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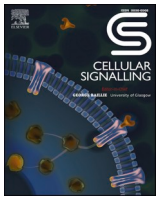

miRNA/epithelial-mesenchymal axis (EMT) axis as a key player in cancer progression and metastasis: A focus on gastric and bladder cancers

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ABSTRACT

The metastasis a major hallmark of tumors that its significant is not only related to the basic research, but clinical investigations have revealed that majority of cancer deaths are due to the metastasis. The metastasis of tumor cells is significantly increased due to EMT mechanism and therefore, inhibition of EMT can reduce biological behaviors of tumor cells and improve the survival rate of patients. One of the gaps related to cancer metastasis is lack of specific focus on the EMT regulation in certain types of tumor cells. The gastric and bladder cancers are considered as two main reasons of death among patients in clinical level. Herein, the role of EMT in regulation of their progression is evaluated with a focus on the function of miRNAs. The inhibition/induction of EMT in these cancers and their ability in modulation of EMT-related factors including ZEB1/2 proteins, TGF-β, Snail and cadherin proteins are discussed. Moreover, lncRNAs and circRNAs in crosstalk of miRNA/EMT regulation in these tumors are discussed and final impact on cancer metastasis and response of tumor cells to the chemotherapy is evaluated. Moreover, the impact of miRNAs transferred by exosomes in regulation of EMT in these cancers are discussed.

1. Introduction

1.1. Gastric cancer

Gastric cancer is the fifth most common cancer around the world and a leading cause of death, threatening human life being [1,2]. Comparison to incidence rate, mortality rate among gastric cancer patients is high and this is maybe due to late diagnosis of patients lacking signs and symptoms at early stages. For instance in USA, late diagnosis of gastric cancer patients has resulted in 5-year survival rate of 31% [3]. Moreover, the fund allotted for stomach cancer research is low and this has resulted some challenges [4]. More than 90% of gastric cancer cases are gastric adenocarcinoma that results from malignant transformation of epithelial cells in gastric gland. Environmental factor, host behavior, genetic and epigenetic alterations and gut microbiota are involved in regulating progression of gastric cancer [5]. Up to 1 million gastric cancer cases are diagnosed annually around the world and half of them are related to China [6]. Among to previous factors, infection with Helicobacter. Pylori (Hp), sex, age, eating habits and smoking are among the factors that increase risk of gastric cancer development [7,8]. Hp infection has been considered as the most common reason in development of gastric cancer due to providing inflammation, gastric atrophy and gastric intestinal metaplasia [9]. Treatment and eradication of Hp can significantly decrease chance of gastric cancer development [10]. The high incidence rate of gastric cancer has been observed in Western and Eastern Asia, Eastern Europe and South America [11,12]. The gender dispersity is observed from birth until age of 75 and it is 0.57% for women, while 1.36% for men. Although cases of gastric cancer have increased in last five decades, the number of gastric cancer cases has shown a decrease due to improvements in eradication of Hp infection

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[13]. Therefore, gastric cancer demonstrated gender bias and it is more predominant in men compared to women and the risk is equal for women in post-menopause period [14–16].

The major treatments for gastric cancer include surgery (at early stages), chemotherapy, radiotherapy and immunotherapy. Furthermore, nanoplatforms have been emerged as new kinds of tools in gastric cancer treatment [17]. Moreover, the potential of chemotherapy and radiotherapy in gastric cancer eradication has been significantly reduced due to development of resistance [18,19]. Therefore, researchers have focused on developing new kinds of therapies (gene therapy) based on signaling networks involved in gastric cancer progression. One of the most important problems in gastric cancer treatment is development of metastasis. Neutrophil extracellular traps can induce epithelial-mesenchymal transition (EMT) in enhancing gastric cancer invasion in a TGF-β-dependent manner [20]. ALKBH5 down-regulation results in increase in expression level of PKMYT1 in enhancing gastric cancer invasion [21]. SOAT1 promotes expression levels of SREBP1 and SREBP2 to induce VEGF-C signaling in promoting lymph node metastasis in gastric cancer [22].

1.2. Bladder cancer

Urinary bladder cancer is considered as one of the most heterogeneous diseases in which morphological and clinical features are different [23]. The global incidence rate for bladder cancer was higher in 2019 compared to the 1990, showing that this cancer is progressing and advancing [24]. According to the estimations, the incidence rate of bladder cancer was 357,000 in 2002 and 145,000 patients died unfortunately due to this disease [25]. The epidemiological data annually change. For instance, in 2019, 500,000 cases of bladder cancer were diagnosed that is higher compared to the 2002 [26]. Therefore, new concepts for the treatment and diagnosis of bladder cancer should be provided. A challenge is lack of a sensitive biomarker for the diagnosis of bladder cancer patients and on time diagnosis of those patients that need the treatment at early stages. Therefore, the new biomarkers not only for the diagnosis of bladder cancer patients, but also for understanding their response to the chemotherapy is required [27–30]. The bladder cancer causes too much socioeconomic burden in the society and just in USA, it provides $4 billion cost for the healthcare system [31]. The risk of bladder cancer development in men is four times higher than females and moreover, the bladder cancer risk development in white men is two times higher than black men. The urothelial cell carcinoma is the most common type of bladder cancer that comprises 90% of cases [32]. A number of signs and symptoms can be observed in bladder cancer patients including urinary frequency, discomfort and pain that is obvious during urination [33]. There are several risk factors for the development of bladder cancer including smoking that increases risk of development by four folds. The reason is that smoking can cause inflammation that mediates bladder cancer development. The workers in a number of industries including dye, rubber, leather and aluminum are also in risk of bladder cancer development. The diagnosis of bladder cancer patients is based on cytology. Moreover, since 80% of patients demonstrate relapse, the process of treatment is a problematic issue and tight follow up of patients is required [34]. The abnormal molecular interactions in bladder cancer can cause progression of this tumor. The PHGDH upregulates SLC7A11 expression to induce ferroptosis inhibition in increasing cancer progression [35]. The NAT10 stimulates the mRNA N4-acetylcytidine modification to increase levels of BCL9L, SOX4 and AKT1 for bladder cancer progression [36]. The ubiquitination process is also affected in regulation of carcinogenesis. RNF126 as a tumor-survival factor induces ubiquitination of PTEN to reduce its stability in cancer progression [37]. Moreover, the RNA molecules with no ability in protein coding such as circRNAs and their interaction with miRNAs can determine the progression of bladder cancer [38,39]. The levels of p53, p21 and pRB are regulated by Rad54L in bladder cancer and through changing cell cycle progression and senescent, it can accelerate bladder cancer progression [40]. The polyadenylation is affected by NUDT21 in bladder cancer whose expression reduces in tumor cells. NUDT21 modulates Wnt/β-catenin and NF-κB to impair progression of bladder cancer [41]. Since YAP participates in regulation in cancer progression, its upregulation by MINDY1 is suggested to be a negative factor for the survival of patients [42].

1.3. microRNAs

miRNAs are non-coding RNAs (ncRNAs) that their length is 22 nucleotides and they are important post-transcriptional regulators of genes. The biogenesis of miRNA is started with generation of precursor-miRNA (pre-miRNA) in nucleus that due to function of Drosha complex, it is changed into primary-miRNA (pri-miRNA) and then, transfer to cytoplasm by Exportin 5 (Fig. 1) [43]. By function of RNase Dicer, a mature miRNA with 20-25 nucleotides is produced in cytoplasm [43]. The function of miRNA is achieved after its loading in RNA-induced silencing complex (RISC). Dysregulation of miRNAs has been considered as one of the most important factors in development of cancer. The process of tumorigenesis can be increased/inhibited by dysregulation of miRNAs. Increasing evidence has evaluated role of miRNAs in gastric cancer progression. miRNAs can be enriched in exosomes and by transferring to gastric cancer cells, they regulate molecular pathways involved in drug resistance [44]. Moreover, miR-130a-3p elevates progression of gastric cancer through inducing TGF-β1/Smad3 axis [45]. On the other hand, miR-23a-3p reduces CCL22 phosphorylation to inhibit PI3K/Akt signaling in treatment of gastric cancer [46]. Hence, miRNAs are potent regulators of cancer hallmarks and chemotherapy response in gastric cancer. The aim of current review is to understand role of miRNAs regulating epithelial-mesenchymal transition (EMT) mechanism in affecting gastric cancer progression. First, we provide an overview of EMT mechanism in gastric cancer and then, role of miRNAs in regulating EMT mechanism and its effect on metastasis and therapy response of gastric tumor cells is evaluated.

