Therefore, miR-101-3p decreased cisplatin-resistance in bladder urothelial carcinoma through repressing EZH2 and MRP1 [42]. Gemcitabine is a deoxycytidine analogue which disrupts DNA synthesis, induces replication-associated DNA double-strand breaks, and triggers apoptosis in cancer cells. Gemcitabine is effective in improving overall survival (OS) in metastatic BCa patients [149].

NOTCH signaling pathway has a pivotal role in various cellular processes such as cell cycle, migration, metabolism, and apoptosis [150, 151]. MiR-129-5p is involved in tumor cells drug response via modulation of NOTCH signaling receptor DLK1 [152]. WNT5a is also a member of WNT ligand family, which has critical role is regulation of cell proliferation and migration [24]. WNT5a increases the GSK-3-independent degradation of β-catenin [153–155]. Some studies have revealed that WNT5a induces resistance to chemotherapy via up regulating ABCB1 [156] and inducing PI3K/AKT signaling pathway [157]. It has been reported that lower levels of miR-129-5p was correlated with lower sensitivity of BCa cells to gemcitabine therapy; however, overexpression of miR-129-5p inhibits resistance to gemcitabine in BCa cells and promotes their apoptosis via targeting WNT5a [43].

Substantial epigenetic changes along with genetic variations are the origin of all cancerous features [158]. These epigenetic changes and defects have a more significant impact on tumor cells phenotype and gene expression than genetic changes. Detection of aberrant DNA methylation at promoter sequence of oncogene and tumor suppressor genes is an efficient method of early diagnosis [159–161]. MiR-193a-3p impedes tumor proliferation and decreases drug resistance through down regulation of various genes such as CCND1, ERBB4, and PTEN [162, 163]. HOXC9 belongs to highly conserved homeobox family of genes, and encodes proteins that function as homeodomain transcription factors playing a crucial role in morphogenesis in all multicellular organisms. It has been revealed that the miR-193a-3p mediated HOXC9 down regulation which resulted in poorer sensitivity of BCa to chemotherapeutic drugs. Oxidative stress and DNA damage response were also influenced by epigenetic suppression of HOXC9 through miR-193a-3p [44]. Presenilin (PSEN1) is a catalytic element of the γ-secretase complex that performs intramembrane cleavage of numerous protein substrates leading to activation of the NOTCH pathway [164]. Studies have shown the positive impact of PSEN1 on overexpression of ABCC1/ MRP1 via NOTCH signaling [165]. It has been reported that the PSEN1 was directly targeted by miR-193a-3p and executed its impact on the multi-chemo resistance. PSEN1 up regulation rendered H-bc cells more sensitive to chemotherapy-induced cell death. However, RNA interference-mediated repression of PSEN1 gene resulted in lower rates of apoptosis and desensitizing 5637 cell line to chemotherapy-induced cell death [45]. Platinum compounds are frequently used for treatment of various malignancies by forming bifunctional DNA adducts which results in transcriptional suppression and apoptosis induction [46]. C/EBP is a family of transcription factors with pivotal roles in regulation of cellular differentiation, proliferation, and apoptosis [166–168]. CEBPD is also involved in genomic stability through transcriptional modulation of DNA damage response proteins. It was observed that CEBPD and cisplatin increased the expression levels of miR-193b-3p. Moreover, miR-193b-3p had regulatory effect on ETS1 and CCND1. MiR-193b-3p was also important for CDDP-triggered cell cycle arrest, cell cytotoxicity, and inhibition of cellular migration. CEBPD/miR-193b-3p axis had key roles in cisplatin response of urothelial carcinoma cells in which CEBPD up regulates the miR-193b-3p and improved cisplatin cytotoxicity in urothelial carcinoma. This process was associated with ETS1 and CCND1 down regulations, cell migration inhibition, cell cycle arrest, and cisplatin-triggered cytotoxicity in NTUB1 cell line [46]. The oncogenic function of miR-193a-3p is due to its suppressive effects on various genes such as KRAS and c-KIT [169, 170]. Lysyl oxidase homolog 4 (LOXL4) is a member of the lysyl oxidase family which is necessary for the biogenesis of connective tissue by formation of crosslinks between collagens and elastin fibers. It has been indicated that the miR-193a-3p induced multi-drug resistance in BCa cells through down regulating LOXL4, and thus initiating oxidative stress pathway [47]. Hypermethylation of the promoter and enhancer regions are associated with epigenetically silenced status of ncRNAs and protein-coding genes. The PLAU encodes the urokinase-type plasminogen-activator protein, a serine protease which has key functions in degradation of extracellular matrix during tumor progression and metastasis. The HIC2 is a transcription factor involved in systemic lupus erythematosus [171] and digeorge syndrome [172]. SRSF2 belongs to the serine/arginine-rich family of pre-mRNA
splicing factors [173]. HIC2 interacts with CCNT1 to positively regulate MYC/Max pathway [174, 175]. It has been reported that the HIC2, SRSF2, and PLAU achieve their role in relaying mir-193a-3p’s effect on chemo resistance in BCa through regulation of Myc/Max, NF-jB, DNA damage response, and NOTCH pathway [48].

