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Non-coding RNA transcripts, incredible modulators of cisplatin chemo-resistance in bladder cancer through operating a broad spectrum of cellular processes and signaling mechanism

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ABSTRACT

Bladder cancer (BC) is a highly frequent neoplasm in correlation with significant rate of morbidity, mortality, and cost. The onset of BC is predominantly triggered by environmental and/or occupational exposures to carcinogens, such as tobacco. There are two distinct pathways by which BC can be developed, including non-muscle-invasive papillary tumors (NMIBC) and non-papillary (or solid) muscle-invasive tumors (MIBC). The Cancer Genome Atlas project has further recognized key genetic drivers of MIBC along with its subtypes with particular properties and therapeutic responses; nonetheless, NMIBC is the predominant BC presentation among the suffering individuals. Radical cystoprostatectomy, radiotherapy, and chemotherapy have been verified to be the common therapeutic interventions in metastatic tumors, among which chemotherapeutics are more conventionally utilized. Although multiple chemo drugs have been broadly administered for BC treatment, cisplatin is reportedly the most effective chemo drug against the corresponding malignancy. Notwithstanding, tumor recurrence is usually occurred following the consumption of cisplatin regimens, particularly due to the progression of chemo-resistant trait. In this framework, non-coding RNAs (ncRNAs), as abundant RNA transcripts arise from the human genome, are introduced to serve as crucial contributors to tumor expansion and cisplatin chemo-resistance in bladder neoplasm. In the current review, we first investigated the best-known ncRNAs, i.e. microRNAs (miRNAs), long ncRNAs (lncRNAs), and circular RNAs (circRNAs), correlated with cisplatin chemo-resistance in BC cells and tissues. We noticed that these ncRNAs could mediate the BC-related cisplatin-resistant phenotype through diverse cellular processes and signaling mechanisms, reviewed here. Eventually, diagnostic and prognostic potential of ncRNAs, as well as their therapeutic capabilities were highlighted in regard to BC management.

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1. Introduction

Bladder cancer (BC), which is common among urogenital neoplasms, is responsible for 5–10 % of all male specific cancers. The male-to-female ratio of this malignancy has been estimated to be 2: 1 to 6: 1 according to the geographical region [1]. BC has the ability of either being localized or develop to the bladder's muscle layer, the lymphatic system, and distant organs. In this regard, invasive BC is attributed to a condition, in which a tumor with the origin of bladder invades into the muscle layer of the corresponding organ. Unfortunately, systemic spread threats BC patients even in the presence of adequate eradication of localized disease [2].

In clinical setting, cisplatin is commonly administered to cure BC patients; however, this is not an efficient chemotherapeutic agent, and thus should be used in combination with other chemo drugs, *viz*. methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) combination therapy as well as gemcitabine and cisplatin (GC) regimen. These cisplatin-based adjuvant therapies have also been realized to be important in treatment of MIBC, which is known as muscle-invasive BC. Nevertheless, only 50 % of MIBC cases respond to cisplatin-based chemotherapies [3,4]. Moreover, gradual development of drug resistance disrupts the process of chemotherapy in a significant portion of patients as it induces the recurrence and expansion of tumors. Hence, impeding the chemo-resistance concurrent with finding more effective therapeutic strategies is necessarily required to overcome the bladder neoplasm [5]. Substantially, achieving this goal depends on the discovery of molecules and biological pathways, contributing to the occurrence of cisplatin resistance.

In this framework, non-coding RNAs (ncRNAs) have been identified to be in correlation with cisplatin chemo-resistance during BC. NcRNAs are particular RNA molecules transcribed from the human genome, which most of them do not contain the ability of encoding proteins. They are involved in a vast array of biological processes from gene expression regulation to protein function modulation [6,7]. Among diverse subsets of ncRNAs, microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs) are the commonest molecules participated in BC and its drug resistance. It has been confirmed that the corresponding RNA molecules can positively and/or negatively regulate cisplatin resistance by targeting multiple signaling mechanisms [8]. MiR-203 and circELP3 are respectively exemplified as a miRNA and a hypoxia-induced circular RNA that regulate cisplatin resistance through BC progression [9,10].

For a better understanding of the existing crosstalk between ncRNAs and cisplatin resistance in BC, the current review aims to detail molecular mechanisms and signaling pathways by which ncRNAs are linked to cisplatin resistance in BC, which might provide new insights for minimizing this type of drug resistance in the near future. Recent methodological advancements, such as single-cell sequencing, have provided new perspectives on eradication of cancer drug resistance. Indeed, the corresponding technologies uncover a range of information on individual drug-resistant cells to clarify mechanisms, being central to ncRNA-mediated cisplatin resistance in BC patients. Unraveling these mechanisms may in turn help other technologies for further suppression of cisplatin resistance, especially in conjugation with nanotechnology. In parenthesis, designing ncRNA-based nano-delivery systems will improve BC cisplatin resistance in a more reliable manner.

2. A brief survey on bladder cancer and conventional therapies

"Different geographical classifications represent diverse degrees of BC incidence", WHO says. In this regard, BC is more prevalent in developed countries compared to the less developed counterparts. BC is a multifactorial neoplasm that its onset is affected by smoking, overweight, alcohol consumption, and uncontrolled use of red meat, in which tobacco smoking is the commonest risk determiner [11]. BC can manifest as NMIBC, MIBC, or metastatic BC, each with different molecular characteristics. Improved knowledge of bladder cancer biology, along with extensive gene expression and sequencing studies, have resulted in more clinically beneficial targeted therapies and potent immunotherapies. These improvements have also enabled clinicians to classify bladder cancer into different molecular and histological subtypes (Fig. 1) [2].

MIBC is usually controlled by preventing the local and metastatic recurrence; however, the neoadjuvant platinum-based chemotherapy followed by radical cystectomy is currently used as the standard of care for MIBC therapy [12,13]. Hence chemo-resistance is an obstacle in this area, finding routes responsible for chemo-sensitivity may spare unnecessary cytotoxicity and posiible fatal delay in radical cystectomy for chemo-resistant BC patients [13]. Cisplatin is the commonest chemo-drug used in BC therapy and there are a number of genes have been found to be involved in cisplatin resistance as well as other drugs resistance to diverse degrees. Copper transporter 1 (CTR1) that conducts the transportation of cisplatin into BC cells [14], is a great example in this framework, which has been realized to be considerably overexpressed in patients who have more desirable therapeutic outcomes [15]. Beyond, a plenty of chemo agents typically act by binding to and then disrupting the DNA that is detectable in BC through the under-expression or loss of function of the DNA damage response genes, *viz*. excision repair cross complementation group 1 (ERCC1) and ERCC2 [16], as well as breast cancer gene 1 (BRCA1) [17], as the strong indicators of cisplatin sensitivity and patient OS enhancement [18,19]. According to a recently conducted phase II clinical trial, the co-expression extrapolation (COXEN) biomarker concept has been recognized to predict patient's tumor response by considering the sensitivities of *in vitro* cell lines and their well-known genomic profiles [20]. This trial proudly presented that COXEN Gemcitabine + Cisplatin had the ability of being an ideal predictor for down-staging when study participants in the Gembitabine + Cisplatin and dose dense MVAC (Methotrexate + Vinblastine Sulfate + Doxyrubicin Hydrochloride (Adriamycin) + Cisplatin) arms were combined (Fig. 1) [21].

Compared to other neoplasms, MIBC, like melanoma and non-small cell lung cancer (NSCLC), contains the highest mutational profile. Such malignancies respond to immune checkpoint inhibitors (ICIs) in a very desirable manner. In this context, atezolizumab, as a monoclonal antibody that binds to the programmed cell death ligand 1 (PDL1) immune checkpoint, received the Food and Drug Association (FDA) approvement for being administered to cure MIBC patients [22,23]. Although this agent was found to be successful in treatment of advanced BC, the FDA did not consider its benefit-risk profile suitable for all patients resistant to cisplatin. Thus, the therapeutic indication for both atezolizumab and pembrolizumab was then modified to include only MIBC patients with high expression levels of PDL1 that do not respond to cisplatin-based chemotherapies or those who are resistant to any platinum-based chemotherapy without consideration for PDL1 expression patterns [24]. After a while, the anti-PDL1 drug avelumab was approved for a dramatic treatment selection for first-line maintenance therapy for MIBC patients who are chemotherapy responder. Furthermore, the corresponding avelumab is approved by the FDA for patients who experience MIBC recurrence. This agent is also beneficial against metastatic BCs as well as locally advanced urothelial BC during the phase II and III trial evaluations. Thereby, it can be assumed that MIBC has no particular maintenance therapy in clinic, however ICI agents are likely to shine like precious diamonds [25,26].

To enhance the efficacy of conventional cisplatin-based therapies, researchers noticed that they should maximize the contact time of chemo drug with regard to the cancer cells lining the bladder lumen through implantation of carriers that provide a localized diffusion of the drug over time [27]. The major challenge on this road is cisplatin resistance, which is discussed in detail in the following paragraphs.

3. Chemo-resistance in bladder cancer; focusing on cisplatin resistance

BC is generally a chemo-sensitive neoplasm with a therapeutic response rate of 50–70 % to first-line therapies; however, it has a very poor prognosis in patients who experience post-chemotherapy recurrence. There is not yet a consensus in the eradication of or even minimizing cisplatin-resistance during BC [28]. In some European countries, vinflunine is accepted as a second-line chemotherapy for patients developed BC during frontline or perioperative platinum-containing treatments. Taxans and/or gemcitabine-containing regimens can also be secondarily valuated case by case [29]. The median time from randomization to progression or death, which is briefly defined as progression-free survival (PFS), has been found to vary from 3 to 4 months for second-line therapies [29].

As mentioned before, cisplatin is the backbone for chemotherapy regimens during BC treatment. It can be used as in combination with methotrexate, vinblastine, Adriamycin, and cisplatin, as the MVAC regimen or even as a part of gemcitabine and cisplatin (Gem-Cis) combination therapy. Considering the cisplatin ability of being diffused into the cell, it can interacts with the DNA strands. Following this interaction, cisplatin becomes activated by substituting its two chloride ligands with water molecules. The activated cisplatin will then disrupt the DNA structure, and the cell will be died due to the DNA damage-mediated activation of apoptotic flux [30]. Notwithstanding, cisplatin is mostly challenged by chemo-resistance in BC, by which the response rate hardly exceeds 50 % [29,31]. Thus, BC patients would likely benefit from a predictive test that can be analyzed on the biopsy specimens taken from the bladder tissue. A comprehensive understanding of molecular mechanisms involved in chemo-resistance is definitely needed to develop a suitable predictive marker.

A vast array of mechanisms, including drug inactivation, changes in drug target, drug efflux, DNA damage repair, apoptosis suppression, the epithelial–mesenchymal transition (EMT), and cholesterol metabolism impairment, have been realized to be responsible for the development of cisplatin resistance in BC cells (Fig. 2) [32]. Beyond the mentioned mechanisms, the m6A demethylation, which is the commonest internal RNA modification in eukaryotic cells, has been determined to affect the chemo-resistance against cisplatin [33]. In this regard, AlkB homolog 5 RNA demethylase (ALKBH5), as a m6A demethylase, is repressed in BC tissues and cell lines, which in turn provokes cisplatin resistance. Once the ALKBH5 is overexpressed, it triggers chemo-sensitivity through glycolysis mediated by casein kinase 2 (CK2) α in a m6A-dependent manner to regulate the survivability during BC [34]. Cisplatin effectiveness can also be diminished in the presence of high androgen concentrations; brix domain-containing protein 2 (BXDC2) is a molecule at the downstream of androgen receptor signaling pathway that can block the androgen receptor (AR) activity [35]. On this road, cisplatin sensitivity has interestingly been found to be enhanced in BC by regulating the BXDC2 activity that is resulted by the suppression of the AR pathway in conjugation with the extracellular signal-induced kinase (ERK) signaling [35].

The glycoprotein 130 (gp130) is a receptor subunit responsible for intracellular signaling that is needed for the cellular motivation and action of multiple cytokines. Previous studies tell us that this glycoprotein tends to have a direct relationship with cisplatin resistance [36]. The before stated relationship is further confirmed when gp130 down-modulation enhances cisplatin-chemo-sensitivity by triggering DNA repair mechanisms through induction of Ku 70, which is known for its ability in launching the canonical non-homologous end joining repair (c-NHEJ) along with blocking the apoptotic tract. A positive correlation exists between Ku 70 and gp130, such that gp130 silencing by a small molecule inhibitor (SMI) combined with cisplatin could trigger DNA double stranded breaks, apoptotic cell death, and decreases cell viability in BC through exerting an inhibitory effect on Ku 70 [36].