2. EMT mechanism: basics and function in oncology

The induction of genomic mutations in normal cells can lead to development of cancer cells due to alterations in chromatin remodeling, biochemical processes and biological mechanisms [47,48]. The final result of these changes is development of malignant cells that demonstrate metastatic nature that is responsible to 90% of cancer-related deaths [49,50]. The experimental and clinical studies have focused on understanding the underlying reason responsible for metastasis in cancer. A “changing face” is observed in tumor cells and that is the change of cells from epithelial to mesenchymal that is called EMT [51,52]. The change of epithelial cells to mesenchymal phenotype results from various biochemical alterations and this process is reversible that mesenchymal cells are changed into epithelial cells known as mesenchymal-epithelial transition (MET) [53,54]. Upon EMT induction, the cancer cells are no more localized to a region in body and they can disseminate to different organs. For process of metastasis, tumor cells should increase their migratory ability to intravasate into blood and lymphatic vessels to reach to desired place that is followed by extravasation and colonization in a new place [55,56]. Tissue differentiation and embryogenesis are processes that require EMT mechanism. For instance, during organ development, it is vital for epithelial cells to be changed into mesenchymal cells and that is why EMT mechanism happens [57]. The EMT induction in adult tissue is observed for wound healing and tissue fibrosis. However, process of tumorigenesis is accelerated due to EMT mechanism that enhances progression of tumor cells. ZEB proteins, TGF-β, Twist and Snail are EMT-inducing transcription factors (EMT-TFs) that stimulate EMT in increasing cancer invasion. Biochemical changes include E-cadherin down-regulation and N-cadherin and vimentin upregulation in EMT induction (Fig. 2). In recent years, EMT mechanism has been of interest in field of cancer therapy,

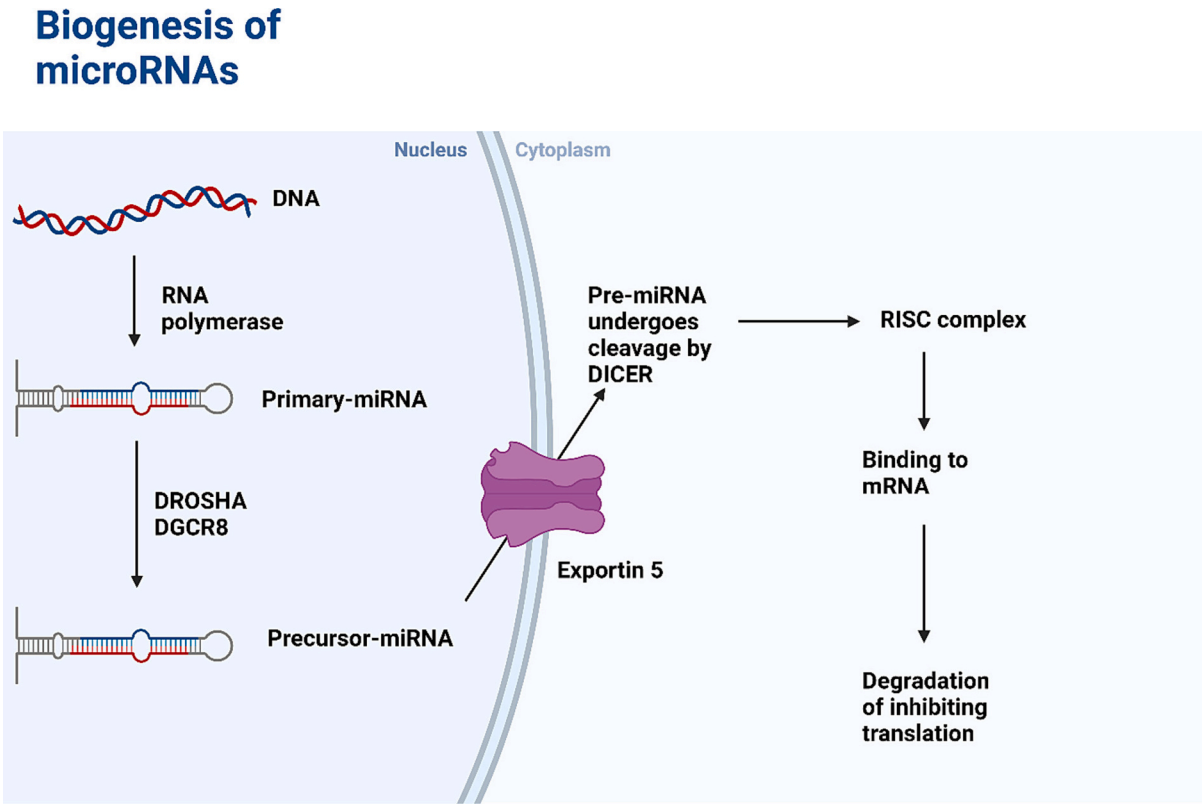

Fig. 1. An overview of miRNA synthesis. The mechanism of miRNA biogenesis is interesting and occurs in several steps that in first step, RNA polymerase should work on DNA to transcribe pri-miRNA. Then, pri-miRNA is transformed into pre-miRNA via function of DROSHA and DGCR8 that with help of exportin 5, pre-miRNA is transferred to cytoplasm that binds to Argonature proteins and is loaded in RISC complex to bind to mRNA in reducing gene expression. (Biorender.com)

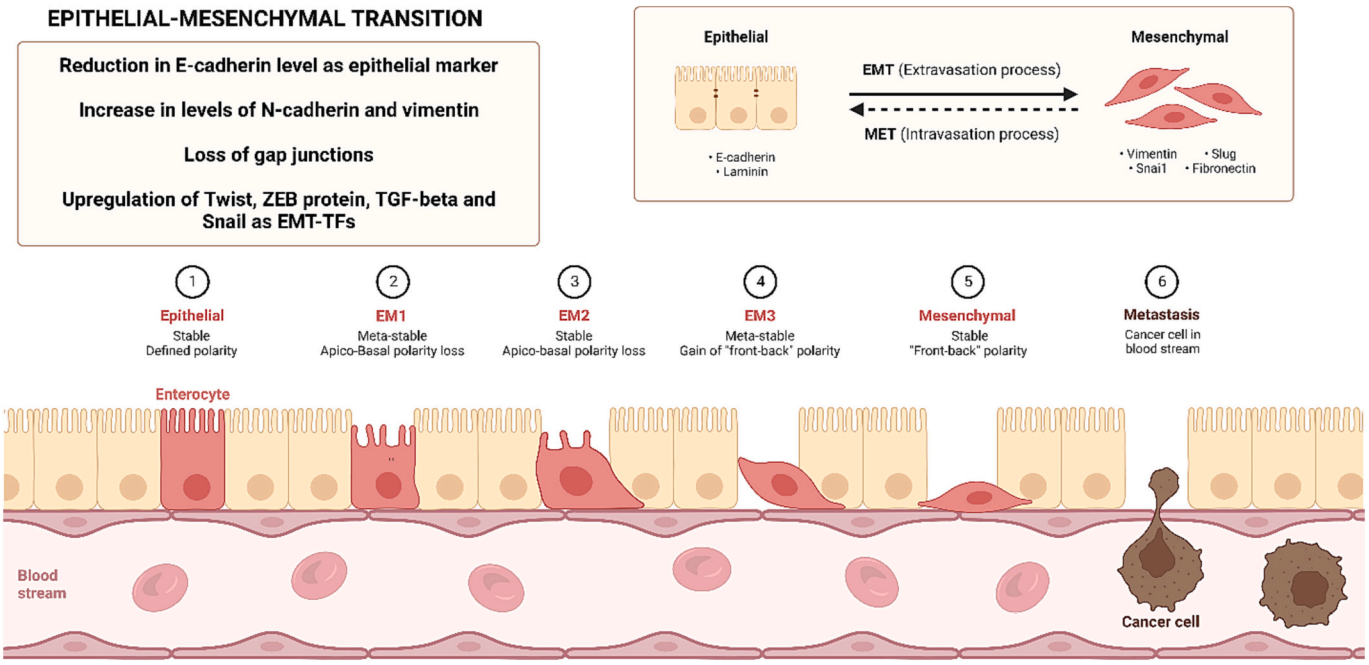

Fig. 2. An overview of EMT mechanism. The process of EMT has been well-understood and it has several steps that they can also occur simultaneously. In these steps, it is necessary to change epithelial cells into mesenchymal cells. (Biorender.com)

especially in gastric cancer. For instance, NFE2L3 stimulates EMT in gastric cancer to promote cancer invasion [58]. BOP1 is capable of increasing N-cadherin levels in gastric cancer [59]. Moreover, PADI4 enhances levels of IL-8 to induce EMT in increasing cancer invasion [60]. It should be mentioned that EMT is not related to only one cancer and it can be observed in different tumor cases including lung cancer [61] and hepatocellular carcinoma [62], showing that it is a target of pharmacological compounds, it is regulated by the epigenetic and

genetic factors, and there are novel concepts that nanoparticles can be introduced for EMT regulation and cancer metastasis inhibition. Therefore, EMT mechanism is regulated by various signaling networks in gastric cancer [63,64]. Furthermore, melittin as anti-cancer agent inhibits Wnt/BMP axis in EMT inhibition and reducing gastric cancer invasion [65]. In the next sections, regulation of EMT mechanism by miRNAs in gastric cancer is discussed.