**MicroRNA-200b, 203, 214, 218, and 222**

Members of miR-200 family are potent inhibitors of EMT through inhibiting the expression of ZEB1 and ZEB2 [176, 177]. IGFBP3 is an important mediator of insulin growth factor (IGF) signaling pathway. IGF1 shows higher affinity for interaction with IGFBP3 than its specific receptor (IGF1R), thereby IGF1’s binding to IGFBP3 interrupts accurate interaction between IGF1 and IGF1R, dampening the anti-apoptotic functions of IGF1 [178]. TNFSF10 belongs to the TNF superfamily and promotes the apoptosis of tumor cells through activation of death receptors [179]. It has been reported that there was a correlation between epigenetic silencing of miR-200b and cisplatin resistance in BCa. Microarray analysis showed that genes associated with CDDP sensitivity or cytotoxicity, such as TNFSF10, ICAM1, and IGFBP3 were induced in the resistant cells as a result of miR-200b/cisplatin treatment [49].

Although, Cisplatin is the main drug in BCa combination chemotherapy regimens including GC (gemcitabine and cisplatin) and MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin), almost half of the MIBC patients do not respond to the cisplatin-based treatment [180]. BCL-w exerts its anti-apoptotic effects through regulation of the intrinsic apoptotic pathway [181]. Anti-apoptotic activity of survivin is accomplished through blocking the caspases in a complex with XIAP [182]. It has been reported that there was a correlation between miR-203 down regulation and poor prognosis in BCa patients who were under cisplatin-based chemotherapy. MiR-203 up regulation also increased cell proliferation and decreased cisplatin sensitivity [193].

**Conclusions**

Regarding the importance of ncRNAs in regulation of drug response in tumor cells, in present review we have summarized all of the reported ncRNAs which are associated with chemotherapeutic resistance in BCa. It was observed that the IncRNAs were the most reported ncRNAs associated with drug response of BCa. This review paves the way of introducing a prognostic panel of ncRNAs for the BCa patients to improve the selection of an efficient chemotherapeutic strategy based on ncRNA profile of BCa patients.

**Abbreviations**

NMBBC: Non-Muscle-Invasive Bladder Cancer; BCa: Bladder cancer; ncRNAs: Non-coding RNAs; MIBC: Muscle-invasive bladder cancer; BCG: Bacille Calmette-Guérin; IncRNA: Long non-coding RNAs; miRNA: Micro RNAs; circRNA: Circular RNAs; SIRT1: Siruin-1; HMGA1: High-mobility group A1; IGF-1R: Insulin-like growth factor-1 receptor; UCA1: Urothelial carcinoma associated 1; EMT: Epithelial-mesenchymal transition; GHET1: Gastric carcinoma proliferation-enhancing transcript 1; Dox: Doxorubicin; NET1: neuroepithelial cell transforming 1; GSH: Glutathione; COX-2: Cyclooxygenase-2; GOLPH3: Golgi phosphoprotein 3; ABC: ATP-binding cassette; OS: Overall survival; PSEN1: Presenilin; C/EBP: CCAAT/enhancer binding protein; IGF: Insulin growth factor
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ASZ, HRR, MMojarrad were involved in search strategy and drafting. MMoghbeli supervised the project and revised and edited the manuscript. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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