In addition to all those mechanisms, hypoxic conditions, simulated in laboratory, were found to block cisplatin chemo-sensitization of BC cells, as hypoxia provokes cisplatin resistance by inducing autophagy in

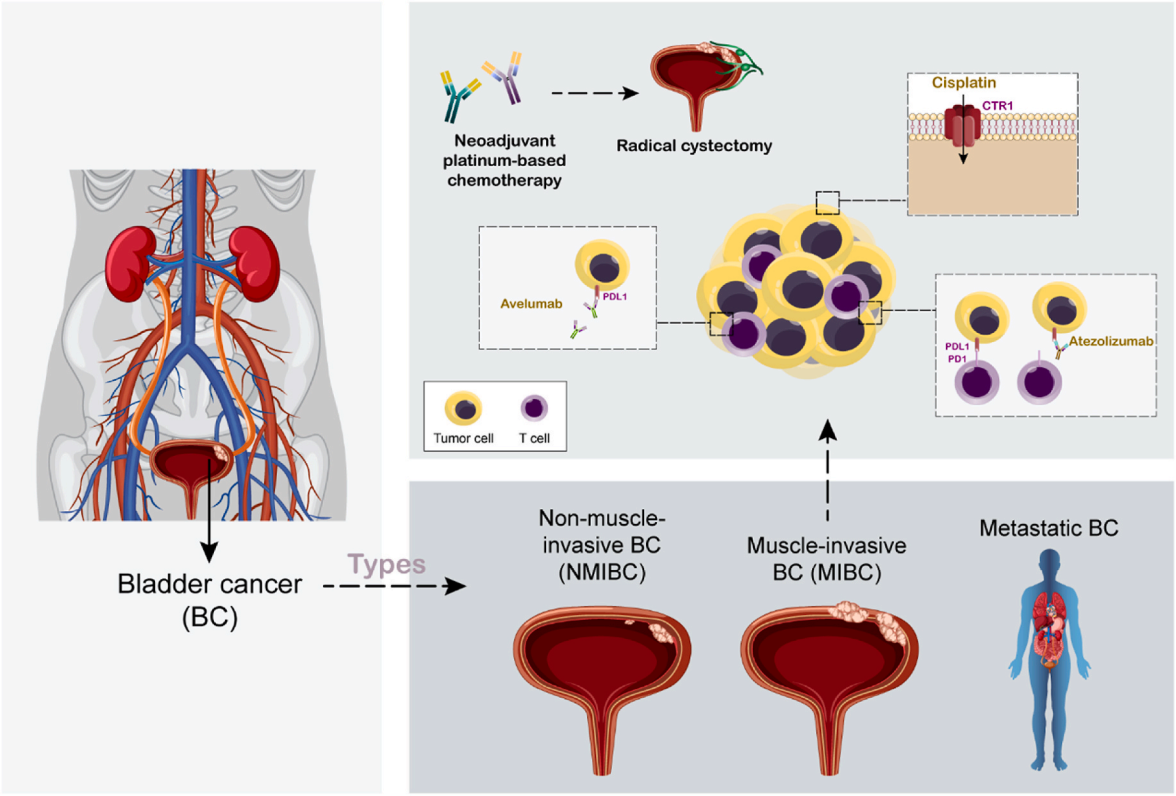

Fig. 1. Bladder cancer and conventional therapies.

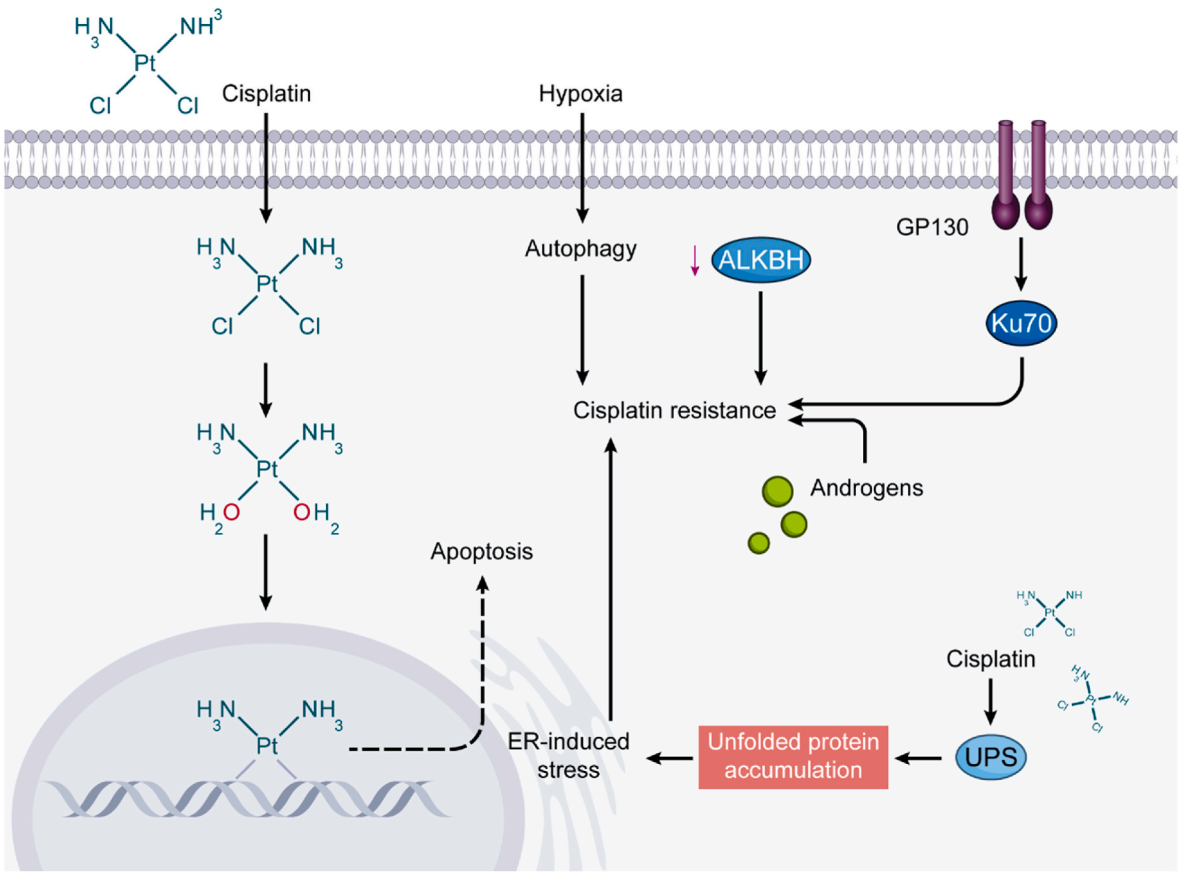

Fig. 2. Cisplatin resistance in bladder cancer.

BIU-87 BC cell line [37]. Apoptosis and autophagy, mediated by cisplatin, were switched off concurrent with the addition of a hypoxia-inducible factor (HIF-1α) – inhibitor. This finding put on an avenue to the possible roles of hypoxia-autophagy pathway in clinical management of BC cisplatin resistance [37]. The existing interaction between cisplatin resistance and the ubiquitin proteasome systems (UPS) is the last mechanisms discussed here; literally, cisplatin can stimulate the UPS activation and then chemo-resistance by activating the endoplasmic reticulum (ER) stress through the unfolded protein aggregation, demonstrating the substantial role of UPS in the regulation of cisplatin resistance during BC [38].

4. Non-coding RNAs, small molecules with big roles: recent advances and emerging trends

NcRNAs, as RNA molecules without the ability of producing functional proteins have various functions inside the cell. The study of ncRNAs is advancing fast, as new information about their different types, uses, and roles is constantly being discovered. NcRNAs that can regulate the expression of other genes are especially important, as they can affect both normal and abnormal cellular processes. ncRNAs are widely involved in many biological functions, and therefore have great potential for biomedical applications. They can be used as biomarkers, which are indicators of disease states, or as therapeutic agents, which are substances that can treat diseases. Many ncRNA-based therapies have been suggested for varied conditions, and some have even been tested in clinical trials. However, to make an RNA product that can be used for medical purposes, certain standards must be met, such as ensuring the purity, stability, and bioactivity of the RNA [39].

In this context, ncRNA transcripts are attractive candidates for treating cancer and other human diseases. These ncRNAs do not produce proteins, but they can regulate the expression of other genes. In the past decade, many RNA-based therapies have used antisense oligonucleotides and small interfering RNAs, which can bind to and silence specific RNA molecules. Some of these therapies have received FDA approval, but the results of clinical trials have been inconsistent, with some showing significant benefits and others having little effect or causing side effects. New approaches are being tested, such as anti-miRNAs, which can block the function of miRNAs. There is also a growing interest in lncRNA-based therapies, which can modulate various cellular processes [40,41].

Genome editing systems have made great strides in finding new ways to treat human diseases, with the CRISPR/Cas9 mediated ncRNA editing system standing out for its ability to directly alter target genes or create multifunctional tools. These systems have also shown promise in treating other diseases that are discussed in this article. At the same time, gene editing technologies have helped improve cell imaging, gene expression control, epigenetic change, drug development, gene function testing, and gene diagnosis. Novel genome editing combinations and more precise nanoscale carriers have increased the effectiveness and decreased the harm of delivering the gene editing tools, making them more suitable for clinical use. It is likely that genome editing technology can eventually reveal the biological secrets behind disease onset and progression, offer new treatments, and advance the field of life sciences, with more research on this technology [40,42].

Almost 98 % of the human genome is transcribed to ncRNA transcripts [43]. NcRNAs were initially considered as transcriptional noises or the waste of RNA processing, until more specialized evaluations have found these RNA molecules as functional contributors to the majority of cellular processes, such as apoptosis, cell proliferation, autophagy, migration, necrosis, etc [44,45]. Regarding the substantial role of ncRNAs in physiological and pathological pathways, much attention has

been paid to them through the recent decades. There are several ncRNAs identified to date, but miRNAs, lncRNAs, and circRNAs are the best-known ncRNAs subtypes that are categorized on the basis of size, function, and structure (Fig. 3) [44–46].

4.1. MicroRNAs

MiRNAs are small single-stranded RNA molecules with about 22 nucleotides in length that regulate mRNA stability and/or translation by facilitating base-pairing between the 5′ regions 2–7 or 2–8 of the miRNA and ~7 bp MREs in the 3′-UTR of the target mRNAs within the RISC [45,47]. Primary transcript of most miRNAs is generated in the form of pri-miRNAs, and then processed intracellularly by the DROSHA-DGCR8 microprocessor complex [47,48]. In this context, single nucleotide polymorphisms (SNPs) in DROSHA-coding gene are strongly correlated with the expansion of many tumors. Once pre-miRNA enters the cytoplasm, the DICER-transactivating response RNA-binding protein (TRBP) complex begins to unwind the double-stranded pre-miRNA, which in turn facilitates the interaction of miRNA's one strand (so-called the guide strand) with the RISC complex containing catalytic Argonaut proteins, such as AGO2. The other strand, i.e. passenger strand, which did not interact with RISC, undergoes degradation [49].

There are several studies that have confirmed the alterations in miRNA expression profiles through cisplatin resistance in diverse cancer lines, such as gastrointestinal cancers [50], hepatocellular carcinoma (HCC) [51], ovarian cancer, NSCLC, and germ line malignancies [52,53]. Consistently, miRNA-27a can be exemplified as a key regulator of chemo-resistance and prognosis in BC; a recently conducted study demonstrated that miRNA-27a was under-expressed in fixed formalin paraffin embedded samples collected from the bladder cancerous tissues from patients with recurrence and disease expansion, which was not observed in those who experienced a complete response [54].

4.2. Long non-coding RNAs

LncRNAs are the other subgroup of ncRNAs, including large transcribed RNAs with a length of more than 200 nucleotides without the ability of coding proteins, just like miRNAs [4][7] [55]. During the process of lncRNA biogenesis, these RNA molecules are transcribed by RNA polymerase II (RNAP2) under the control of transcriptional activators of the SWItch/Sucrose non-fermentable (SWI/SNF) chromatin remodeling complex. The newly generated lncRNAs then undergo a variety of post-transcriptional modifications from splicing to 3′-polyadenylation and 5′ 7-methylguanosine capping [56]. Despite having poorly conserved sequences, lncRNAs are considered to be functional molecules. Through cancer expansion they can act as tumor suppressors or even oncogenes to modulate gene expression through their cooperation with DNA, as well as different miRNAs, mRNAs, and proteins [57]. LncRNAs have also the ability of controlling both coding and non-coding genes and contribute to the regulation of chromatin remodeling, transcriptional activation and/or suppression, mRNA stability, and post-transcriptional regulation of protein activity in tissue and developmental-stage specific manners [56,57]. LncRNAs have multiple partners like RNA/DNA-binding proteins, diverse transcription factors, various RNA transcripts, mRNAs, miRNAs, and even DNA and chromatin [58]. In the context of miRNAs, these long non-coding RNA transcripts can employ their recognition elements to serve as competing endogenous RNAs (ceRNAs) that sponge miRNAs to prevent them from binding to and modulating the target mRNAs, a mechanism that has been detected in a wide range of regulatory processes [56,58]. RISC complex

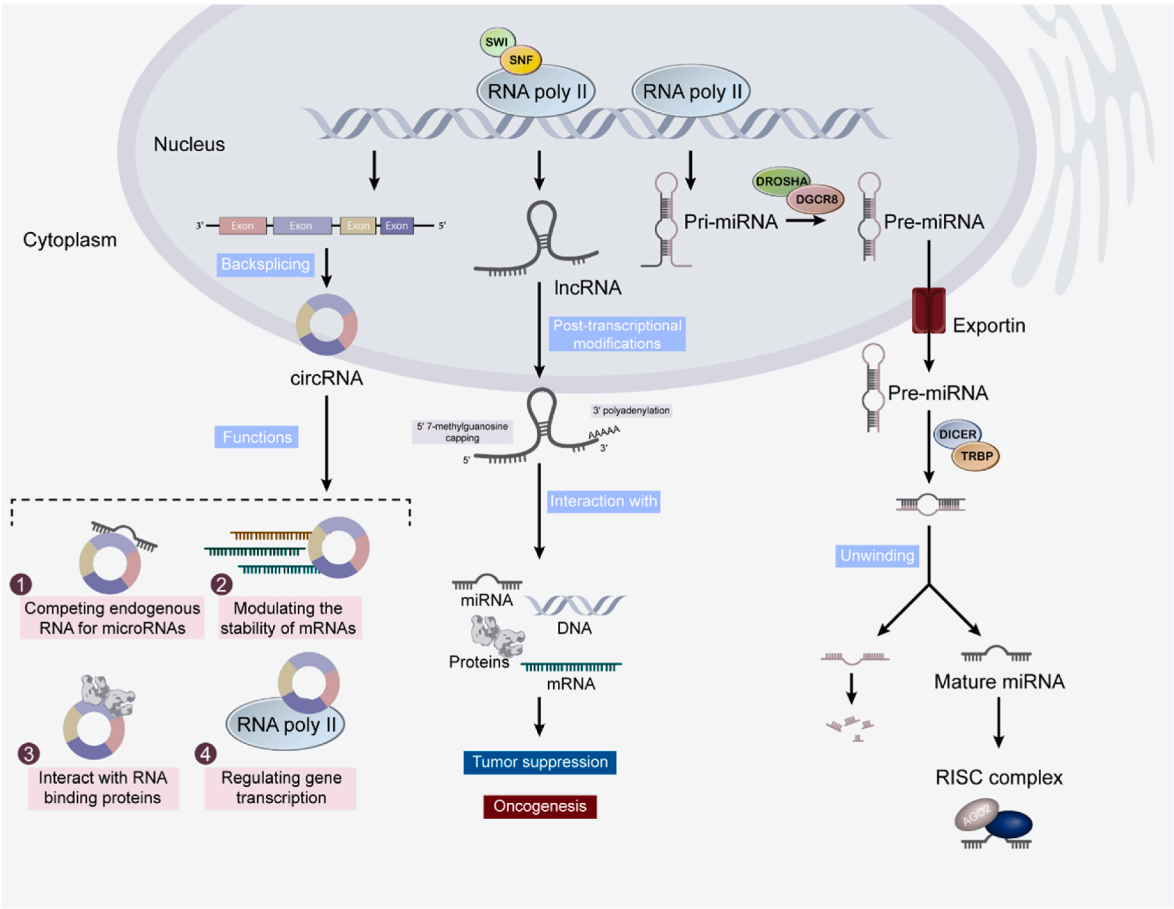

Fig. 3. MiRNAs, lncRNAs, and circRNA: Biogenesis and functions.

is responsible for the regulation of lncRNA-miRNA interaction and also clarifies the degrees of post-transcriptional modulations [57]. Like miRNAs, lncRNAs have also been found to involve in cancer-related processes, such as cell cycle modulation, cell proliferation, angiogenesis, migration, invasion, EMT, apoptosis, and cancer-correlated immune responses [59,60]. Targeting lncRNA-mediated ceRNA networks can surprisingly sensitize tumor cells to cisplatin, gemcitabine, and doxorubicin. Moreover, the TUG1 lncRNA, which is up-regulated in BC cell lines and tissues triggers EMT and weakens the cancer cell response to ionizing radiation therapies through the miR-145/ZEB2 regulatory axis [61].