3. Biological functions

3.1. microRNA/EMT axis in metastasis in gastric cancer

Although EMT mechanism has been identified as the most common mechanism for increasing progression and metastasis of gastric tumor cells, the molecular pathways regulating EMT in gastric cancer are complicated. On the other hand, there are a high number of miRNAs that regulate EMT mechanism in gastric cancer and therefore, the aim of current section is to give a general view of miRNA/EMT axis with related molecular pathways in regulating gastric cancer invasion. Overexpression of PPP2R2A has been considered as a driver of gastric cancer invasion via inducing EMT mechanism. Silencing PPP2R2A remarkably decreases progression of gastric cancer cells and their metastasis. miR-665 is a down-regulated factor in gastric cancer; elevating miR-665 expression is of importance in suppressing EMT mechanism via reducing PPP2R2A expression to impair gastric cancer invasion [66]. Polo-like kinase 1 (PLK-1) is an oncogenic factor and its stability increases by SKA3 in increasing tumor proliferation [67]. Due to function of PLK-1 in enhancing tumor progression, delivery of siRNA for its down-regulation by exosomes has been performed in cancer therapy [68]. miR-505 is able to suppress EMT in reducing metastasis of gastric cancer cells. The expression level of miR-505 shows down-regulation in gastric cancer and restoring its expression can impair cancer metastasis. miR-505 reduces expression level of PLK-1 to impair EMT in gastric cancer [69].

miR-599 is an inhibitor of cancer proliferation and invasion. For reducing progression and invasion of tumor cells, miR-599 is capable of suppressing EMT [70]. Similarly, in gastric cancer, anti-cancer activity of miR-599 is related to its negative impact on EMT mechanism. miR-599 demonstrates negative association with EIF5A2 expression in preclinical and clinical samples of gastric cancer and by decreasing EIF5A2 expression, miR-599 suppresses EMT mechanism to reduce gastric cancer invasion [71]. Interestingly, miRNAs regulating EMT mechanism can be considered as biomarkers in cancer. miR-153 is an anti-cancer factor and its upregulation can significantly suppress invasion of gastric tumor cells. miR-153 decreases expression level of SNAI1 to suppress EMT via E-cadherin elevation and vimentin reduction in impairing metastasis of gastric cancer cells. Notably, miR-153 is a prognostic marker in cancer and its poor expression mediates unfavorable prognosis in gastric cancer [72].

Each experiment has focused on a certain type of miRNA and a unique downstream target in regulating EMT mechanism in gastric cancer. Due to the fact that miRNAs can affect more than one genos, and one gene can be affected by more than one miRNA, the molecular pathways regulating EMT mechanism in gastric cancer are completely complicated. An important controversy in field of miRNAs in oncology is dual function of these ncRNAs. For instance, miR-370 has been shown to be an inhibitor of metastasis in osteosarcoma via EMT inhibition [73,74], other studies reveal that miR-370 can be considered also an inducer of cancer invasion [75,76]. In gastric cancer, miR-370 is an inhibitor of EMT. miR-370 is capable of reducing expression level of PARQ4 in EMT inhibition and reducing malignant behavior of gastric tumor cells [77]. Therefore, understanding function of each miRNA in gastric cancer as inhibitor or inducer of EMT should be carefully followed.

However, there are also miRNAs that can induce EMT mechanism in increasing gastric cancer metastasis via affecting molecular pathways related to EMT. One of the most related molecular pathways related to EMT mechanism is PI3K/Akt signaling. Increasing evidence demonstrates that stimulation of PI3K/Akt signaling can lead to EMT induction and enhancement in invasion of tumor cells [78–80]. On the other hand, activation of PI3K/Akt signaling increases progression and stemness of gastric cancer [81–83]. FOXO1 suppresses PI3K/Akt signaling to inhibit EMT-induced metastasis in gastric cancer cells. However, when expression level of miR-552 enhances, it causes poor prognosis and mediates gastric cancer invasion via FOXO1 down-regulation to induce PI3K/Akt signaling, resulting in EMT induction and increase in gastric cancer invasion [84]. One of the important aspects is the role of PI3K/Akt signaling in inducing glycolysis in cancer progression [85]. Furthermore, glycolysis has been involved in promoting tumor metastasis via EMT induction [86]. Therefore, future studies can focus how glycolysis induction by PI3K/Akt signaling can increase cancer invasion and metastasis.

miR-4513 is an oncogenic factor and it prevents apoptosis, while it promotes growth rate of tumor cells [87–89]. The role of miR-4513 is enhancing gastric cancer invasion can be attributed to targeting EMT mechanism. Upregulation of miR-4513 in gastric cancer increases tumor invasion via EMT induction and in this way, miR-4513 reduces KAT6B expression [90]. It appears that ability of miRNAs in regulating EMT mechanism in gastric cancer is based on targeting related molecular pathways. Therefore, miRNAs indirectly affect EMT mechanism in gastric cancer. Table 1 and Fig. 3 provide a summary of miRNAs regulating EMT mechanism in gastric cancer.

3.2. microRNA/EMT axis in metastasis in bladder cancer

The general aspects of EMT regulation by miRNAs in the bladder cancer has broadened the insight towards understanding the molecular interactions at genetic and epigenetic levels as critical regulators of cancer metastasis. Since the bladder cancer patients suffer from high metastasis that causes death among them, such revealing of pathways can bring new concepts for the development of novel therapeutics for the bladder cancer. In the current section, the general aspects related to the regulation of cancer metastasis by miRNA/EMT axis is provided. The function of miR-520h is to increase the metastasis of bladder cancer; it has been brought into attention that miR-520h can be sponged by circNDRG1 to accelerate Smad7 expression as a suppressor of EMT [91]. The metastasis and malignancy of bladder cancer as biological behaviors of this tumor depend on the EMT mechanism. miR-203 has a role of reducing cancer invasion and metastasis and this epigenetic factor has been implicated in Twist1 downregulation to disrupt EMT and metastasis of bladder cancer [92]. The changes in the phenotype and molecular profile of tumor cells can be observed after regulation of EMT. However, a negative point of current studies is lack of significant attention to the role of miRNAs in regulation of phenotype of tumor cells and main focus is on the modulation of genes and proteins. The SphK1 suppression by miR-613 has been considered as a main factor for suppressing EMT and metastasis of bladder cancer. This is accompanied with upregulation of E-cadherin and reduction in levels of Snail, vimentin and N-cadherin [93]. Since miRNAs have multifunctional role in cancers, their function in bladder cancer is beyond just modulation of EMT and metastasis. miR-451 is able to suppress EMT and invasion, and stimulate apoptosis in bladder cancer. miR-451 downregulates N-cadherin, vimentin and Snail expression to suppress EMT in bladder cancer [94]. The downregulated miR-22 in bladder cancer can promote metastasis; miR-22 binds to E2F3 and downregulates its expression to impair EMT, metastasis and proliferation of tumor cells [95]. The expression level of NSBP1 as a molecular target of miR-186 is downregulated by this epigenetic factor. This demonstrates that NSBP1 suppression by miR-186 can inhibit EMT through regulation of related markers including vimentin and N-cadherin suppression and E-cadherin acceleration (Table 2) [96].