4.3. Circular RNAs

CircRNAs are a different group of ncRNAs superfamily that are recognized for their particular closed-loop structures. During the canonical introns deletion, the backsplicing event can lead to the production of circRNAs that are immediately transferred out of the cytoplasm [62,63]. CircRNAs are very stable molecules with evolutionarily conserved sequences, making them central to different cellular activities. CircRNA levels are under the tight regulation of exon-skipping processes, RNA-binding proteins (RBPs), and complementary sequences of flanking introns [64,65]. In a lncRNA-similar manner, circRNAs can also serve as ceRNAs to sponge miRNAs, minimizing the miRNA-mediated blockade of target mRNAs [66]. Surprisingly, some circRNAs have recently been found to be translated into functional proteins; for instance, circ-SHPRH generates a SHPRH-146aa protein which is a potential tumor suppressor protein as well as a protective decoy for its full-length SHPRH protein in glioblastoma [67]. CircRNAs are also linked to cancer progression by contributing to multiple pathophysiological and neoplastic processes, *viz*. cell proliferation, invasion, migration, etc. In this framework, homeodomain-interacting protein kinase 3 (HIPK3) gene is cloned from a multidrug-resistant (MDR) cell line (KB–V1) and principally acts as a co-repressor of homeodomain transcription factors. CircRNA HIPK3 (circHIPK3) that is encoded by the corresponding gene, has a huge second exon (1099 nt) from the HIPK3 gene flanked on either side by long introns. Once circHIPK3 is accumulated, invasion, migration, and angiogenesis of BC cells are disrupted *in vitro*, and tumor cell growth and metastasis are blocked [68,69].

5. Non-coding RNAs in regulation of cisplatin chemo-resistance during bladder cancer; where do these RNA transcripts stand at the upstream of signaling mechanisms?

5.1. Apoptosis

Apoptosis, as a physiological process leading to programmed cell death, was first used in a 1972 by Kerr, Wyllie, and Currie to describe a biological flux that maintains cell homeostasis by eliminating injured cells [70]. Apoptosis is a conserved process that is genetically regulated [71]. Apoptosis defects are usually results in chemotherapy resistance and subsequent cancer expansion. There are several genes responsible for apoptosis controlling, among which Bcl-2 family and tumor suppressor p53 are the best-known ones. Bcl-2 genes, which primarily regulate mitochondrial apoptosis, have two major subdivisions as pro-apoptotic and anti-apoptotic genes; anti-apoptotic genes markedly contribute to the development of cancer drug resistance. Moreover, p53 activity is triggered as the consequence of multiple stresses and stressful conditions, such as DNA damage [72]. During the process of apoptosis, a group of cytosolic proteolytic enzymes, called caspases, mediate the expansion of the process. Concurrent with the activation of a caspase, other pro-caspases become activated and a caspase cascade will finally be induced, which gives rise to cell death that is occurred through three major pathways, including intrinsic, extrinsic, and perforin/granzyme-mediated pathways. In summary, the intrinsic pathway is mitochondrial and triggered by death signals like DNA damage and/or removal of trophic factors, while extrinsic pathway is stimulated by death receptors, such as tumor-necrosis factor and Fas receptors, located on plasma membrane, which ultimately induces the activation of aforementioned caspases [73,74]. For the third pathway, i.e. perforin/granzyme pathway, apoptosis can be developed by either the granzyme A or granzyme B. Like intrinsic and extrinsic pathways, granzyme B can induce apoptosis through caspase-3 cleavage, while granzyme A triggers the apoptotic tract through a caspase-independent manner. This amazing flux has been found to be in strong association with BC progression and cisplatin drug resistance [75,76]. More interestingly, apoptosis and its related genes are under the tight regulation of genetic and epigenetic mechanisms, among which ncRNA-based regulatory networks are of great significance (Table 1). Thereupon, the following paragraphs will focus on the role of ncRNAs in BC cisplatin resistance through apoptosis regulation through.

5.1.1. NcRNAs modulate apoptosis-related molecular mechanisms during BC cisplatin resistance

Polyribonucleotide nucleotidyltransferase 1 (PNPT1), is an enzyme located in the inner membrane of mitochondria, responsible for importing chromosomally encoded RNA transcripts into the mitochondrial matrix [13]. PNPT1 overexpression can significantly increase apoptotic cell death [77]. Thus, this nucleotidyltransferase has a considerable contribution to cancer cell survival and chemo-sensitivity. Consistently, tumor cells can be sensitized to chemo drugs as a consequence of targeting Bcl-2, which is central to mitochondrial apoptotic tract. In this context, PNPT1 involves in cisplatin-induced apoptosis during BC and can be targeted by miR-183–5p, as an onco-miRNA in BC, for further regulation of Bcl-2-modifying factor (BMF) during mitochondrial outer membrane permeabilization (MOMP) and mitochondrial apoptosis, due to the substantial correlation between mitochondria and tumor cell growth and also chemo-sensitivity. For instance, mitochondrial DNA (mtDNA)-depleted hepatoma cells have been reported to be resistant to hydrogen peroxide and ROS-inducing agents, which might be the result of manganese superoxide dismutase and glutathione peroxidase overexpression [78]. All these outcomes propose that targeting mitochondrial injuries can desirably inhibit chemo-resistance and restore the chemo-sensitivity trait in cancer cells. Beyond the drug resistance, PNPT1 expression has also been found to be correlated with the clinical stage of BC patients, demonstrating the PNPT1 involvement in cancer progression [79]. The corresponding miRNA/MOMP/PNPT1 regulatory loop is not only responsible for cisplatin resistance modulation and BC but also involves in mediating the doxorubicin chemo-resistance in breast cancer, along with other cancer types, under the supervision of miR-125b [80].

To obtain further information about the contribution of miRNAs to BC cisplatin resistance, researchers developed cisplatin-resistant bladder cancer cell models by exposing 5637 and T24 BC cell lines to cisplatin, and then analyzed miRNA expression profiles in the newly established cell lines. According to their investigations, miR-325 was found to be under-expressed in both cisplatin-resistant cells compared to the normal 5637 and T24 cells. They also realized that miR-325 recovery in the aforementioned cisplatin-resistant cells could desirably resensitize them to platinum-based therapeutics. Thus, miR-325 dysregulation was found to be related to BC cisplatin resistance, possibly in an apoptosis-dependent manner. Further mechanistic evaluations detected a footprint of hematopoietic cell-specific protein 1-associated protein X-1 (HAX-1), as an anti-apoptotic protein [81]. HAX-1 is primarily responsible for blocking the mitochondria collapse and loos of MMP, and thereby, reduces the release of cytochrome *c* from mitochondria, which in turn blocks the activation of caspase-9, -7, and -3 [82]. HAX-1 overexpression causes chemo-resistance against a variety of drugs, such as cisplatin [83,84], and thereby can be harbored as a potential therapeutic target to overcome cisplatin resistance. The above-stated miRNA, i.e. miR-325 was shown to be down-regulated during cisplatin resistance in BC, concurrent with HAX-1 up-modulation. In cisplatin-induced

Table 1
Role of ncRNAs in the regulation of BC-related cisplatin resistance by targeting signaling mechanisms.

NcRNAs	Study model	Sample type	Effect on cisplatin resistance/ sensitivity	Targets/Signaling pathways	Underlying mechanism	Ref.
MiRNAs						
MiR-183–5p	Human	BC tissues	Not applicable (N/A)	PNPT1	MiR-183-5p-PNPT1 regulatory axis regulates the apoptosis of BC cells. Oncogenic miR-183–5p directly targets the 3′ UTR of PNPT1 and reversed the tumor suppressive role of PNPT1.	[79]
	In vitro	Cell line			MiR-183–5p also modulates BMF to inhibit the mitochondrial outer membrane permeabilization (MOMP) in BC cells.	
	In vivo	BALB/c-nu mice				
MiR-7-5p	Human	BC tissues	↑ chemoresistance to cisplatin	ATG7	MiR-7-5p inhibits migration, invasion, and autophagy both *in vitro* and *in vivo*.	[232]
	In vitro	BC cell line			MiR-7-5p targets ATG7 to inhibit its expression, which in turn inhibits autophagy.	
	In vivo	mice (BALB/C)				
MiR-325	In vitro	BC cell line	↑ sensitivity of 5637/R and T24/R cells to cisplatin-induced mitochondrial apoptosis	HAX-1	Overexpression of miR-325 attenuates the cisplatin resistance of 5637/R and T24/R through suppression of HAX-1. MiR-325 promoted the mitochondria collapse and cisplatin-induced apoptosis in bladder cancer cells.	[85]
MiR-486–5p	In vitro	BC cell line	↑ cisplatin sensitivity	MMP-9, CD44, and ROCK	MiRNA-486–5p can induce apoptosis and inhibit cell migration. MiRNA-486–5p mimic in combination with cisplatin decreases cell migration ability and metastasis through down-regulation of the MMP-9, CD44, and ROCK genes; this indicates its possible anti-metastatic roles in MIBC cells.	[91]
MiR-222	In vitro	BC cell line	↑ cisplatin resistance	PPP2R2A/Akt/ mTOR axis	Blocking the activation of Akt with LY294002 or mTOR with rapamycin significantly prevents miR-222-induced proliferation and restores the sensitivity of BC cells to cisplatin.	[144]
MiR-101	In vitro	BC cell line	↑ cisplatin chemo-sensitivity	VEGF-C	MiR-101 overexpression significantly inhibits the migration and invasiveness, while significantly enhancing cisplatin sensitivity. MiR-101 negatively regulates VEGF-C protein expression, and VEGF-C overexpression rescues the effects of miR-101 overexpression, indicating that miR-101 negatively regulates VEGF-C protein expression post-transcriptionally. MiR-101 and VEGF-C interference independently enhances cisplatin cytotoxicity in BC cells.	[202]
MiR-150	In vitro	BC cell lines	↓ chemo-sensitivity	PDCD4	PDCD4 is identified as a direct target of miR-150 in MIBC cells, and increases PDCD4 expression *via* transfection with the pLEX-PDCD4 plasmid efficiently sensitized MIBC cells to cisplatin chemotherapy and inhibites MIBC cell invasiveness	[178]
MiR-101	In vitro	BC cell line	↑ cisplatin sensitivity	COX-2 pathway	MiR-101 overexpression significantly increases the anti-proliferative effects and apoptosis induced by cisplatin, whereas knockdown of miR-101 significantly decreases the anti-proliferative effects and apoptosis induced by cisplatin.	[253]
	In vivo	Nude mouse xenografts			Down-regulation of miR-101 induces cell survival and cisplatin resistance through the up-regulation of COX-2 expression.	
MiR-27a	Human	Tumors from BC patients	N/A	Cystine/glutamate exchanger SLC7A11	MiR-27a negatively regulates SLC7A11 in cisplatin-resistant BC cells	[264]
	In vitro	BC cell line				
MiR-34a	Human	MIBC tissues	↑ MIBC cells sensitivity to cisplatin	CD44	MiR-34a overexpression significantly sensitizes MIBC cells to cisplatin and inhibites the tumorigenicity and proliferation of cancer cells *in vitro* and *in vivo*	[155]
	In vitro	BC cell line				
	In vivo	Mice				
MiR-34a	Human	BC patients samples	N/A	CDK6 and SIRT-1	MiR-34a inhibition causes chemo-resistance and up-regulation of CDK6 and SIRT-1 expression	[265]
	In vitro	BC cell line				
MiR-424	In vitro	BC cell line	N/A	UNC5B and SIRT4	UNC5B and SIRT4 are the direct downstream target genes of miR-424. Cisplatin-mediated suppression of xenograft bladder tumor growth was prohibited by the addition of miR-424, whereas ectopic expression of UNC5B or SIRT4 partially restored miR-424-dependent decrease in cisplatin sensitivity of BC 5637 and T24 cells.	[266]
	In vivo	Mice			UNC5B or SIRT4 knockdown prohibits cisplatin-mediated proteolytic cleavage of PARP and also decreases cisplatin sensitivity of these cells	

(*continued on next page*)

Table 1 (*continued*)

NcRNAs	Study model	Sample type	Effect on cisplatin resistance/ sensitivity	Targets/Signaling pathways	Underlying mechanism	Ref.
MiR-214	Human In vitro	Clinical specimens BC cell line	↓cisplatin resistance	Netrin-1	MiR-214 may reduce cisplatin resistance and Akt signaling by targeting netrin-1.	[114]
MiR-193a-5p	In vitro	BC cell line	↓cisplatin sensitivity	AP-2α	MiR-193a-5p stimulates, but AP-2α suppresses cell migration. MiR-193a-5p targets the coding region of AP-2α mRNA and rs111681798 affects the binding of miR-193a-5p. MiR-193a-5p inhibits the expression of AP-2α	[210]
MiR-193a-3p	In vitro In vivo	BC cell line BALB/c male nude mice	↑ cisplatin resistance	LOXL4	MiR-193a-3p promotes the multi-chemoresistance of BC *via* repressing the LOXL4 expression and therefore activating the oxidative stress pathway	[262]
LncRNAs						
MST1P2	In vitro	BC cell line	N/A	SIRT1/p53	MST1P2 silence enhances the killing effects of cisplatin on resistant BC cells through miR-133b regulation. MiR-133b directly targets the SIRT1 3′-UTR to inhibit its expression. MST1P2/miR-133b axis affectea the resistance of BC cells to cisplatin *via* SIRT/p53 signaling.	[97]
NEAT1	In vitro	BC cell line	N/A	Myc, OCT4, and p53	NEAT1.1 is harmful for overcoming BC cisplatin resistance, and silencing NEAT1 can enhance the suppression of cell growth, invasion and transcriptional activation of NEAT1 modulates by multiple transcription factors in T24R cells.	[189]
HIF1A-AS2	Human	Clinical specimens	↑cisplatin resistance	HMGA1	HIF1A-AS2 suppresses the transcription activity of p53 family proteins by promoting the expression of HMGA1. The induction of HMGA1 physically interacts with p53, p63, and p73, and therefore constrains their transcriptional activity on Bax. Knockdown of HIF1A-AS2 or HMGA1 rescues the expression of Bax, which therefore enhances the killing effect of Cis.	[267]
UCA1	Human In vitro In vivo	Patients BC cell line SPF nude mic	↑ cisplatin/gemcitabine resistance	CREB	UCA1 may contribute to cisplatin/gemcitabine resistance *via* CREB u-regulated miR-196a-5p targeting p27Kip1 in human BC	[268]
MALAT1	Human In vitro	Tissue specimens BC cell line	↓cisplatin sensitivity	VEGF-C	MALAT1 suppression enhances the drug sensitivity and inhibites the cisplatin resistance of the BC cells	[215]
TUG1	Human In vitro In vivo	Patients BC cell line Nude mice	↑cisplatin resistance	CCND2	TUG1 knockdown attenuates the expression of EZH2, and it alleviates the promoter hypermethylation of miR194–5p and induced its expression. MiR-194–5p overexpression or TUG1 under-expression significantly sensitizes BC cells to cisplatin, inhibites the proliferation, and induces apoptosis. Besides, CCND2 is a direct target of miR-194–5p, while miR-194–5p is regulated by TUG1.	[164]
DLEU1	Human In vitro	Tissue samples BC cell line	↑ cisplatin resistance	HS3ST3B1	DLEU1 induces cell proliferation, invasion, and cisplatin resistance of BC cells	[171]
UCA1	Human In vitro	Tissue samples BC cell lines	↑ cisplatin resistance	Wnt signaling	UCA1 overexpression significantly increases the cell viability during cisplatin treatment, whereas UCA1 knockdown reduces the cell viability during cisplatin treatment. UCA1 positively regulates the expression of Wnt6 in human BC cell lines	[269]
CircRNA						
CircZNF609	Human In vitro In vivo	BC tissues BC cell line BALB/C nude mice	↓cisplatin sensitivity	CDC25B expression regulation by sponging miR-1200	CircZNF609 enhances BC cells proliferation, migration, and cisplatin chemo-resistance.	[224]
CiRS-7	Human In vitro In vivo	BC tissues BC cell line BALB/C nude mice	↑cisplatin sensitivity	CiRS-7/miR-1270/ APAF1 axis	CiRS-7 can adsorb miR-1270 in BC, restores its suppressed APAF1 expression level, induces apoptosis, and increases cisplatin chemosensitivity.	[140]
Hsa_circ_0000285	Human In vitro	BC tissues and serum samples BC cell line	↓ cisplatin resistance	N/A	N/A	[270]
Circ_0058,063	Human In vitro In vivo	BC tissues BC cell line Male BALB/c nude mice	↓ cisplatin sensitivity	↑ B2M through acting as miR-335–5p sponge	Circ_0058,063 down-regulation suppresses cell proliferation and tumor growth, whereas induces cell apoptosis in the cisplatin-resistant BC cells *in vitro* and *in vivo*	[175]

apoptosis, miR-325 targeted the HAX-1 to induce the activation of caspases as the result of the release of cytochrome *c*. Therefore, miR-325 recovery could restores the sensitivity of cisplatin-resistant BC cells to apoptosis induced by cisplatin, depending on the presence of HAX-1 [85].

MiRNA-486–5p is another miRNA contributing to inhibition or stimulation of tumorigenesis in different cancers types; in other words, it can either serve as a tumor-suppressor miRNA or an onco-miR to be respectively down-regulated or up-modulated through the cancer expansion [86]. Moreover, miR-486–5p has the ability of promoting the

tumorigenic process by targeting particular tumor suppressor genes or suppressing tumor cell growth and migration by direct or indirect targeting of specific oncogenes [87]. Phosphoinositide-3-kinase regulatory subunit 1 (PIK3R1), cyclin-dependent kinase 4 (CDK4), and forkhead box O (FOXO) are the major oncogenes targeted by miR-486–5p to regulate cancer cell migration/invasion, cell cycle progression/arrest, and cell proliferation, respectively [88–90]. Interestingly, using miR-486–5p mimic in conjugation with cisplatin has been recognized to induce apoptosis, decrease cell migration, and cease the cell cycle in BC compared to treatment with cisplatin or the miRNA mimic alone. MiR-486–5p mimic is an efficient BC suppressor, and thus can be considered as a promising therapeutic target against BC [87]. This potential miRNA mimic not only induces apoptosis and reduces tumor cell growth and survival but also enhances the sensitivity of BC cells in response to cisplatin. These findings were confirmed by *in vitro* analysis of both 5637 and A549 BC cells. Indeed, miR-486–5p mimic can help to minimize the effective dose of cisplatin in BC cells [91]. With a mechanistic view, the apoptotic flux was found to be triggered in BC cells treated with miR-486–5p mimic, especially combined with cisplatin. Flow cytometric detection of nuclear fragmentation further confirmed the post-treatment occurrence of apoptosis. Consistent with these findings, it was also determined that miR-486–5p combined with cisplatin could induce caspase-9 and -3, as well as p53, while suppressed the anti-apoptotic genes sirtuin 1 (SIRT1), olfactomedin 4 (OLFM4), SMAD4, and Bcl-2. Thus, it can be concluded that miR-486–5p mimic can help cisplatin to exert more efficient apoptotic effects on BC cell [92–94]. In detail, apoptosis induction caused by concurrent administration of this miRNA mimic and cisplatin chemo drug is primarily regulated through subG1 phase arrest during the cell cycle [91].

SIRT1, which was mentioned in the previous paragraph, is a sirtuin protein belonging to the NAD-dependent histone deacetylases superfamily. Once DNA damage downstream signaling is developed, SIRT1 begins to decelerate the apoptosis of tumor cells by blocking the repressive effects of p53 on cancer cells to mitigate the radiotherapy- and chemotherapy-related cytotoxic effects on tumors. Thereupon, SIRT1 suppression might promote cancer cell death by activating the tumor suppressor p53 in a wide range of neoplasms, such as osteosarcoma, HCC, and gliomas, as well as BC [95,96]. MiR-133b in this context has the potential of down-regulating SIR1 through establishing a direct linkage to the 3′-UTR of SIRT1-coding gene. In cisplatin-resistant SW780 and RT4 cell lines resembling BC in laboratory conditions, miR-133b inhibition was found to decrease the levels of cleaved caspase-3 and acetyl-p53 protein, while increase SIRT1 protein levels. In line with this fact, in cisplatin-resistant BC cells, the macrophage stimulating 1 pseudogene 2 (MST1P2) was detected to be overexpressed in contrast to the miR-133b, suggesting that a negative regulatory interaction existed between MST1P2 and miR-133b. Silencing MST1P2, just like the induction of miR-133b, could favorably restore the sensitivity of cisplatin-resistant BC cells to conventional cisplatin regimens. Taken together, MST1P2/miR-133b axis regulates the BC cell cisplatin resistance through operating the SIRT1/p53 signaling pathway [97].

Rather, molecular analyses have realized that the p53-Rb signaling axis is substantially linked to the expansion of muscle invasive-transitional cell carcinoma of bladder (MI-TCC) [98,99]. p53 and p21, as the major components of this axis, principally participate in the process of determinig response to chemotherapy [100]. MiR-34a is known for its effector roles at the downstream of p53. In patients with chronic lymphocytic leukemia (CLL), miR-34a was realized to predict cancer expansion in association with p53, suggesting its role as a surrogate biomarker. In other cancers, miR-34a can also be considered a cancer progression predictor but in an independent manner [101–103]. MiR-34a has the ability of targeting multiple components of the p53-Rb signaling loop, such as CDK6 as the regulator of Rb phosphorylation, and E2F3 that is a direct effector at the downstream of Rb. Thereby, miR-34a potentially contributes to the abrogation of effects mediated by p53-Rb signaling axis dysfunction, which is introduced as the chaotic progression of the cell cycle [104]. MiR-34a is also a potential regulator of chemo-resistance, especially in BC and MI-TCC, and the suppression of CDK6 and SIRT-1 significantly involves in the regulation of pre-miR-34a chemo-sensitivity. Literally, CDK6 is a principal modulator of Rb activity, particularly in complex with CDK4 and cyclin D1. Although CDK6 overexpression has not been declared in TCC cases, the expression of CDK6 regulators, such as p21, p16, and cyclin D1, is commonly observed to be related to TCC expansion [104,105]. Researchers believe that there is a relationship between miR-34a promoter methylation, p53 mutation status, and CDK6 expression in association with MI-TCC chemo-resistance but they are not sure whether this miRNA can be a beneficial predictor of chemotherapeutic response or even a therapeutic target [104].

MiR-200 family members, including miR-200b, −200a, and −429, were previously identified to be mediate the cisplatin-resistant phenotype in tumor cells in their down-regulated status. The miR-200 family members are responsible for suppressing the EMT through targeting E-cadherin repressors zinc finger e-box binding homeobox 1 (ZEB1) and ZEB2 [106,107], while in the absence of these miRNAs, EMT and aggressive cancer traits are undesirably promoted [108]. There are a particular number of CpG islands located in the upstream of miR-200 subtypes, which can be targeted by hypermethylation in a variety of cancers, such as BC [109,110]. Indeed, the simultaneous under-expression of these miRNAs has been found to be in correlation with the amplification of DNA methylation of CpG islands located at their upstream. Among the corresponding miRNAs, miR-200b down--modulation was realized to be associated with cisplatin resistance in BC cells. We know TNFSF10 (tumor necrosis factor ligand super family member 10), a. k.a. TRAIL, as a member of the TNF superfamily that triggers the apoptotic flux in multiple cancers through activating death receptors [111]. Although TRAIL has not been declared to be linked to cisplatin sensitivity, growing body of evidence demonstrates that cisplatin can increase the susceptibility of tumor cells to TRAIL-mediated apoptosis in BCs, as well as some other neoplasms (e.g. lung cancer and esophageal carcinoma) [112,113]. In this context, it was recently realized that miR-200b- and cisplatin-induced TRAIL expression may result in an amplified cytotoxicity in BC cells [110].

MiR-214 was another miRNA found to be associated with BC. The expression levels of this miRNA are increased in BC tissues and cell lines, and it was experimentally determined to have inhibitory effects on BC cell proliferation and invasion. Since there was not enough information about the contribution of miR-214 to BC-related cisplatin chemo-resistance, an *in vitro* analysis was conducted on J82 and T24 BC cell lines. The results of this study indicated that miR-214 mimic markedly decreased the expression levels of caspase-3 and poly-ADP ribose polymerase (PARP), while enhanced the levels of cleaved caspase-3 and cleaved PARP, suggesting that miR-214 could induce apoptosis in BC cells [114]. Furthermore, the corresponding miRNA was also found to have the ability of suppressing the Akt phosphorylation, which is responsible for the modulation of apoptosis through up-regulating the Bcl-2 family protein members [115]. Owing to this fact, it has been proposed that regulatory effects of miR-214 on chemo-resistance is mediated by the Akt/Bcl-2 signaling axis, and thus the apoptotic tract. Using the TargetScan software, major target genes of miR-214 were predicted, and netrin-1 was recognized as one of the most important targets. In BC, just like many other cancer species, netrin-1 serves as an oncoprotein, which its overexpression correlates with poor prognosis in BC patients [116]. The impact of netrin-1 was assessed on apoptosis and Akt signaling during BC, and the obtained results showed that netrin-1 plasmid transfection markedly decreased apoptosis and significantly increased the Akt phosphorylation in BC cells. Additionally, miR-214 mimic markedly down-regulated the netrin-1 mRNA and protein expression levels [114]. Thereby, it can be concluded that a negative crosstalk exists between miR-214 and netrin-1 mRNA expression levels BC tissues. The luciferase reporter assays further clarified that miR-214 could directly attach to the 3′-UTR of netrin-1, demonstrating the

capability of netrin-1 to be a direct target for miR-214. In the line of cisplatin resistance, miR-214 was found to suppress netrin-1, leading to the inhibition of p-Akt and subsequent blockade of the chemo-resistance. As netrin-1 plasmid transfection could restore the cisplatin resistance suppressed by miR-214, it is suggested that this miRNA can block cisplatin chemo-resistance in BC in a netrin-1-dependent manner [114].