Table 1
The role of miRNAs in affecting gastric cancer metastasis via regulating EMT mechanism.

miRNA	Molecular pathway	Remark	Ref
miR-135b	CAMK2D/EMT	miR-135b reduces CAMK2D expression to induce EMT in cancer progression enhancement	[97]
miR-140-5p	miR-140-5p/LRP4/PI3K/Akt	miR-140-5p increases LRP4 expression to induce PI3K/Akt signaling in EMT induction	[98]
miR-503	-	miR-503 suppresses EMT mechanism via elevating E-cadherin levels and decreasing vimentin, fibronectin, N-cadherin and SNAIL levels	[99]
miR-6884-5p	S100A16	miR-6884-5p reduces S100A16 expression to inhibit EMT mechanism	[100]
miR-338	Wnt/β-catenin	miR-338 inhibits Wnt signaling to suppress EMT-mediated invasion	[101]
miR-216a	JAK2/STAT3/EMT	miR-216a inhibits JAK2/STAT3 axis to suppress EMT in reducing progression and invasion of cancer cells	[102]
miR-33a	Snail/Slug	miR-33a inhibits activation of Snail/Slug axis in EMT inhibition	[103]
miR-642b-3p	CSMD1/Smad	miR-642b-3p miR-642-3p increases Smad7 expression via CSMD1 down-regulation to induce EMT via enhancing N-cadherin levels and decreasing E-cadherin levels	[104]
miR-205	ZEB1/EMT	miR-205 reduces ZEB1 expression to suppress EMT in reducing cancer metastasis and invasion	[105]
miR-345	FOXO1/EMT	miR-345 reduces FOXO1 expression to inhibit EMT in reducing cancer invasion and metastasis	[106]
miR-495	Twist1/EMT	miR-495 reduces Twist1 expression to suppress EMT	[107]
miR-338	NRP1	miR-338 reduces NRP1 to inhibit phosphorylation of ERK1/2, MAPK and Akt in reducing cancer metastasis via EMT inhibition	[108]
miR-145-5p	ZEB2	miR-145-5p reduces ZEB2 expression to suppress EMT in reducing cancer invasion	[109]
miR-340	NF-κB1	miR-340 suppresses NF-κB1signaling to inhibit EMT	[110]
miR-498	BMI-1/Akt	miR-498 inhibits BMI-1/Akt signaling in suppressing EMT mechanism	[111]
miR-588	EIF5A2	miR-588 reduces EIF5A2 expression to suppress EMT	[112]
miR-379	FAK/AKT	miR-379 inhibits FAK/AKT axis to suppress EMT	[113]
miR-195-5p	Snail	Propofol administration increases miR-195-5p expression to suppress Snail/EMT axis	[114]
miR-130a-3p	TBL1XR1/EMT	miR-130a-3p reduces expression level of TBL1XR1 to suppress EMT	[115]
miR-17	DEDD/EMT	miR-17 stimulates drug resistance and EMT mechanism via DEDD down-regulation	[116]
miR-22	MMP14 Snail	Down-regulation of MMP14 and Snail by miR-22 in decreasing cancer invasion and metastasis	[117]
miR-95	DUSP5/EMT	Silencing miR-95 increases DUSP5 expression to inhibit EMT mechanism	[118]
miR-124	Snail2/EMT	miR-124 reduces Snail2 expression in suppressing EMT in gastric cancer	[119]
miR-195-5p	PD-L1	Astragaloside IV reduces PD-L1 expression via upregulating miR-195-5p to suppress EMT	[120]

3.3. microRNAs regulating EMT-TFs in gastric cancer

3.3.1. ZEB proteins

ZEB1 and ZEB2 proteins are considered as factors involved in enhancing progression of gastric tumor cells. ZEB1 enhances expression level of LINC015559 to recruit IGF2BP2 in enhancing ZEB2 stability in EMT induction [128]. CPEB4 promotes ZEB1 expression to induce EMT in enhancing cancer progression [129]. Circ-000684 reduces miR-186 to upregulate ZEB1 in inducing gastric cancer metastasis [130]. Moreover, ZEB2 proteins are involved in increasing gastric cancer progression via EMT induction and it can also result in drug resistance [131–133]. miRNAs regulate both ZEB1 and ZEB2 in affecting gastric cancer invasion. miR-144-3p is beneficial in increasing sensitivity of gastric cancer cells to radiotherapy and reducing tumor progression. miR-144-3p reduces ZEB1 expression to impair gastric cancer progression [134]. Importantly, miR-203 expression decreases in gastric cancer, while ZEB1 shows enhancement in expression. miR-203 decreasing ZEB1 expression to impair cancer progression and to promote sensitivity of gastric tumor cells to radiotherapy [135]. miR-27 shows upregulation in gastric cancer and it significantly promotes progression of tumor cells. miR-27 elevates expression levels of ZEB1, ZEB2, Slug and vimentin to reduce E-cadherin levels in triggering EMT and promoting gastric cancer invasion [136].

miR-205-3p is a suppressor of tumor progression and its down-regulation by Linc00284 can result in cancer malignancy via c-Met overexpression [137]. Moreover, miR-205-3p decreases MAPK10 expression in suppressing proliferation and invasion of tumor cells [138]. miR-205-3p has been considered as an inhibitor of gastric cancer metastasis; for this purpose, miR-205-3p decreases expression levels of ZEB1 and ZEB2 in suppressing EMT and decreasing cancer invasion [139]. The miRNA/ZEB axis not only regulates gastric cancer metastasis, but also affects drug sensitivity of tumor cells. miR-338-5p decreases ZEB2 expression level to suppress gastric cancer migration and to promote cisplatin sensitivity [140]. Based on these studies, miRNAs are potential regulators of ZEB1 and ZEB2 in regulating gastric cancer invasion.

3.3.2. Twist

The expression level of Twist has been closely related to affecting progression of gastric cancer cells. A basic study has shown that expression level of Twist increases in up to 80% of gastric cancer samples [141]. CDC27 is involved in promoting expression level of Twist to induce EMT in promoting gastric cancer invasion [142]. Silencing Twist expression using siRNA is beneficial in increasing E-cadherin levels and impairing gastric cancer invasion [143]. miR-381 is able to reduce expression level of Twist in impairing gastric cancer progression [144]. However, most of the studies have emphasized on the regulation of miRNA/Twist axis by upstream mediators in gastric cancer. LncRNA NORAD is considered as an inducer of gastric cancer progression and it is involved in growth acceleration and apoptosis inhibition via affecting miR-214 [145]. LncRNA NORAD has been involved in enhancing gastric cancer invasion. LncRNA NORAD sponges miR-496 to increase IL-33 in promoting gastric cancer progression and one of the controversial results is that silencing NORAD promotes expression levels of Twist in cancer-associated fibroblasts [146]. Similarly, upregulation of lncRNA H19 has been beneficial in promoting progression of gastric cancer cells via inducing glycolysis and proliferation, and it is capable of regulating miRNA expression [147,148]. LncRNA H19 promotes expression level of TCF4 via miR-152-3p inhibition in gastric cancer that is beneficial for promoting expression level of Twist along with other factors such as Slug, Snail and N-cadherin in triggering EMT [149].

3.3.3. Snail, Slug and vimentin

These factors are also EMT-TFs that can be regulated by miRNAs in gastric cancer. miR-9-5p shows anti-cancer activity in gastric tumor, while NFIC increases tumor progression. miR-9-5p decreases expression

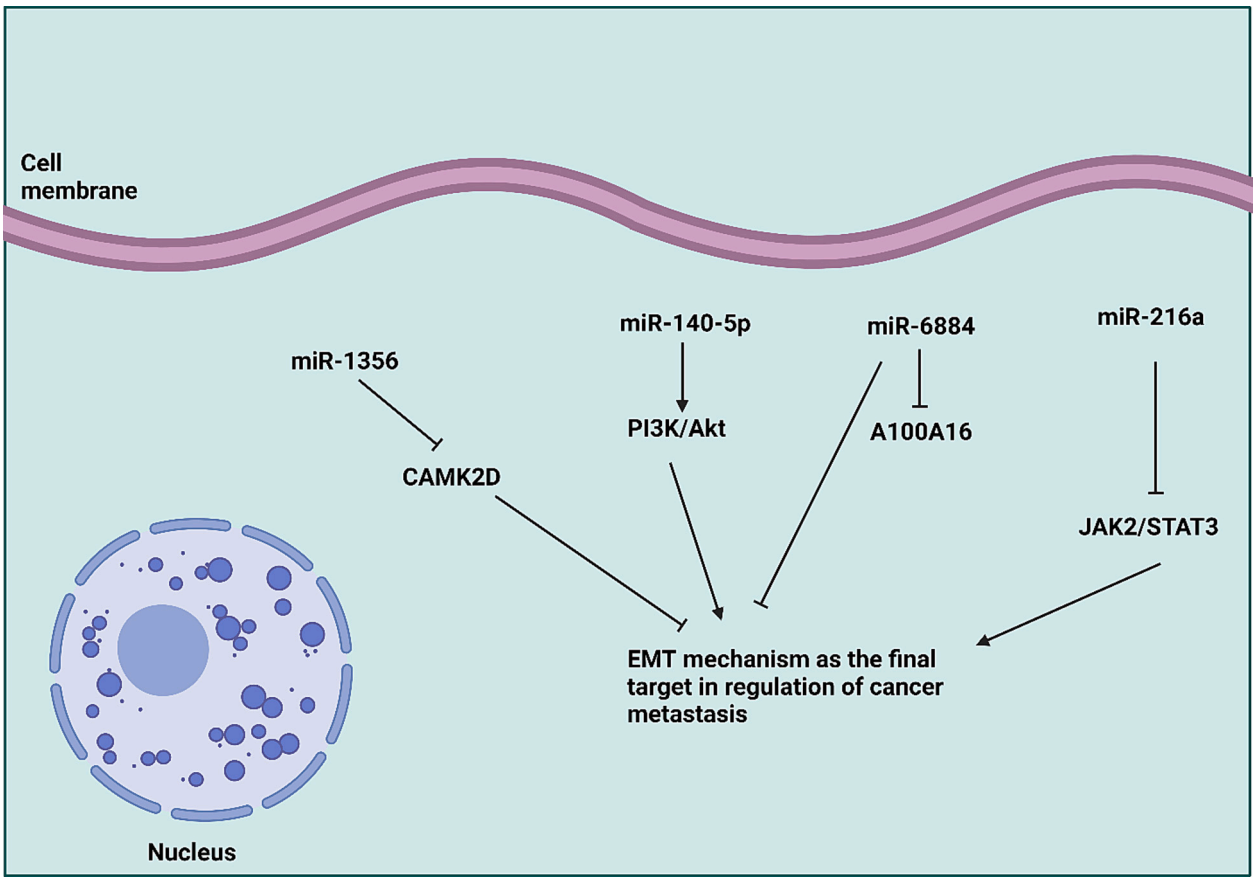

Fig. 3. A summary of miRNA/EMT axis in regulating gastric cancer invasion. (Biorender.com)