In this framework, miR-424 is a direct target of HIF-1α that can minimize cisplatin sensitivity of BC cells by inhibiting the expression of UNC5B and SIRT4 pro-apoptotic genes [117]. MiR-424 was initially recognized as a differentiation-specific miRNA that regulated the monocyte/macrophage differentiation program [118]. Moreover, accumulating evidence proposed that miR-424 might serve as either tumor-suppressor or oncogene during the process of tumorigenesis, relying on its downstream target genes [119–121]. In BC, miR-424 has an oncogenic role as it is overexpressed in BC tissues in correlation with poor clinical outcomes. The overexpression of miR-424 and its mimics were found to cause cisplatin resistance in cell culture and animal models of BC. This valuable finding was confirmed when miR-424 inhibition increased cisplatin-induced cytotoxicity in 5637 and T24 BC cells. Mechanistically, in BC cells, miR-424 exerts its promoting effects on cisplatin resistance through modulating HIF-1α, thereby demonstrating that miR-424 targeting might provide a therapeutic background to cure refractory BC [117].

LncRNAs are the other members of ncRNAs superfamily with the ability of modulating the cancer cell proliferation, migration, and chemoresistance, under the normoxic and/or hypoxic conditions. Hypoxia-inducible factor 1α antisense RNA 2 (HIF1A-AS2), as a hypoxia-related lncRNA, was found to involve in BC-related cisplatin resistance caused by hypoxia stress [122]. Mechanistically, high mobility group AT-hook 1 (HMGA1) is at the downstream of HIF1A-AS2, is a crucial mediator of cisplatin resistance in BC cells. HIF1A-AS2 was previously found to act by interacting with RBPs such as insulin-like growth factor 2 binding protein 2 (IGF2BP2) and DExH-box helicase 9 (DHX9) to induce the expression of their target mRNAs, such as HMGA1, to further increase in their protein levels [123]. In human BC cells, HMGA1 can block the transcription activity of p53 family proteins. which in turn results in the repression of their tumor-suppressive effects. Once HMGA1 is silenced by a siRNA, p53 is transcriptionally activated, leading to an increase in cancer cell apoptosis [124]. Although the contribution of HMGA1 is seldom declared in BC, researchers have reported that HMGA1 has substantial roles in BC, especially in cisplatin resistance by hindering the transcription activity of p53. Once HMGA1 is up-modulated by HIF1A-AS2, it links to p53 family proteins to inhibit their transcriptional effects on the pro-apoptotic Bax protein [122]. Accordingly, new perspectives have opened in BC precision therapy in related HMGA1 targeting.

UCA1 is another lncRNA involved in cisplatin/gemcitabine resistance of BC cells *in vitro* and *in vivo*. UCA1 overexpression has been realized to remarkably mitigate cell apoptosis and increase cell viability, while its silencing promoted apoptosis and reduced cell viability through cisplatin/gemcitabine treatment. It was also observed that cisplatin/gemcitabine regimen combined with sh-UCA1 blocked tumor growth and enforced the apoptotic tract in 5637 BC cells [125]. Further, UCA1 up-regulation was identified to increase the expression status of Wnt6 or serine–arginine protein kinase 1 (SRPK1), provoking cisplatin resistance [126,127]. UCA1a, which is transcribed by the UCA1 gene, has also the ability of enhancing cisplatin resistance through antagonizing apoptosis in BC cells [128]. For further determination of the mechanism(s) by which UCA1 regulates cisplatin/gemcitabine resistance in BC cells, researchers concentrated on the role of miR196a-5p, as a potential onco-miR overexpressed in many tumors by contributing to diverse processes from cancer initiation to its progression and metastasis [129,130]. More recently, the inhibition of miR-196a-5p was proposed to reverse cisplatin chemo-resistance NSCLC cell lines in relation to drug-resistant proteins including MDR1, multidrug resistance-associated protein 1 (MRP1), ERCC1, survivin, Bcl-2, etc. [131]. Experimentally, UCA1 was determined to be able of increasing miR-196a-5p expression to suppress the cisplatin/gemcitabine-resistant trait induced by UCA1. These findings together suggested that miR-196a-5p could serve as a promising target to cure BC patients resistant to cisplatin/gemcitabine. Beyond the aforementioned data, UCA1 can also activate the Akt signaling to provoke the phosphorylation of cAMP-response element binding protein (CREB), which in turn reduce the miR-196a-5p levels. In the following, mutations of CREB-binding sites in the miR-196a-5p promoter abolish the promoting effects of UCA1, confirming the involvement of CREB in the regulation of miR-196a-5p expression. Moreover, UCA1-dependent activation of CREB is essential for operating the miR-196a-5p transcription in BC cells. Considering the existing miRNA/mRNA networks in different neoplasms, the negative regulatory effect of miR-196a-5p on p27Kip1, as a G1-checkpoint CDK inhibitor involved in drug resistance modulation, was described by checking their interactions with the 3′-UTR [132,133]. p27Kip1 promotes the activation of cleaved caspase-3 to trigger the progression of cell apoptosis [134]. In the line of BC-related cisplatin resistance, 5637 sh-UCA1 cells represented an increase in p27Kip1 expression levels independent of cisplatin/gemcitabine treatment, and miR-196a-5p blocked this effect of UCA1. This finding supported the fact that miR-196a-5p-dependent down-modulation of p27Kip1 by UCA1 substantially participates in UCA1-induced cisplatin/gemcitabine chemo-resistance. In conclusion, the lncRNA UCA1 can be highlighted as a major contributor to cisplatin/gemcitabine resistance through CREB/miR-196a-5p/p27Kip1 modulatory axis in human BC, and thus UCA1 could be considered either as a novel biomarker for monitoring the poor response to cisplatin/gemcitabine regimen or a promising target for BC chemotherapy [125].

There are a limited number of studies focused on the role of circRNAs in BC-associated cisplatin resistance. Nonetheless, apoptosis protease-activating factor 1 (APAF1), which is a major factor in regulating apoptosis, was recently found to be modulated by a particular circRNA during BC cisplatin resistance. In apoptosis, APAF1 accelerates the formation of a ring-like apoptosome to activate caspase-3, -6, and/or −7 for triggering cell devastation [135]. Cisplatin therapy triggers free radicals that damage the cardiolipin on the mitochondrial membrane, leading to the release of cytochrome C, which boosts the APAF1 activity for further stimulation of apoptotic cell death [136]. CDR1as, also known as ciRS-7 or CDR1NAT, is one of the previously mentioned circRNAs generated by reverse splicing of the antisense strand of the CDR1 gene, which is associated with cerebellar degeneration. CiRS-7 can trap miR-7 to regulate the expression of downstream genes [137,138]. It can also trap miR-135a instead of miR-7, to restore p21 and induce cell cycle arrest in BC cells [139]. The increased expression of ciRS-7 was shown to have the ability to improve cisplatin sensitivity of T24 and EJ BC cells by enhancing cell apoptosis. In this context, ciRS-7 acts as a sponge of miR-1270, which reduces the inhibitory effects of this miRNA on APAF1 gene. CiRS-7 also increases the expression level of APAF1. The silencing of APAF1 results in a decrease in cisplatin sensitivity and a shutdown of apoptosis. Therefore, ciRS-7 imbalance can increase the sensitivity of BC cells to cisplatin by facilitating the apoptotic pathway [140].

5.2. Cell proliferation

Proliferation plays a significant role in cancer development. The proliferative trait is mostly expanded by dysregulation of cell cycle-related proteins. Furthermore, the activation of diverse signaling pathways triggers the cell growth, and thus proliferation. Early steps in tumor progression are conducted by a fibrogenic response and the enlargement of hypoxic environment that favors the survival and proliferation of cancer stem cells (CSCs) [141]. The survival strategy of CSCs is partly controlled by cell metabolism alterations. Tumor cell growth and metastasis are generally supported by particular hormones (indeed in hormonally dependent neoplasms), angiogenesis, EMT,

autophagy, and taking signals from nearby stromal cells. It has also been reported that a set of signaling pathways related to HIF-1α, nuclear factor kappa B (NF-κB), PI3K/Akt, IGFR1, Wnt, CDKs, and androgen and estrogen receptors are responsible for regulating the cell proliferation [142]. Interestingly, proliferation and cisplatin chemo-resistance have been found to be potentially intercorrelated within the networks controlled by various ncRNAs, as discussed in the following paragraphs.

5.2.1. Non-coding RNAs are responsible for cell proliferation regulation during BC-related cisplatin resistance

MiR-222 is a miRNA, which its overexpression has been detected to be in association with chemotherapy [143]. In BC cells, miR-222 overexpression can antagonize cisplatin-induced cell destruction, while its down-regulation increases the cytotoxic and anti-tumor effects of the corresponding chemo drug. When this axis was investigated mechanistically, protein phosphatase 2 regulatory subunit B alpha (PPP2R2A) was determined to be suppressed by miR-222 in cell culture models of BC [144]. Literally, PPP2R2A is a PP2A regulatory subunit B, which its activity is inversely associated with the activation of prolife ration-related kinases [145,146]. In addition to proliferation, PP2A also regulates a variety of cellular signaling, as well as the cell cycle, metabolism, apoptosis, and protein synthesis [147]. Akt is one of the well-known substrates of PP2A that can be activated following the miR-222-induced repression of PPP2R2A [148–150], for further activation of the mTOR signaling pathway. We know that PI3K/Akt/mTOR pathway is strongly related to tumor growth, as its inactivation immediately blocks cancer cell growth [151]. Collectively, PPP2R2A is considered a direct target for miR-222, and consistently, Akt/mTOR is activated in miR-222-overexpressing BC cells. In other words, the PPP2R2A/Akt/mTOR regulatory axis contributes to the miR-222-induced proliferation of BC cells [144]. The whole network, i.e. miR-222/PPP2R2A/Akt/mTOR, significantly modulates cisplatin sensitivity in BC. Thus, we can consider miR-222 as a propitious target for BC therapy and overcoming the cisplatin chemotherapy resistance [144].

MiR-222 is not the only miRNA participated in BC-correlated proliferation and chemo-resistance, and other miRNAs, such as miR-34a, are also involved in the corresponding processes. MiR-34a generally serves as a tumor-suppressive miRNA and is under-expressed in a wide spectrum of neoplasms [104,152]. The miRNA of interest is principally inducted by p53 and ectopic miR-34a expression has the ability of stimulating the apoptosis and cell-cycle arrest and changing chemo-sensitivity by operating different genes in p53 signaling cascade, such as SIRT-1, CDK6, E2F3, and Bcl-2 [153,154]. Notwithstanding, the mentioned mechanism seems not explaining the cisplatin-based chemotherapy of BC, as miR-34a can sensitize BC cells to cisplatin treatment without consideration of the p53-Rb pathway [155]. It has benn found that promoter hypermethylation was the major leading cause of miR-34a under-expression in BCs [156,157]. The expression status of a group of well-known miR-34a targets, including Myc, Bcl-2, Notch1, CDK6, SIRT1, E2F1, CDK4, HGF, Notch2, SOX2, and CD44, were analyzed in 5637, T24, and HT-1376 BC cell lines following the cisplatin treatment to elucidate the key target of miR-34a that was responsible for the interaction between miR-34a overexpression and cisplatin chemo-sensitivity [158–160]. Through this evaluation, an inverse association was recognized between miR-34a and CD44 expression, but not others. Further confirmatory analyses proved the tumor-suppressive and chemo-sensitivity effects of miR-34a through suppression of CD44. In parenthesis, CD44 has been previously introduced as a marker to detect human chemo-resistant BC-CSCs [161,162].

Other than miRNAs, the footprint of lncRNAs is also detected here. TUG1, which was previously introduced, has been realized to be significantly overexpressed in a group of malignancies, and stimulates the expression of LIM domain kinase 2b (LIMK2b) through binding to EZH2 to induce cell proliferation and chemo-resistance [163]. Furthermore, TUG1 not only modulates intranuclear gene transcription by linking to polycomb repressive complex 2 (PRC2) but also controls downstream targets inside the cytoplasm by serving as a sponge to target different miRNAs, including miR-9-5p, miR-455–3p, and miR-335–5p. According to recently published studies, TUG1 affected cisplatin sensitivity concurrent with its up-modulation in BC. In this regard, a negative interaction was detected between TUG1 and methylation-regulated miR-194–5p, as a tumor suppressor miRNA in several cancers, such as BC by targeting Ras-associated protein 2B (RAP2B) [164,165]. TUG1 also increases cell growth and cisplatin resistance by regulating CCND2 that is achieved by down-regulation of miR-194–5p in BC [164]. CCND2 is a cell cycle protein, which is known for its crucial roles in the process of tumorigenesis and progression of diverse cancers [166]. This cyclin principally mediates G1/S transition by interacting with CDK4 or CDK6. TUG1 actually acts as a powerful oncogene in BC[167]. In addition, Liu et al. [168] declared that TUG1 under-expression could suppress cell proliferation and triggered the apoptotic pathway through the TUG1-miR-142/Zeb2 axis in BC cells [168].

DLEU1 is another lncRNA which is aberrantly overexpressed in multiple cancers and involves in carcinogenesis and tumor expansion [169,170]. DLEU1 overexpression is also an indicator for poor prognosis in BC patients. This lncRNA has been found to be responsible for proliferation and invasion, as well as the regulation of cisplatin resistance through up-modulating the expression of oncogene HS3ST3B1 (heparan sulfate-glucosamine 3-sulfotransferase 3B1) by repressing miR-99b, which is a known as a direct inhibitor of HS3ST3B1 in BC cells [171]. Dual-luciferase reporter assay, along with RIP assay confirmed the direct relationship between DLEU1 and miR-99b. MiR-99b as a tumor-suppressive miRNA, has the potential of provoking tumor cell migration, invasion, and metastasis in a spectrum of neoplasms [172]. The under-expression of this miRNA reflects poor survival in patients suffering from BC. MiR-99b has also been found to reverse DLEU1-induced cell proliferation, invasion, and cisplatin resistance, suggesting critical roles for this ncRNA transcript in blocking BC development and overcoming cisplatin resistance in BC cells [171]. Altogether, the DLEU1/miR-99b/HS3ST3B1 axis can be considered a key pathway in the progression and cisplatin chemo-resistance of BC, and DLEU1 itself might be employed to cure BC in the near future [171].

Circ_0058,063, which regulates cell growth and acts as an oncogene in various cancers, also affects BC-related cisplatin resistance. This circRNA mechanistically targets miR-145–5p to drive BC progression, and miR-335–5p to up-modulate Beta-2 microglobulin (β2M) in a ceRNA-dependent route, which mediates cisplatin-resistance. It has also been stated that inhibiting miR-335–5p or silencing circ_0058,063 can reverse circ_0058,063 effects on BC-related cisplatin-sensitivity. Together, the circ_0058063/miR-335–5p pathway may modulate cisplatin-resistance in BC by targeting β2M, but more research is needed to clarify the molecular mechanisms and signaling pathways [173–175].

5.3. Invasion

The invasive trait of cancer cells along with migration and metastasis have made these cells dangerous rebels. Collective cell migration and individual cell migration are the two major patterns of tumor invasion, by which malignant cells can break down the barriers of extracellular matrix (ECM) to migrate to the adjacent tissues [176]. Each of the corresponding patterns is identified by particular morphological and molecular signatures. It has been realized that mesenchymal and amoeboid are the principal migrating cancer cells observed in invasion patterns, and thus tumor cell migration is divided into epithelial-mesenchymal, collective-amoeboid, mesenchymal-amoeboid, and amoeboid-mesen chymal transitions. Also, there is a significant interplay between the invasion phenotype and cisplatin resistance in BC, which can be controlled by ncRNAs at the crossroads of molecular mechanisms and signaling pathways that is subsequently discussed [176,177].

5.3.1. The interplay between ncRNAs and invasion in cisplatin resistance

As an onco-miR, miR-150 expression was found to be significantly amplified in the MIBC cell lines (i.e. 5637 and T24) compared to non-cancerous human bladder epithelial SV-HUC-1 cells, which its inhibition significantly increased BC cell sensitivity to cisplatin and diminished the invasiveness of both 5637 and T24 cells [178]. Post-transcriptional modulation mediated by miR-150 usually results in a decrease in the levels of the pro-apoptotic protein P2X7 receptor within the cancer epithelial cells in comparison to normal cells, and thereby miR-150 inhibitor could enhance P2X7 expression in tumor cells [179]. MiR-150 may function in a cancer type-dependent, as in gastric cancer cells, it exerts oncogenic effects by targeting the pro-apoptotic gene EGR2 to induce proliferation [180], in lung cancer, it triggers proliferation and migration by targeting p53 [181]and SRC kinase signaling inhibitor 1 [182], respectively, while it represents a tumor suppressive role in malignant lymphoma [183]. Using the TargetScan database, programmed cell death 4 (PDCD4) was opted for further molecular confirmation of the existing correlation between miR-150, cisplatin sensitivity, and invasion in MIBC cells [178]. PDCD4 was identified to have a highly conserved binding site for miR-150 for being targeted by this miRNA in MIBC cells. Regarding the contribution of PDCD4 to chemotherapy response, it was found that ectopic expression of this protein could increase cisplatin sensitivity and repress invasiveness in MIBC cells [178]. Besides, in other neoplasms such as glioblastoma, loss of PDCD4 might result in cheno-resistance development by de-repression of Bcl-xL translation [184]. It can be concluded that PDCD4 has tumor-suppressive roles by affecting a number of cancer-related processes, *viz*. invasion, as well as tumor cell growth and cell transformation, through blocking the transcription factor AP-1 and the eukaryotic initiation factor (elF) 4A [185]. Aberrant expression of PDCD4 markedly inhibits cell proliferation, migration, and invasion by enhancing PTEN and suppressing Akt activity [186], as well as blocking cell growth and survival through a miRNA-mediated repression of c-Myc and Bcl-2 in a group of malignancies [178].

In line with miR-150, the intranuclear lncRNA NEAT1 has also been realized to be involved in invasion of BC cells. NEAT1 is a well-known transcriptional modulator of a wide spectrum of genes responsible for cancer expansion. It has also been determined that NEAT1 can regulate cisplatin sensitivity in diverse neoplasms, such as osteosarcoma and HCC [187,188]. In the case of BC, NEAT1.1 but not NEAT1.2, does respond upon the effect of cisplatin. It should be mentioned within the parenthesis that NEAT1.1 and NEAT1.2 are the transcript isoforms of the corresponding NEAT1. Consistently, NEAT1.1 will be down-regulated after cisplatin administration, demonstrating the role of cisplatin in restraining the NEAT1's transcriptional activity. Therefore, NEAT1.1 repression gives rise to cell proliferation, invasion, and migration and induces tumor cell apoptosis in cisplatin-resistant BC cells. Further observations of NEAT1.1 overexpression during cisplatin treatment in T24R cells have suggested a group of unknown regulatory factors connecting cisplatin to NEAT1.1 for transferring signals from cisplatin to NEAT1 transcription [189]. Although it is not clearly elucidated what modulates NEAT1 transcription, c-MYC, OCT4 (octamer-binding transcription factor 4), C/EBPβ, and p53 are determined to bind at the NEAT1's promoter to affect its transcription activity. These transcription factors were also found to be interestingly correlated with cisplatin resistance [158,190–192]. Using the ChIP-qPCR assay, the free proteins of c-MYC, OCT4, and p53 are overexpressed in cisplatin-resistant BC cells, and also c-MYC, OCT4, and p53 are greatly concentrated on NEAT1 promoter when bladder tumor cells are affected by cisplatin. Furthermore, other critical enzymes have been speculated to be responsible for RNA splicing of NEAT1 in cisplatin-resistant BC cells that need to be further clarified [189]. Ultimately, NEAT1.1 is considered to be harmful for overcoming BC cisplatin resistance, and its knockdown can increase the repression of cell growth, invasion, and apoptosis of BCs cells during cisplatin therapy [189].

5.4. Migration

In tumor environments, the metastatic pathway is principally conducted by a particular trait that is called migration. Migration is responsible not only for the long-range tumor cell translocation but also for short-range translocations, accelerating tumor growth and expansion [193,194]. A comprehensive understanding of tumor cell migration is necessary to gain insight into metastasis and subsequent cancer development [195]. More recently, migration and metastasis have been reported to be regulated by ncRNA transcripts in cisplatin chemo-resistant or chemo-sensitive BC cells. The following paragraphs will provide detailed information in the context.

5.4.1. NcRNAs are responsible for migration regulation in cisplatin-resistant bladder tumor cells

Vascular endothelial growth factor C (VEGF-C), as a crucial lymphangiogenic molecule, is regarded as a promoter of the lymphatic vessels permeability. Under cancerous conditions, VEGF-C positively correlates with lymphatic spread in BC, and provokes cell migration to lymphatic vessels, as well as regulating cisplatin resistance in a group of malignancies [196]. Although VEGF-C have angiogenic effects on endothelial cells [197], it mostly acts lymphatically by operating the Flt4/VEGFR-3 and KDR/VEGFR-2 receptor tyrosine kinases (RTKs) that have been reported to be expressed in the lymphatic and high venular endothelia of lymph nodes [196]. In this regard, VEGF-C hyper--activation has been found to generate lymphatic endothelial proliferation and hyperplasia of the lymphatic vasculature [198]. Among several miRNAs involved in cisplatin resistance, miR-101 has been well-defined as a tumor-suppressive miRNA with inhibitory effects on proliferation, migration, and invasion, which its under-expression was previously found to be linked to BC [199]. In TCC, miR-101 has also been revealed to suppress proliferation and colony formation by blocking EZH2 methyltransferase, directly [199]. The histone H3 demethylase Not dead yet-1 (NDY1)/histone lysine demethylase 2B (KDM2B)-miR-101-EZH2 axis is an active pathway in BC cells [200], wherein miR-101 blocks the motility of BC cells through targeting the c-Met's 3′-UTR [201]. By getting assistance from the TargetScan database, VEGF-C was identified as a potential target for miR-101. In this area, miR-101 negatively modulates the protein expression levels of VEGF-C post-transcriptionally. Together, miR-101 and VEGF-C can independently increase the cisplatin cytotoxicity in BC cells, and VEGF-C itself rescued the effect of miR-101 on BC-related cisplatin chemo-sensitivity as well [202]. Despite the necessity of further explorations to determine other possible targets of miR-101, this miRNA has promised as an ideal molecular target for BC management [202].

The transcription factor AP-2 alpha (AP-2α or TFAP2A) is a newly identified biomarker for monitoring the prognosis of chemotherapy. This transcription factor primarily serves as a tumor suppressor through modulating the expression status of multiple cancer-related genes, including p21, matrix metalloproteinase 9 (MMP9), E-cadherin, Bcl-2 and Bax [203,204]. It was interestingly defined that AP-2α expression has a positive interaction with chemo-sensitive trait in BC, as well as other neoplasms such as breast, bladder, and endometrium cancers [205–207]. Under the neoplastic conditions, AP-2α is often suppressed by promoter hypermethylation or the action of miRNAs, which in turn causes drug resistance [208,209]. MiR-193a-5p is one of those regulatory miRNAs that can block the AP-2α by targeting its coding sequence [210]. MiR-193a-5p suppression or AP-2α gene overexpression were experimentally found to reduce cisplatin resistance in BC cell line UM-UC-3 (211). The involvement of miR-193a in MIBC was also clinically evaluated, which resulted in clarification of a negative association between miR-193a and patient OS [211]. Whilst, the AP-2α itself was found to serve as a predictive marker for good response and survival after cisplatin-based chemotherapy [212,213]. AP-2α protein overexpression was also recognized to be related to good response to cisplatin in BC, whereas its suppression promoted the proliferation of

the SW780 BC cells along with decreasing sensitivity to cisplatin and gemcitabine regimen [207]. Thereby, miR-193a-5p can be considered as a cisplatin resistance inducer by inhibiting the AP-2α expression [210]. In consistent, once SV-HUC-1 urothelial cells were infected with lentiviral AP-2α gene or miR-193a-5p inhibitor, migration and cisplatin resistance were attenuated, which were inverted following AP-2α knockdown of miR-193a-5p up-regulation [210].

Like other previously stated processes, lncRNAs are also involved in migration and metastasis. MALAT1, as a markedly conserved nuclear lncRNA with particular oncogenic roles, is a well-defined transcript in this context that has recently been determined to modulate migration, proliferation, invasion, and apoptosis in a broad spectrum of cancers, such as BC [214]. Since MALAT1 can mediate cisplatin-resistance by up-regulating the drug resistance-related proteins, including MRP1 and MDR1, *via* signal transducer and activator of transcription protein 3 (STAT3) activation, the elucidation of its underlying mechanisms of action may help decreasing the chemotherapy resistance as well as increasing the efficacy of conventional therapeutics [215]. In BC cells, MALAT1 suppression affects the cisplatin chemo-resistance of BC cells, as it can increase cisplatin-induced suppression of cell viability in the corresponding cells. It can be concluded that ectopic expression of MALAT1 might cause cisplatin resistance in BC. According to the recently conducted mechanistic analyses, lncRNAs have been determined to act on chromatin or the transcription process, as well as the stability, editing, transportation, and translation of the RNA transcripts [216]. Growing body of evidence also supports that lncRNAs exert their major effects by harboring ceRNAs. The ceRNA hypothesis declares that lncRNAs could competitively bind with and decoy the miRNAs as potential molecular sponges, and thus restoring the expression and activities of the targets of miRNA, leading to the generation of new lncRNAs/miRNAs/mRNA regulatory pathways [217,218]. One of these modulatory loops has been found to be existed between MALAT1 and miR-101–3p for further controlling of cisplatin resistance in BC cells. Experimentally, miR-101–3p was demonstrated to be down-regulated in EJ-M3-CDDP and 5637-CDDP cells in comparison to that in EJ-M3 and 5637 cells. It should also be noted that in BC-related cisplatin resistance, MALAT1 and miR-101–3p are intercorrelated in an inverse manner [215].

CircZNF609 is the other ncRNA, recently established to be related to migration in line with cisplatin resistance. Like many other circRNAs, it can induce tumor expansion by sponging diverse miRNAs [219]. For instance, by sponging miR-1200, circZNF609 can serve as an oncogene because miR-1200 generally blocks the tumor development and increases cisplatin sensitivity in a group of cancers [219–221]. Similarly, in BC, miR1200 boosts the sensitivity of tumor cells to cisplatin and decelerates the tumor expansion by down-modulating the CDC25B. CDC25B, is a cell cycle modulator that has the ability of changing cell cycle phases distribution in cancer cells [222]. Cisplatin can eradicate tumor cells more efficiently in the G1 phase [223], and CDC25B overexpression has been importantly found to decrease the number of BC cells during G1 phase, and thus attenuates cisplatin chemo-sensitivity [224].

5.5. Autophagy

To the best of our knowledge, autophagy is an evolutionarily conserved flux responsible for self-catabolic organelle recycle that is principally activated due to starvation, cellular stress, and the presence of reactive oxygen species (ROS) to protect against exacerbation of the circumstances [225,226]. Autophagy acts as a double-edged sword; for instance, sufficient autophagy maintains a steady state of an organ, while its excessive activation may induce the progression of organ failure [227]. In this regard, chemo-resistant tumors can undesirably keep themselves alive by over-activating the autophagy flux. Therefore, autophagy is also considered to be one of the factors inducing chemical resistance [228]. Autophagy is under the regulation of a set of genes, called autophagy-related genes (Atgs), and the proteins encoded by these genes (i.e. ATGs) [229]. Atg7 is one of the before mentioned genes that plays a synergistic role in the migration and invasion of BC cells. ATG7, as the related protein, principally involves in intracellular autophagy response and can triggers BC attacks in an autophagy-dependent manner that is mediated by enhancing the stability of ARHGDIB mRNA [230,231]. Although there is limited evidence on the existing ncRNA-regulated network between autophagy and migration in cisplatin chemo-resistant BC cells, the succeeding paragraph will highlight this regulatory axis.