Table 2
The EMT regulation by miRNAs in bladder cancer.

miRNA	Target	Outcome	Ref
miR-325-3p	MT3	MT3 suppression by miR-325-3p to EMT inhibition	[121]
miR-92b	DAB2IP	DAB2IP is inhibited by miR-92b to accelerate EMT	[122]
miR-454-3p and miR-374b-5p	ZEB2	Decrease in the metastasis of tumor cells through ZEB2 suppression	[123]
miR-19a	RhoB	RhoB downregulation by miR-19a in EMT acceleration	[124]
miR-22	Snail and MAPK1/Slug/vimentin	EMT suppression by miR-22 through inhibiting the Snail and MAPK1/Slug/vimentin feedback loop	[125]
miR-96	TGF-β1	The control of TGF-β1 by miR-96 in inducing EMT	[126]
miR-5581-3p	SMAD3	miR-5581-3p impairs the SMAD3 expression for EMT suppression	[127]

level of NFIC to down-regulate vimentin and Snail in impairing gastric cancer metastasis [150]. Epstein-Barr virus (EBV) is one of the reasons for development of gastric cancer and this herpes virus infects up to 90% of adult individuals around the world [151]. EBV infection is associated with development of malignancies, especially gastric cancer [152,153]. Importantly, EBV-miR-BART12 is capable of impairing progression of gastric cancer. EBV-miR-BART12 decreases expression level of Snail to suppress EMT in gastric cancer [154]. Snail overexpression in gastric cancer can result in down-regulation of E-cadherin for enhancing invasion. Noteworthy, miR-491-5p suppresses Snail expression. Furthermore, miR-491-5p reduces Snail expression via FGFR4 down-regulation to suppress E-cadherin expression, leading to EMT induction [155]. ATM is suggested to be an oncogenic factor in gastric tumor and silencing PP2Ac α leads to upregulation of ATM in inducing METTL3 expression for aggravating cancer progression [156]. DNA damage result in activation of ATM signaling for promoting gastric tumor progression [157]. Upregulation of ATM is required for Snail overexpression; however, miR-203 decreases ATM expression in down-regulating Snail expression and suppressing EMT mechanism in reducing gastric cancer invasion [158]. Moreover, down-regulation of miR-95 occurs in gastric cancer that is beneficial for increasing metastasis and EMT induction via upregulating Slug expression [159].

3.3.4. *TGF-β*

In addition to previous factors, TGF-β is another EMT-TFs and its function in increasing gastric cancer progression has been investigated. TGF-β is capable of increasing expression level of RSK2 to induce phosphorylation of VGLL-1 and mediates its interaction with TEAD4, leading to MMP-9 overexpression and development of gastric cancer metastasis [160]. IGHG1 stimulates TGF-β/Smad3 axis in EMT induction and promoting progression of gastric cancer [161]. Therefore, upregulation of TGF-β is required for EMT induction in gastric tumor [162]. Accumulating data has shown regulation of TGF-β signaling by miRNAs in gastric cancer. miR-21 is able to induce gastric cancer invasion and for this purpose, it reduces expression level of PTEN. Then, activation of TGF-β signaling occurs that promotes vimentin, Slug, N-cadherin and β-catenin in inducing EMT [163]. On the other hand, miR-381 reduces expression level of TMEM16A to suppress TGF-β signaling in impairing EMT mechanism for decreasing gastric cancer progression [164]. One of the important aspects is the regulation of miRNAs by TGF-β signaling in gastric cancer. Smad4 is an executive arm of TGF-β signaling and it promotes expression level of miR-574-3p by binding to its promoter in aggravating gastric cancer invasion [165]. Based on these studies,

miRNA and TGF-β dual interaction is of importance in determining gastric cancer invasion.

3.4. Exosomal microRNAs in gastric cancer

Exosomes are minute structures that can be secreted by almost all eukaryotic cells to extracellular matrix (ECM) and they have particle size of 40-150 nm. Tumor cells demonstrate higher ability in secretion of exosomes compared to normal cells. Furthermore, cells in tumor microenvironment including macrophages and cancer-associated fibroblasts can secrete exosomes in regulating progression of cancer cells. Exosomes can be used for delivery of proteins, lipids and genetic materials to tumor cells. Furthermore, miRNAs can be enriched in exosomes in regulating progression of cancer cells [166,167]. Exosomal miRNAs have been considered as potential regulators of gastric cancer progression. M2 polarized macrophages secrete exosomal miR-487a to increase growth rate of gastric cancer cells [168]. Moreover, exosomal miR-10b-5p diminishes KLF11 expression in increasing gastric cancer growth [169]. Decrease in levels of exosomal miR-590-5p can lead to poor prognosis in gastric cancer [170]. More importantly, exosomes containing miRNAs can regulate progression of gastric cancer cells [171]. GIT1 upregulation in gastric cancer cells can result in increase in metastasis via EMT induction. miR-122-5p demonstrates a decrease in expression in exosomes derived from serum of gastric cancer patients. Exosomal miR-122-5p decreases expression level of GIT1 to suppress EMT-mediated metastasis in gastric cancer [172]. Interestingly, gastric cancer cells that are resistant to paclitaxel chemotherapy can secrete exosomes in increasing cancer progression. Exosomal miR-155-5p derived from paclitaxel-resistant gastric cancer cells can reduce expression levels of GATA3 and TP53INP1 in EMT induction and enhancing cancer invasion [173]. However, A few studies have focused on the role of exosomal miRNAs in regulating gastric cancer metastasis via EMT modulation and therefore, more experiments in future should be performed in this case.

3.5. LncRNAs regulating microRNA/EMT axis

3.5.1. Gastric cancer

miRNAs are linear RNA molecules that do not encode proteins. Similar to them, long non-coding RNAs (lncRNAs) have not capacity in protein encoding and their difference is in size that lncRNAs have more than 200 nucleotides. Furthermore, lncRNAs can be found in both cytoplasm and nucleus, while mature and functional miRNAs are only found in cytoplasm. Interestingly, expression level of miRNAs can be suppressed by lncRNAs via sponging. Accumulating data has shown role of lncRNAs in regulating gastric cancer progression via affecting miRNAs [174]. For instance, lncRNA CASC11 sponges miR-340-5p to increase CDK1 expression in promoting gastric cancer malignancy [175]. Besides, lncRNA MACC1-AS1 decreases miR-145-5p in triggering drug resistance and enhancing stemness and fatty acid oxidation in gastric cancer [176]. This section focuses on the role of lncRNAs in regulating miRNA/EMT axis in gastric cancer. miR-490-3p has shown abnormal expression during gastric cancer progression and it is an inhibitor of EMT mechanism. However, gastric cancer cells switch among molecular pathways to induce EMT. LncRNA AL139002.1 reduces expression level of miR-490-3p to induce HAVCR1/MERK/ERK axis in EMT induction and promoting progression and metastasis of gastric tumor cells [177]. Moreover, CXCR1 is a driver of gastric cancer progression; CXCR1 induces Akt and ERK1/2 molecular pathways to reduce E-cadherin levels in increasing gastric cancer invasion [178]. LncRNA PCED1B-AS1 enhances expression level of CXCR1 via miR-215-3p sponging to induce EMT in increasing gastric cancer invasion [179].