5.5.1. NcRNAs and autophagy are interconnected in cisplatin resistance during BC

MiR-7-5p is an anti-tumor miRNA that is slightly expressed in BC tissues than in adjacent counterparts. The overexpression of miR-7-5p can favorably suppress the migration and invasion, as well as autophagy in BC cells, probably converting this RNA molecule to a novel therapeutic target for BC eradication. Experimental data revealed that the corresponding miRNA could decrease autophagy, blocked BC migration, and induced cisplatin sensitivity primarily by down-regulating the ATG7 [232]. As mentioned before, autophagy has a dual role in cancer development, which can act either as an oncogene or a tumor suppressor [233]. ATG7 has also been identified to be associated with CD44s in BC cell invasion and metastasis [234], and also the regulatory axis ETS2/miRNA196b/FOXO1/p27 has been reported to target ATG7 in BC cells [235]. The interaction between miRNAs and ATGs have also been reported in chemo-resistance of other cancers, as miR-27b-3p and ATG10 together regulate the chemo-resistant phenotype in colorectal cancer [236]. Furthermore, the miR-146a-5p/TRAF6/NF-kB/p65 axis is known for its modulatory role on pancreatic cancer drug resistance [237].

5.6. Inflammation and oxidative stress

There are a significant number of epidemiological and experimental analyses that have verified the correlation between inflammation and cancer expansion. The same investigations have also declared that anti-inflammatory therapies can be efficiently result in cancer prevention and treatment [238,239]. Many years ago, it was realized that inflammatory cells are present inside the tumors and the tumors actually arise at sites of chronic inflammation [238,239]. Inflammatory bowel disease and chronic pancreatitis are great examples of this kind that are correlated with the risk of colon adenocarcinoma [240,241] and pancreatic cancer [242], respectively. The precise mechanisms by which a wound-healing process turns into neoplasm are currently under investigation [243,244], and a variety of possible mechanisms such as induction of genomic instability, epigenetic modifications, and subsequent inappropriate gene expression, can increase cell proliferation, resistance to apoptosis, and invasion through tumor-related basement membrane, and metastasis [245].

On the other hand, oxidative stress is known as an imbalance between ROS content and the antioxidant levels, that is associated with the progression of many diseases from neurodegenerative disorders to diverse neoplasms [246]. Human cells have been equipped with multiple biochemical and genetic facilities to maintain the before mentioned balance. Tumor cells often represent extopoic redox homeostasis, but since ROS promote tumorigenesis, high levels of ROS are cytotoxic [247]. Cancer cell proliferation can be accompanied by ROS over-production and they are adapted to survive under circumstances wherein oxidative burden pushes the redox balance away from a reduced status; it has been found that tumor cells achieve this by enhancing their antioxidant status to boost ROS-driven proliferation, and inversely avoiding ROS thresholds that would trigger senescence and apoptosis [248]. The reduced glutathione (GSH), thioredoxins (TXN1 and TXN2), and NADPH, along with the mechanisms governing their abundance under physiological conditions and during the onset,

development, and metastatic stages of cancer, as well as post-therapy recurrence are the crucial contributors to oxidative stress-mediated pathologies. The heterogeneity inherent in the evolution of malignancies may explain the anomalous effects of antioxidants on the expansion and metastatic distribution of neoplastic maladies [249].

Both inflammation and oxidative stress have been reported to be significantly associated with cisplatin resistance in BC, under the regulation of ncRNAs. More detailed information in this context has been provided below.

5.6.1. NcRNAs at the upstream of inflammation and oxidative stress in cisplatin-resistant BC cells

MiR-101 has been recognized to suppress cell proliferation and invasion in bladder carcinoma and prostate cancer [250,251]. Zhang et al. [252] additionally declared that miR-101 down-regulation served as an oncogene by inducing cell proliferation and invasion and repressing paclitaxel-induced apoptosis in NSCLC. MiR-101 expression was significantly down-modulated in cisplatin-resistant BC cells compared to that in parent cells [253]. Using the TargetScan software, COX-2 was speculated to serve as a direct target for miR-101 due to a seed region in miR-101 that is able to attach to the COX-2 mRNA 3′-UTR. A luciferase reporter vector (pGL3-COX2-wildtype) with the 3′-UTR of COX-2 with a putative miR-101 complementary region was experimentally constructed, and then a markedly lower level of luciferase activity was monitored when T24/CDDP cells were co-transfected with the miR-101 mimic and pGL3-COX2-wildtype, demonstrating a direct relationship between miR-101 and COX-2 mRNA. COX-2 inhibitors can further sensitize chemo-resistant cancer cells to chemotherapy [253]. Therapeutic approaches targeting chemo-resistance in relation to miRNAs, such as hsa-miR-101, may promisingly increase therapeutic efficacy [253].

MiR-27a is the part of a larger signature of miRNA expression that stratifies cisplatin resistance in BC and a substantial role has unveiled for this miRNA in mediating cisplatin BC cells by regulating SLC7A11 expression, leading to an increased cystine import and subsequent enhancement of glutathione synthesis [254]. SLC7A11 up-modulation has been reported as a mechanism of cisplatin resistance in a group of cancers. Enhanced drug efflux, diminished influx or sequestration seem to be amongst the major mechanisms of drug resistance in solid tumors. The reduced form of glutathione (GSH) has a crucial role in this context, as this thiol-containing tripeptide is a strong electron donor and protects against the harmful effects of various endogenous stresses by quenching free radicals and radical centers on DNA as well as other biomolecules [255]. GSH has also the ability of protecting cells from the cytotoxic effects of diverse chemotherapeutic agents, including cisplatin, and radiotherapies [256].

Regarding the oxidative stress, LOXL4, a target of miR-193a-3p, affects BC chemo-resistance by miR-193a-3p. LOXL4 expression is influenced by hypoxia, DNA methylation, and miR-193a-3p, and it is principally related to tumor invasion, metastasis, and treatment. Moreover, Nrf2, a transcriptional factor of the oxidative stress pathway, mediates chemo-resistance. The abnormal expression of Nrf2 makes the cells resistant to various anti-tumor agents, while siRNA-mediated suppression of Nrf2 in cells with high expression levels of Nrf2 sensitizes cells to the drug toxicity. The chemo-resistant H-bc cells have a significantly higher level of both Nrf1 and Nrf2 and a higher oxidative stress pathway activity than the chemo-sensitive 5637 cells [257–263].

6. Clinical applications of non-coding RNAs in bladder cancer theranostics

NcRNAs has recently attracted much attention to be clinically used in cancer management (Table 2). NcRNAs target various mRNAs, which are responsible for encoding proteins involved in modulation of a specific mechanism. Several ncRNAs are now under clinical investigation to be clarified where they stand in cancer pathogenesis. Nevertheless, challenges like delivery to specific regions, bioavailability, and specificity might restricted the therapeutic use of ncRNAs in clinical settings [58,271]. Next paragraphs will highlight the clinical contribution of ncRNAs to BC theranostics (Fig. 4).

6.1. NcRNAs for bladder cancer diagnosis and prognosis

According to biomarker studies, miRNAs have considerable diagnostic and prognostic potentials during BC, which can be exemplified by miR-200 overexpression that is in correlation with better prognosis along with overall and recurrence-free survival [272]. On the other

Table 2
Clinical applications of ncRNAs in BC management.

NcRNA	BC subtype	Expression pattern	Clinical application	Reference
MiRNAs				
MiR-183–5p	BC	Up	Therapeutic target	[79]
MiR-7-5p	BC	Down	Therapeutic target	[232]
MiR-325	BC	Down	Therapeutic target	[85]
MiR-486–5p	MIBC	Not reported.	Therapeutic target	[91]
MiR-222	BC	Up	Therapeutic target Prognostic biomarker	[144]
MiR-101	BC	Down	Therapeutic target	[202]
MiR-150	MIBC	Up	Therapeutic target	[178]
MiR-101	BC	Down	Therapeutic target	[253]
MiR-27a	BC	Up	Therapeutic target Prognostic biomarker	[264]
MiR-34a	MIBC	Down	Therapeutic target	[155]
MiR-34a	BC	Not reported.	Therapeutic target	[265]
MiR-424	BC	Not reported.	Therapeutic target	[266]
MiR-193a-3p	BC	Not reported.	Therapeutic target	[262]
LncRNAs				
NEAT1	BC	Not reported.	Therapeutic target	[189]
HIF1A-AS2	BC	Up	Therapeutic target	[267]
UCA1	BC	Up	Therapeutic target	[268]
MALAT1	BC	Up	Therapeutic target	[215]
TUG1	BC	Up	Therapeutic target	[164]
DLEU1	BC	Up	Therapeutic target Prognostic biomarker	[171]
UCA1	BC	Up	Therapeutic target Diagnostic biomarker	[317]
CircRNAs				
CircZNF609	BC	Up	Prognostic biomarker	[224]
CiRS-7	BC	Not reported.	Therapeutic target	[140]
Hsa_circ_0000285	BC	Down	Prognostic biomarker	[270]
Circ_0058,063	BC	Up	Prognostic biomarker	[175]

hand, the overexpression of hsa-miR-663a and hsa-miR-3648 accompanied by the under-expression of hsa-miR-185–5p, hsa-miR-30c-5p, hsa-miR-1270, hsa-miR-200c-3p, and hsa-miR-29c-5p is markedly linked to shorter OS in BC patients [273,274]. A 7-miRNA-containg panel (incl. miR-6087, miR-6724–5p, miR-3960, miR-1343–5p, miR-1185-1-3p, miR-6831–5p and miR-4695–5p) has been recognized to be beneficial in specific differentiation of BC from non-cancerous conditions and other tumor species [275]. Furthermore, the combination of miR-181b-5p, miR-183–5p, miR-199–5p and miR-221–3p can be desirably employed to diagnose BC [276].

Circulating miRNAs have the ability of being used as BC potential biomarkers through liquid biopsy-based diagnosis. It has been shown that urinary content of miR-7-5p, miR-22–3p, miR-29a-3p, miR-126–5p, miR-200a-3p, miR-375, and miR-423–5p could serve as very non-invasive biomarkers for BC detection (Mitash et al., 2017). In line with these urinary miRNAs, miR-148b-3p, miR-3187–3p, miR-15b-5p, miR-27a-3p, and miR-30a-5p, which are markedly detectable in serum specimens, are capable biomarkers for a great BC prognosis [277]. Xie et al. [278] demonstrated that hsa-miR-185–5p, hsa-miR-663a, hsa--miR-30c-5p, hsa-miR-3648, hsa-miR-1270, hsa-miR-200c-3p, and hsa-miR-29c-5p were up-modulated in serum samples obtained from BC patients compared to the control subjects [276,278]. If the corresponding miRNAs become dysregulated, a decrease in the OS of BC patients will then be observed.

Like miRNAs, lncRNAs also represent desirable characteristics to serve as diagnostic or prognostic indicators for BC. Regarding the low expression levels of lncRNAs, the overexpressed lncRNAs are more conducive to diagnosis for BC [279]. In this framework, UCA1 is one of the well-studied candidates for BC diagnosis. It has been reported that UCA1 mRNA expression levels are significantly related to the grade of bladder neoplasm [280,281]. UCA1 is actually a hypersensitive biomarker for the BC T2-T4 stage, thus providing a good prognosis of BC patients [282]. H19 and HOTAIR molecules are other lncRNAs that exhibit overexpression in BC tissues in comparison to non-cancerous counterparts [283]. It has been demonstrated that HOTAIR up-modulation concurrent with GAS5 overexpression are in line with poor OS among BC patients [284]. HOTAIR in combination with MALAT1 and LINC00477 lncRNAs are valuable urinary biomarkers, as their overexpression has been detected in exosomes extracted from urine specimens of high-grade MIBC patients [285]. Notwithstanding, further studies must be conducted to confirm HOTAIR diagnostic potentials in relation to BC [286]. In the case of GAS5, its down-regulation was found in association with poor OS [287]. Additionally, MALAT1 induction was shown to be substantially correlated with the grade and metastasis in

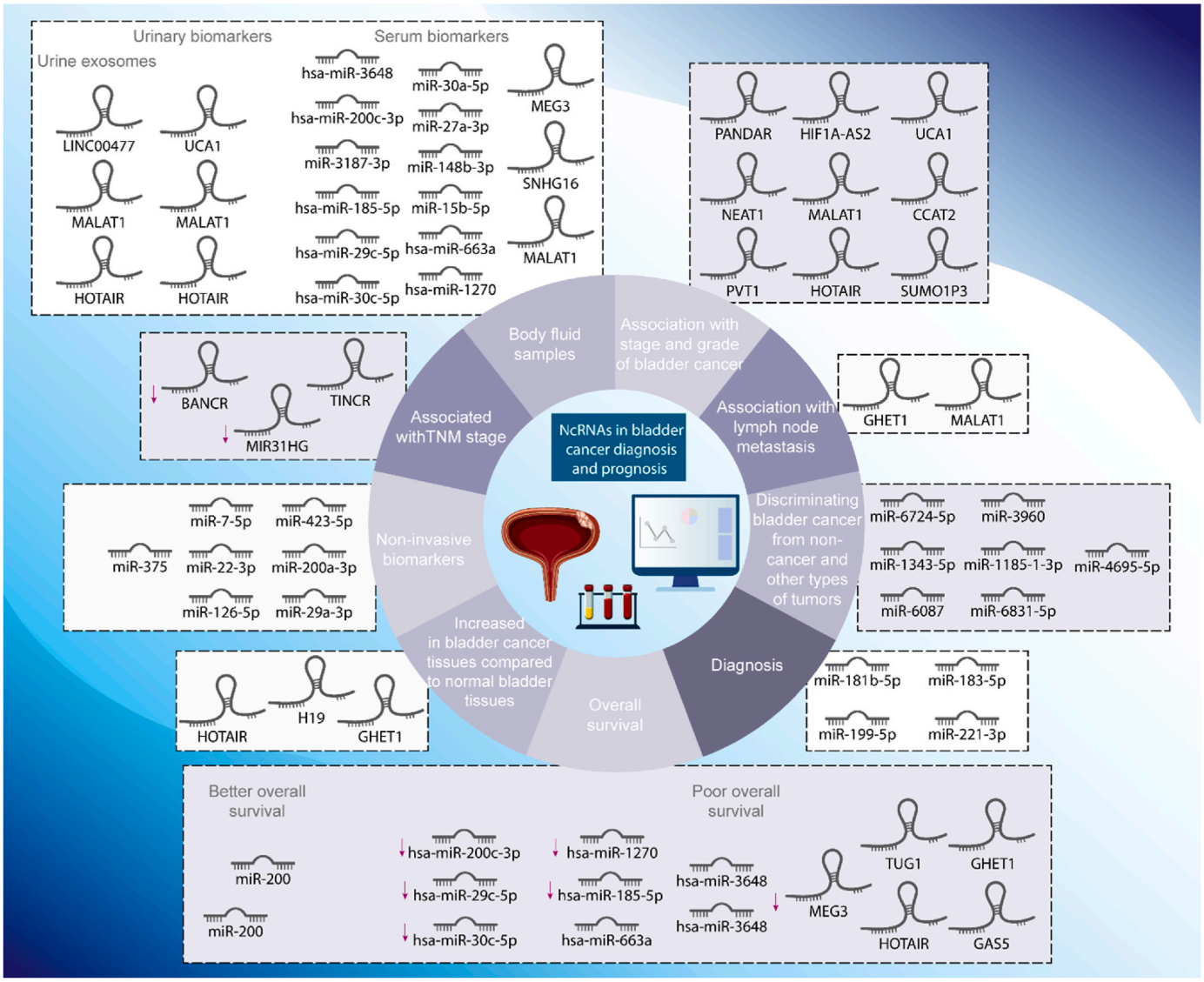

Fig. 4. NcRNAs in bladder cancer theranostics.