An important regulator of gastric cancer progression is Wnt/β-catenin signaling. LRP5 stimulates Wnt signaling and glycolysis in increasing gastric cancer progression [180]. Moreover, KLF1 and PROX1 stimulate Wnt signaling in promoting progression of gastric tumor cells [146,181]. LncRNA TTTY15 has been correlated with increasing gastric tumor metastasis via EMT induction. TTTY15 reduces expression level of miR let-7a-5p via sponging to induce Wnt/β-catenin signaling in EMT induction and promoting progression of tumor cells [182]. Previously, it was mentioned that PI3K/Akt is an inducer of EMT in gastric cancer and its expression level is regulated by miRNAs. More importantly, lncRNAs can affect miRNA/PI3K/Akt axis in gastric cancer. LncRNA TNK2-AS1 reduces expression level of miR-125a-5p to induce PI3K/Akt signaling, leading to EMT induction and enhanced invasion of gastric cancer cells [183]. WNT5A is a ligand of Wnt signaling that its upregulation promotes progression of gastric tumor. miR-186-5p down-regulates WNT5A expression in impairing gastric cancer progression. However, changes occurring in genetic and epigenetic levels during hypoxia can lead to increase in gastric cancer malignancy. Upregulation of lncRNA HCP5 is positive factor for increasing gastric cancer invasion during hypoxia due to its function in miR-186-5p inhibition and subsequent enhancement in WNT5A expression in EMT induction [184]. The process of metastasis in gastric cancer has been complicated by function of autophagy in regulating EMT [185]. Autophagy is a regulator of EMT in both normal and cancer cells. Autophagy defection leads to EMT induction in intrauterine adhesions [186]. Furthermore, cancer cells depend on autophagy to preserve mitochondrial homeostasis during TGF-β1-mediated EMT [187]. LncRNA SNHG11 stimulates both autophagy and Wnt/β-catenin pathway in gastric cancer. SNHG11 suppresses processing of pre-miR-483/pre-miR-1276 to increase CTNNB1 and ATG12 levels in triggering autophagy and enhancing cancer metastasis via EMT induction [185]. According to these studies, lncRNAs tightly regulate miRNA/EMT axis in gastric cancer and targeting these pathways is of importance in cancer therapy (Table 3).

3.5.2. Bladder cancer

The role of lncRNAs as regulators of cancer progression has been evaluated. The studies have provided the mechanism of action of lncRNAs in regulation of bladder cancer progression. The lncRNA CCAT1 enhances tumor grade, stage and size, and based on the findings, it is related to the regulation of miR-181b-5p, miR-152-3p, miR-24-3p, miR-148a-3p and miR-490-3p [188]. Through sponging miR-12-5p, lncRNA RP11-89 increases progression of bladder cancer and prevents ferroptosis [189]. Furthermore, studies have focused on understanding the role of lncRNAs in regulation of immune system function and development of signatures for the prognosis of bladder cancer [190,191]. Although the role of lncRNAs in regulation of cancer progression has been understood, because of highlighting too many lncRNAs, it is suggested to focus on specific mechanisms modulated by lncRNAs in bladder cancer that aim of this section is to focus on EMT mechanism. An important function of lncRNAs is to act as a sponge for miRNAs as downstream targets. The LINC00355 sponges miR-424-5p to upregulate HMGA2 for EMT induction and elevation in metastasis and progression of bladder cancer cells [192]. The oncogenic function of several lncRNAs in bladder cancer has been understood. The lncRNA SNHG3 has capacity of increasing metastasis and EMT in bladder cancer; miR-515-5p sponging by lncRNA SNHG3 can increase GINS2 expression to stimulate EMT [193]. A drawback of the studies is that they have highlighted the function of lncRNAs through regulation and sponging miRNAs in many cases to affect EMT mechanism. The strength point is regulation of proteins at posttranscriptional level to affect EMT. The increase in expression of PCBP2 is vital for stimulation of EMT and increase in metastasis of bladder cancer cells. LncRNA KCNQ1OT1 sponges miR-145-5p to upregulate PCBP2 in EMT induction and enhancement in metastasis and progression of bladder cancer cells [194]. The regulation of EMT-TFs also occurs by lncRNAs to affect EMT and metastasis of bladder cancer. The LINC01410 is able to sponge miR-4319 for increasing Snail1 expression to mediate EMT and progression of bladder cancer [195]. Table 4 is a summary of miRNA/EMT regulation by lncRNAs in bladder cancer.

Table 3
Modulation of miRNA/EMT axis by lncRNAs in gastric cancer.

LncRNA	Molecular pathway	Remark	Ref
SNHG3	miR-326/EMT	SNHG3 reduces miR-326 expression to upregulate TWIST in EMT induction and increasing cancer invasion	[196]
FAM225A	miR-206/ADAM12	FAM225A induces ADAM12 expression via miR-206 down-regulation in increasing N-cadherin levels and decreasing E-cadherin levels	[156]
SNHG6	miR-1297/BCL-2	SNHG6 induces cisplatin resistance and EMT via miR-1297 sponging to increase BCL-2 expression levels	[197]
HULC	miR-9-5p/MYH9	HULC increases MYH9 expression by miR-9-5p inhibition in EMT induction	[198]
HCG18	HNF1A/HCG18/ miR-152-3p/ DNAJB12	HNF1A increases HCG18 expression miR-152-3p down-regulation by HCG18 to induce DNAJB12 expression EMT induction	[199]
SNHG1	miR-15b/DCLK1/ Notch1	SNHG1 induces DCLK1/Notch1 axis via miR-15b down-regulation in EMT induction	[200]
PVT1	miR-30a/Snail	PVT1 increases Snail expression by miR-30a inhibition Elevating cancer metastasis via EMT induction	[161]
LINC00689	miR-526b-3p/ ADAM9	LINC00689 sponges miR-526b-3p Upregulation of ADAM9 EMT induction	[201]
LOXL1-AS1	miR-708-5p/USF1	LOXL1-AS1 stimulates EMT via sponging miR-708-5p and promoting USF1 expression	[202]
SND1-IT1	miR-124/COL4A1	SND1-IT1 sponges miR-124 Upregulation of COL4A1 EMT induction	[203]
GCMA	SP1/GCMA/miR-34a	SP1 increases GCMA expression to sponge miR-34a and miR-124 in EMT induction	[204]
ATB	miR-200A	Xiaotan Sanjie decoction administration suppresses EMT and cancer metastasis via lncRNA ATB down-regulation to increase miR-200A expression	[205]
HOTTIP	miR-218/HMGA1	HOTTIP induces EMT and cisplatin resistance via reducing miR-218 expression to upregulate HMGA1	[206]
LINC00659	SP1/LINC00659/ miR-370/AQP3	SP1 increases LINC00659 expression to increase AQP3 expression via miR-370 sponging in EMT induction	[207]
SNHG6	miR-101-3p/EMT	SNHG6 induces EMT and poor prognosis via miR-101-3p sponging	[208]
ASNR	miR-519e-5p/ FGFR2	ASNR increases FGFR2 expression via miR-519e-5p sponging in EMT induction	[209]
SNHG12	YY1/SNHG12/miR-218-5p/YWHAZ	YY1 negatively regulates SNHG12 expression SNHG12 modulates miR-218-5p/ YWHAZ expression SNHG12 stimulates EMT mechanism	[170]
LINC00649	miR-16-5p/YAP1/ Hippo	LINC00649 sequesters miR-16-5p to induce YAP1/Hippo axis in EMT induction	[210]
TMPO-AS1	miR-140-5p/SOX4/ EMT	TMPO-AS1 sponges miR-140-5p to increase SOX4 expression EMT stimulation	[211]
CASC15	miR-33a-5p/ZEB1	CASC15 sponges miR-33a-5p ZEB1 upregulation EMT induction	[212]
MBNL1-AS1	miR-424-5p/Smad7	MBNL1-AS1 increases Smad7 expression via miR-424-5p inhibition EMT inhibition	[213]

Table 4
The miRNA/EMT regulation by lncRNAs in bladder cancer.

LncRNA	Target	Outcome	Ref
CASC9	miR-758-3p	TGF-beta2 upregulation by CASC9 through miR-758-3p sponging to induce EMT	[214]
UCA1	miR-143/ HMGB1	miR-143 downregulation by UCA1 to induce EMT through HMGB1 upregulation	[215]
ZNRD1-AS1	miR-194 ZEB1	ZNRD1-AS1 increases ZEB1 expression through miR-194 sponging to mediate EMT	[216]
XIST	miR-200c	XIST sponges miR-200c to induce EMT	[217]
LncARSR	miR-129-5p	miR-129-5p sponging by lncARSR to induce EMT through SOX4 upregulation	[218]
H19	miR-29b-3p	miR-29b-3p sponging by H19 in EMT induction	[219]
LINC00612	miR-590	miR-590 sponging by LINC00612 to upregulate PHF14 expression in EMT induction	[220]
UCA1	miR-145	UCA1 increases ZEB1/2 expression to increase EMT and metastasis	[221]
AC114812.8	miR-371b-5p	AC114812.8 sponges miR-371b-5p to increase FUT4 expression in EMT induction	[222]
DANCR	miR-149/ MSI2	miR-149 inhibition by DANCR to increase MSI2 expression in EMT induction	[223]
TUG1	miR-140-3p	TUG1 increases annexin A8 expression through miR-140-3p sponging to mediate EMT	[224]

3.6. CircRNAs regulating microRNA/EMT axis

3.6.1. Gastric cancer

LncRNAs are not the only ncRNAs that can regulate miRNA expression in process of tumorigenesis. Circular RNAs (circRNAs) are new emerging targets in cancer therapy and their aberrant expression has been confirmed in different cancers, especially gastric cancer [225–228]. On the other hand, circRNAs regulate cancer metastasis via affecting EMT mechanism [229–232]. Therefore, current section focuses on regulation of miRNA/EMT axis by circRNAs in gastric cancer. Such interactions and highlighting them can significantly increase our thought towards gastric cancer invasion. In a similar way to lncRNAs, circRNAs have capacity of sponging miRNAs in regulating cancer progression. miR-331-3p suppresses EMT mechanism in reducing progression and metastasis of gastric tumor cells. However, upregulation of circCACTIN is a positive factor for promoting tumor metastasis. CircCACTIN increases expression level of TGFBR1 via miR-331-3p down-regulation to induce EMT for increasing invasion and metastasis of gastric tumor cells [233]. miR-532-3p has been a downstream target of circRNAs in different cancers. For instance, circ-103809 expression decreases in colorectal cancer and it increases FOXO4 expression by miR-532-3p down-regulation [131]. Moreover, circ-103809 sponges miR-532-3p in impairing breast cancer invasion [234]. In gastric cancer, upregulation of miR-532-3p can induce EMT in enhancing tumor invasion. However, circ-FGD4 functions as tumor-suppressor factor and it reduces miR-532-3p expression to suppress β-catenin signaling in EMT inhibition and decreasing gastric cancer invasion [235].

Similar to miRNAs and lncRNAs that can show both oncogenic and onco-suppressor functions in cancer, circRNAs also have such ability. Circ-0005075 reduces miR-335 expression to increase hepatocellular carcinoma malignancy [236]. Furthermore, upregulation of circ-0005075 mediates lymph node metastasis and increases tumor diameter in colorectal cancer [237]. However, in contrast to previous experiments, circ-0005075 has anti-cancer activity in gastric tumor; restoring circ-0005075 expression leads to EMT suppression in gastric cancer. Circ-0005075 increases p53 expression via miR-431 sponging to inhibit EMT-mediated metastasis in gastric cancer [238]. One of the important interactions occurs between miRNAs and EZH2 signaling in cancer. miRNAs can function as upstream regulator of EZH2 and vice versa, EZH2 signaling can affect miRNA expression. A recent experiment has revealed that miR-144-3p reduces EZH2 expression in suppressing EMT and metastasis of gastric cancer. High expression level of circ-

KIF4A mediates EMT and metastasis in gastric cancer. Mechanistically, circ-KIF4A increases EZH2 expression by miR-144-3p inhibition to induce EMT [239]. Future studies can show how induction of EZH2 signaling by circRNAs can affect miRNA expression. Table 5 and Fig. 4 provide a summary of circRNAs modulating EMT mechanism in gastric cancre.

3.6.2. Bladder cancer

The circRNAs are considered as modulators of tumorigenesis in bladder cancer. Despite putting much times and efforts in highlighting function of miRNAs and lncRNAs in bladder cancer, there are specific roles and function for circRNAs that requires understanding. Moreover, since circRNAs have high stability and they can be utilized as potential prognostic factors and biomarkers, their function in bladder cancer improves our knowledge in cancer therapy. The studies have mentioned role of circRNAs in regulation of miRNAs [240], post-transcriptional regulation of PTEN [241], modulation of metastasis and proliferation [242], regulation of ENO1 and SEMA5A [243] and affecting bladder cancer progression in vitro and in vivo [244]. The positive point regarding circRNAs in bladder cancer is their specific functions in posttranscriptional regulation of proteins and changing their stability in tumorigenesis. Moreover, the ability of circRNAs in acting as sponge for miRNAs can affect bladder cancer. The miRNA/EMT axis in bladder cancer can be modulated by circRNAs. The circST6GALNAC6 can avoid the invasion and metastasis of bladder cancer cells. According to the evaluation of molecular pathways, it has been reported that circST6-GALNAC6 sponges miR-200a-3p to increase STMN1 expression for EMT induction and acceleration in metastasis of bladder cancer [245]. The RNA sequencing analysis has revealed a high number of factors in regulation of EMT in cancer. The posttranscriptional regulation of TGFA can increase bladder cancer progression. CircRNA TAF4B sponges miR-1298-5p to upregulate TGFA expression for EMT induction and enhancement in progression of bladder cancer [246]. Moreover, circMTO1 as suppressor of EMT in bladder cancer has been introduced that sponges miR-221 to impair EMT and reduce the metastasis of tumor cells (Table 6) [247].

4. Therapeutic response in gastric cancer

One of the most challenging problems in treatment of gastric cancer is development of drug resistance. Chemoresistance can be categorized into two groups including intrinsic and acquired drug resistance that in first type, cancer cells have resistance to chemotherapy before exposure, but acquired drug resistance is defined as process in which tumor cells switch and activate molecular pathways and mechanisms, and induce changes in genomic profile to mediate drug resistance [268]. Accumulating data has shown role of signaling networks in regulating drug resistance in gastric cancer. STAT3 signaling activation can prevent ferroptosis in triggering drug resistance in gastric cancer [269]. Loss and defection in autophagy can result in impairment in degradation of lncRNA ARHGAP5-AS1 in mediating drug resistance [270]. Tunicamycin suppresses N-glycosylation in promoting ER stress and reversing chemoresistance in gastric cancer [271]. Moreover, SIRT1 impairs AMPK/FOXO3 axis in suppressing stemness of gastric cancer and reversing chemoresistance [272]. Hence, drug resistance development in gastric cancer is regulated by various signaling networks. The aim of current section to reveal role of miRNA/EMT axis in regulating drug resistance in gastric cancer.

A number of studies have shown that miRNAs regulate both EMT and chemotherapy response in gastric cancer in a same time. For instance, miR-574-3p reduces expression level of ZEB1 to suppress both EMT and cisplatin resistance in gastric cancer [273]. miR-95-3p down-regulates EMP1 expression to stimulate PI3K/Akt signaling in mediating EMT and cisplatin resistance in gastric tumor [274]. Moreover, miR-30a is capable of reducing P-glycoprotein (P-gp) expression in reversing drug resistance in gastric cancer and simultaneously, it suppresses EMT via E-cadherin upregulation [275]. Although these studies evaluated role of miRNAs in regulating EMT mechanism, they did not provide any relationship between EMT regulation by miRNAs and its impact on drug resistance capacity of gastric tumor cells. However, there are studies showing that miRNAs can regulate drug resistance in gastric cancer by influencing EMT mechanism. miR-204 expression significantly reduces in gastric cancer and it decreases protein levels of TGFBR2 to suppress EMT in enhancing sensitivity of gastric tumor cells to 5-flourouracil chemotherapy [276]. miR-30a is an inhibitor of gastric cancer progression based on studies and for this purpose, miR-30a reduces APBB2 expression to impair tumor invasion [277]. Another experiment also highlights the role of miR-30a in decreasing expression level of FAPα in impairing gastric cancer invasion [278]. Notably, miR-30a has been involved in enhancing cisplatin sensitivity of gastric tumor cells. miR-30a reduces Snail and vimentin levels in suppressing EMT and induces transformation of fibroblast-like cells to epithelial-like cells, resulting in increase in cisplatin sensitivity of gastric tumor cells [279]. Both TGF-β and ZEB proteins are regulators of EMT mechanism in gastric cancer. Notably, TGF-β can reduce expression level of miR-200a to upregulate ZEB1 and ZEB2 in triggering EMT and decreasing sensitivity of gastric tumor cells to trastuzumab chemotherapy [280].

In addition to chemotherapy, radiotherapy is also used in treatment

Table 5
CircRNAs modulating miRNA/EMT axis in gastric cancer.