BC, suggesting MALAT1 as a prognostic biomarker for BC cases [288].

In a comprehensive study, Duan et al. reported a panel of differentially expressed (DE) lncRNAs extracted from serum specimens, among which MEG3, SNHG16, and MALAT1 were detected to be differentially expressed in the serum of healthy individuals compared to BC patients, as well as those with benign disease. They proposed the corresponding panel as a suitable profile for BC diagnosis [289]. NEAT1, PANDAR, PVT1, SUMO1P3, CCAT2, GHET1 and HIF1A-AS2 are other BC-related lncRNAs that are statistically linked to histological grading and TNM staging of the malady [290–293]. In this area, lncRNA-n336928 has also been indicated to positively correlate with BC stage, histological grade, and patient OS [294,295]. Relevant studies further revealed that TUG1 levels were also increased in metastatic BCs, with a positive association with poor OS, especially in MIBC patients [296] Still, some lncRNAs give us limited information, as TINCR, BANCR, and MIR31HG expression can only reflect the advanced TNM stage [297–299].

A panel of 25 lncRNAs, including DUXAP8, FGFR3-AS1, ZEB1-AS1, CRNDE, SUMO1P3, GAPLINC, ZFAS1, TP73-AS1, NORAD, SNHG5, SNHG16, PCAT-1, XIST, CAT266, CAT1297, CAT1647, CCAT2, CASC2, CASC8, CCEPR, ABHD11-AS1, linc-UBC1, PANDA, LSINCT5, and PTENP1, were recognized to be implicated in BC metastasis, invasion and TNM stage. Moreover, CDKN2B-AS, lncRNA PVT1, GAS5, UCA1, HOTAIR, SNHG16, Linc00857, FOXD2-AS1 were 8 lncRNAs found to be associated with chemo-sensitivity/resistance. TUG1 was the only lncRNA involved in BC radio-sensitivity in bladder cancer [279].

Together, lncRNAs are potential molecules serving as suitable diagnostic and/or prognostic biomarkers for BC management. New lncRNA biomarkers to be used for BC diagnosis should definitely be investigated in previous *in vitro* and clinical studies. Notably, a single lncRNA may often not be a reliable diagnostic indicator for timely detection of BC, and thus lncRNA panels are usually suggested to be used. Further systematic evaluations on lncRNAs will elucidate the diagnostic application of these RNA transcripts for BC patients [279,300].

In the case of diagnostic and prognostic potentials of the other ncRNA subgroup, i.e. circRNAs, obtained data have indicated that some of them are associated with chemo-sensitivity during BC. Using q RT-PCR analysis, circELP3 was identified to be up-modulated in BC cells that were cultured under hypoxic conditions. The hypoxia-induced circELP3 expression could induce cell proliferation and blocked the apoptotic tract in the same BC cells [10]. Hypoxia-induced circELP3 also triggered BC cisplatin resistance *in vitro* [10]. Hsa_circ_0000285 was found to be down-regulated in BC tissues than in normal bladder counterparts [301]. Besides, the levels of hsa_circ_0000285 were lower in cisplatin-resistant BC patients than in cisplatin-sensitive BC patients [301]. As cisplatin resistance causes poor prognosis in patients who are experiencing advanced BC, it is highly recommended to continue to find out clinical implications of the role of circRNAs in cisplatin resistance for further investigation of their potential to be biomarkers and/or therapeutic targets in BC patients, especially non-responders to cisplatin [302].

6.2. NcRNAs for bladder cancer therapy

Owing to comprehensive molecular investigations conducted by The Cancer Genome Atlas (TCGA), the commonest singling pathways such as Notch, PI3K/Akt, RTK-RAS, p53, and Wnt/β-catenin were analyzed in 33 cancer types [303]. Despite the differences between tumor subtypes, soma number of similar genomic changes have been identified. Also, three pathways, including p53/cell cycle regulation, RTK/RAS/PI3K signaling, and chromatin remodeling mechanisms were found to be commonly dysregulated in BC [304]. These signaling mechanisms are interestingly modulated by lncRNAs, *viz*. HOTAIR, XIST, and H19. Thus, regarding the importance of those signaling pathways in BC progression, lncRNAs may have potential therapeutic applications.

Currently, lncRNAs can be silenced by antisense oligonucleotides (ASOs), siRNAs, and small molecules to cease cancer expansion and metastasis [305–308]. The siRNA strategy has the potential of down-regulating the targeted lncRNA in a significant manner, and thus it has recently been considered as a therapeutic modality [309]. Although RNA interfering techniques are beneficial, they cannot be harbored for silencing lncRNAs localized in the nucleus; in such situations, ASOs are the best alternatives. MALAT1 is one of those lncRNAs that is mostly localized within the nuclei of tumor cells, such as BC [310]. ASO-mediated targeting of MALAT1 has shown therapeutic efficacy in a preclinical cancer models [311].

BC-819 (DTA-H19) is a double-stranded DNA plasmid that is employed to target H19 in BC cells [312]. It has been interestingly found that BC can be successfully cured by intravesical infusion of H19-DTA-P4-DTA [313]. A phase II clinical trial analyzed the efficacy and cytotoxicity of BC-819 instillations by studying 47 patients with recurrent BC. The median time to recurrence was 11.3 months, and the recurrence time was 22.1 months in all patients when assessed by response status at 3 months. Accordingly, BC-819 might be considered as a potential therapeutic agent for BCs expressing H19 [314,315].

6.3. NcRNAs in overcoming the cisplatin resistance relative to bladder cancer: clinical evidence

Regarding the clinical evidence, there are limited number of ncRNAs with involvement in BC's cisplatin resistance regulation in clinical settings. One of these RNA transcripts is HIF1A-AS2 as a lncRNA that is induced by low oxygen levels and is specific to certain subtypes of BC. After exposure to cisplatin, HIF1A-AS2 levels increase in both BC cells and tissues, making them less susceptible to cisplatin-mediated cell death. Nonetheless, when HIF1A-AS2 is silenced, the cisplatin-resistant BC cells become more vulnerable to apoptosis. The mechanism of HIF1A-AS2 involves the downregulation of p53 family proteins, which are key regulators of cell cycle and apoptosis, by enhancing the expression of HMGA1, a chromatin-binding protein. HMGA1 forms a complex with p53 family proteins and prevents them from activating the transcription of Bax that promotes apoptosis. Therefore, by reducing HIF1A-AS2 or HMGA1 levels, Bax expression is restored, and cisplatin-induced apoptosis is augmented. Additionally, we observed that HIF1A-AS2 expression was significantly elevated and positively associated with HIF1α and HMGA1 expression in human BC tissues after cisplatin treatment. These results imply that HIF1A-AS2 acts as a tumor promoter by blocking the p53-mediated apoptotic pathway, leading to cisplatin resistance in BC. Furthermore, this study suggests that HIF1A-AS2 may be a potential target for BC therapy [267].

The clinical implication of ncRNAs in BC-related cisplatin resistance can also be exemplified by the lncRNA Urothelial Cancer Associated 1 (UCA1) that is overexpressed in human BC, where it enhances cancer cell growth, movement, invasion, and survival against chemotherapy. It was shown that knocking down the UCA1 lowered the effectiveness of cisplatin/gemcitabine chemotherapy by inhibiting cell growth and promoting cell death, whereas overexpressing UCA1 improved the response to chemotherapy in BC cells. Moreover, UCA1 stimulated the transcription factor CREB, which in turn activated miR-196a-5p by binding to its promoter region. The upregulation of miR-196a-5p was crucial for UCA1's ability to prevent cell death caused by cisplatin/gemcitabine, through targeting the cell cycle inhibitor p27Kip1. These results revealed a new UCA1-CREB-miR-196a-5p mechanism, accounting for UCA1's involvement in cisplatin/gemcitabine resistance and indicated UCA1 as a promising candidate for BC therapy [268].

Last but not least, the expression of lncRNA DLEU1 has also been realized to be increased in BC tissues, and BC patients with high levels of DLEU1 have a lower chance of survival. DLEU1 enhances the growth, movement, and survival of BC cells against chemotherapy by increasing the expression of HS3ST3B1, a gene that encodes an enzyme involved in modifying carbohydrate molecules on the cell surface. DLEU1 does this by reducing the stability of miR-99b that can bind to and silence the HS3ST3B1 gene. BC patients with low miR-99b and high HS3ST3B1

levels have a worse outcome in this era. HS3ST3B1 overexpression or miR-99b under-expression can undo the effects of DLEU1 knockdown, which reduces the expression of DLEU1. All these findings demonstrate that the DLEU1/miR-99b/HS3ST3B1 pathway is important for controlling BC cell growth, invasion, and chemotherapy resistance [316].

7. Conclusions and perspectives

Lots of clinical evaluations have simultaneously demonstrated the crosstalk between up- or down-regulated ncRNAs and the grade, stage, and metastatic status of tumor cells [318]. Once the homeostatic status is disrupted due to the cancer expansion, oncogenic ncRNAs are often overexpressed, while the tumor-suppressive counterparts are down-modulated. Nevertheless, the exact functional role of ncRNAs is still puzzling as the result of the complexity of their expression profiles and targeting proteins. NcRNAs, especially miRNAs and lncRNAs, typically interact with downstream mRNAs to regulate cellular processes related to cancer development such as proliferation, apoptosis, immune response, drug resistance, and autophagy [319,320]. For the last two processes, namely drug resistance and autophagy, blocking autophagy has been shown to make the BC cells more sensitive to cisplatin and gemcitabine and cisplatin. In clinic, BC patients are usually treated by cisplatin-based chemotherapeutics; however, many patients cannot be effectively treated due to cisplatin chemo-resistance, which has recently been discovered to be controlled by various ncRNAs, including miRNAs, lncRNAs, and circRNAs. This interaction is explained by the crucial role of autophagy in the advancement of chemo-resistance, and therefore, ncRNAs with the capacity of blocking autophagy can be used in combination with standard therapies to enhance their efficiency in BC patients soon.

The modulatory roles of ncRNAs in different processes involved in BC formation need to be further investigated to solve the current problems in the field of discovering new diagnostic markers and novel therapeutic options in bladder tumors. The contribution of ncRNAs as potential biomarkers to BC diagnosis and prognosis has been revealed by several studies. Indeed, these RNA transcripts have the ability to be detected in various biological fluids through liquid biopsy-based techniques, or in multiple cancerous and non-cancerous tissues to provide valuable data for disease diagnosis. CircRNAs in this context are considered the most effective circulating biomarkers, as they are resistant to exonucleases found in circulation or other biological circumstances. Regarding the role of ncRNAs in regulation of BC-related processes, different therapeutic approaches can be accurately tailored for the effective treatment of this malignancy. As an example, targeting particular ncRNAs may desirably increase the sensitivity of tumor cells towards routine chemodrug such as cisplatin. The discovery of new cutting-edge methodologies has promoted the ncRNA-based therapeutics to enter the area of precision medicine. The accumulating evidence in this field offer a perspective regarding the molecular profile of BC patients in order to use these ncRNAs as therapeutic agents to target molecular mechanisms involved in cispaltin resistance, as applications in precision medicine.

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Declaration of competing interest

The authors declare that they have no competing interests.

Key abbreviations

Akt	Protein kinase B
ALKBH	AlkB homolog 5 RNA demethylase
BC	Bladder cancer
BMF	Bcl-2-modifying factor
CDK	Cyclin-dependent kinase
ceRNAs	Competing endogenous RNAs
circRNAs	Circular RNAs
COX	Cyclooxygenase
CREB	cAMP-response element binding protein
CSC	Cancer stem cell
EMT	Epithelial-to-mesenchymal transition
FOXO	Forkhead box O
HAX-1	Hematopoietic cell-specific protein 1-associated protein X-1
HCC	Hepatocellular carcinoma
HIF-1α	Hypoxia-inducible factor 1α
HMGA1	High mobility group AT-hook 1
ICI	Immune checkpoint inhibitor
IGFBP	Insulin growth factor-binding protein
lncRNAs	Long non-coding RNAs
LOXL4	Lysyl oxidase homolog 4
MDR	Multi-drug resistance
MIBC	Muscle-invasive bladder cancer
miRNAs	MicroRNAs
MI-TCC	Muscle-invasive transitional cell carcinoma
MMP	Matrix metalloproteinase
MOMP	Mitochondrial outer membrane permeabilization
MRE	MiRNA recognition elements
mTOR	Mammalian target of rapamycin
ncRNAs	Non-coding RNAs
NSCLC	Non-small cell lung cancer
PDL1	Programmed cell death receptor ligand 1
PFS	Progression-free survival
PNPT1	Polyribonucleotide nucleotidyltransferase 1
SRPK1	Serine–arginine protein kinase 1
UPS	Ubiquitin proteasome systems
UTR	Untranslated region
VEGF	Vascular endothelial growth factor
ZEB	Zinc finger e-box binding homeobox

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