CircRNA	Molecular pathway	Remark	Ref
Circ-006100	miR-195/GPRC5A	Circ-006100 increases GPRC5A expression by miR-195 inhibition Apoptosis inhibition Enhancement in migration via EMT induction	[248]
Circ-0000267	miR-503-5p/HMGA2	HMGA2 upregulation by circ-0000267 miR-503-5p inhibition EMT induction and increase in cancer metastasis	[249]
Circ-CORO1C	miR-138-5p/KLF12	Enhanced expression levels of circ-CORO1C and KLF12 miR-138-5p inhibition EMT induction	[250]
Circ-OXCT1	miR-136/SMAD4	TGF-β-dependent increase in cancer metastasis via EMT induction Circ-OXCT1 modulates miR-136/SMAD4 axis in suppressing EMT	[251]
Circ-0081143	miR-497-5p/EGFR	Circ-0081143 and EGFR upregulation and miR-497-5p down-regulation EMT induction in hypoxia	[252]
Circ-0005230	miR-1299/RHOT1	Circ-0005230 and RHOT1 upregulation miR-1299 down-regulation Increase in cancer invasion via EMT induction	[253]
Circ-001988	miR-197-3p	miR-197-3p inhibition by circ-001988 to suppress EMT	[254]
Circ-0009172	miR-485-3p/NTRK3	Circ-0009172 reduces NTRK3 expression by miR-485-3p sponging in EMT inhibition	[255]
Circ-NRIP1	miR-149-5p/Akt1/mTOR	Circ-NRIP1 induces Akt1 expression by miR-149-5p sponging in EMT induction	[256]
Circ-PRKDC	miR-493-5p/IRS2	Circ-PRKDC increases IRS2 expression by miR-493-5p down-regulation in EMT induction	[257]

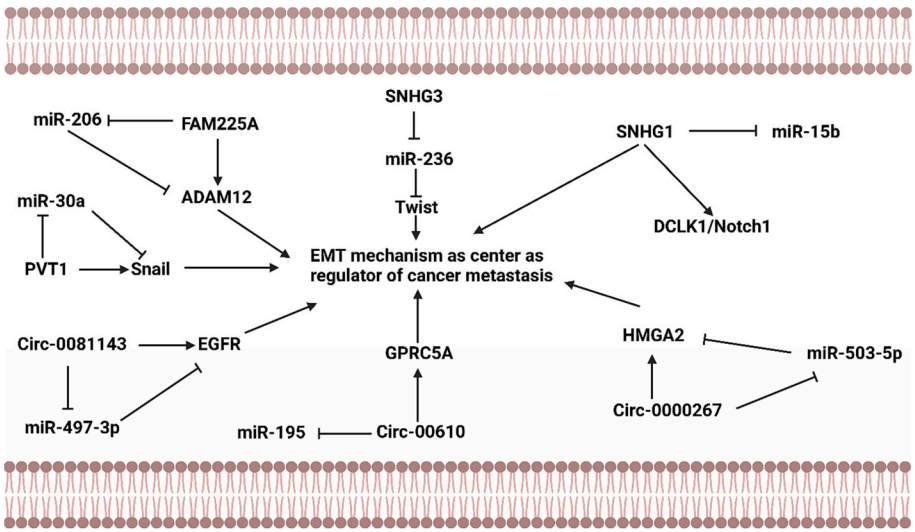

Fig. 4. CircRNAs and lncRNAs regulating EMT mechanism in gastric cancer. The previous figures demonstrated that EMT mechanism can be regulated by miRNAs in gastric cancer. Interestingly, this figure highlights the fact that miRNAs can be sponged by lncRNAs and circRNAs in gastric to affect pathways capable of regulating EMT (upregulation or down-regulation). (Biorender.com)

Table 6
The miRNA/EMT axis regulation by circRNAs in bladder cancer.

CircRNA	Target	Outcome	Ref
CircPICALM	miR-1265	miR-1265 sponge by circPICALM to increase FAK expression for bladder cancer progression and EMT	[258]
CircSTK39	miR-135a-5p/NR3C2	miR-135a-5p downregulation by circSTK39 to impair NR3C2-induced EMT	[259]
hsa_circ_0139402	hsa-miR-326/PAX8	EMT induction in cancer progression	[260]
Circular RNA RBPMS	miR-330-3p/RAI2	EMT suppression and reduction in cancer progression and metastasis	[261]
Circ-BIRC6	miR-495-3p/XBP1	miR-495-3p suppression by circ-BIRC6 to induce EMT	[262]
circSETD3	miR-641/PTEN	circSETD3 promotes PTEN expression by miR-641 sponging in EMT suppression	[263]
Circ_0000658	miR-498/HMGA2	Circ-0000658 promotes HMGA2 expression by miR-498 downregulation to increase EMT	[264]
circ_100984	miR-432-3p	Presence of a feedback loop with c-Jun/YBX-1/β-catenin to stimulate EMT	[265]
CircPPP1CB	miR-1307-3p/SMG1	CircPPP1CB suppresses EMT	[266]
hsa_circ_0014130	miR-132-3p	miR-132-3p sponge and KCNJ12 upregulation to mediate EMT	[267]

Table 7
The role of miRNA/EMT axis and related molecular pathways in gastric cancer progression.

miRNA	Molecular pathway	Remark	Ref
miR-2392	MAML3 WHSC1	miR-2392 reduces expression levels of MAML3 and WHSC1 in impairing EMT	[284]
miR-618	TGF-β2	miR-618 reduces expression level of TGF-β2 in decreasing tumor invasion	[285]
miR-185	XIST/miR-185/TGF-β1	XIST promotes TGF-β1 expression via miR-185 sponging in enhancing progression and invasion of tumor cells	[286]
miR-133b	COL1A1/TGF-β	miR-133b reduces COL1A1 expression to suppress TGF-β signaling in reversing EMT	[287]
miR-128	PCAT-1/miR-128/ZEB1	PCAT-1 increases ZEB1 expression via miR-128 sponging in EMT induction and enhancing cancer invasion	[288]
miR-200 miR-141	ZEB1 ZEB2	Low expression of miR-200 and miR-141 increase ZEB1 and ZEB2 expression levels in promoting gastric tumor progression	[289]
miR-544a	Wnt	miR-544a enhances Wnt expression in triggering EMT	[290]
miR-203	UCA1/miR-203/ZEB2	UCA1 promotes ZEB2 expression via miR-203 sponging to increase cancer progression	[291]
miR-338-3p	ZEB2	miR-338-3p reduces ZEB2 expression in impairing EMT	[292]

of gastric cancer patients. However, changes in genetic and epigenetic profile can lead to development of radio-resistance in gastric cancer [281,282]. Delivery of miR-200c by nanostructures results in suppression of TGF-β, subsequent down-regulation of E-cadherin/β-catenin and eventual inhibition of EMT in enhancing radio-sensitivity of gastric tumor cells [283]. However, only one experiment has evaluated miRNA/EMT axis in regulating radio-resistance in gastric cancer and more studies should be performed in this case. Table 7 provides a summary of miRNA/EMT axis in gastric cancer progression regulation. Table 8 also provides an overview of miRNA/EMT axis in bladder cancer.

5. Conclusion and remarks

The process of metastasis is gastric cancer is complicated and this increase in migration can result in significant decrease in prognosis and survival rate of cancer patients. Therefore, much amount of time has been allotted in understanding pathways and mechanisms involved in regulating invasion of gastric tumor cells. Both miRNAs and EMT have been considered as factors in gastric cancer invasion. The role of EMT is obvious in increasing tumor metastasis, but miRNAs demonstrate dual function and they may increase/decrease cancer progression. The aim of current review was to evaluate role of miRNA/EMT axis in regulating gastric cancer metastasis. miRNAs prefer to regulate EMT mechanism indirectly and they affect SKA3, PPP2R2A, PLK-1, EIFA5A2 and PI3K/Akt in regulating EMT mechanism in gastric cancer. However, there are well-known regulators of EMT mechanism that are called EMT-TFs and miRNAs are capable of regulating ZEB proteins, TGF-β, Slug, Snail, vimentin and Twist in affecting EMT mechanism in gastric cancer. The function of miRNAs can be oncogenic and onco-suppressor, and if they demonstrate oncogenic function, they can induce EMT in enhancing tumor progression. More importantly, lncRNAs and circRNAs can

Table 8
An overview of the miRNA/EMT in bladder cancer progression.

miRNA	Remark	Ref
miR-148a-3p	Modulating the interactions of ERBB3/AKT2/c-myc and ERBB3/AKT2/Snail to disrupt EMT	[293]
miR-186-5p	RAB27A/B downregulation to suppress EMT	[294]
miR-497-5p	CEP55 3'-UTR sponges miR-497-5p to induce EMT	[295]
miR-370-3p	Wnt7a suppression to inhibit EMT	[296]
miR-200c	BMI-1 and E2F3 downregulation to impair EMT	[297]
miR-335	PD promotes miR-335 expression through lncRNA XIST suppression to impair EMT	[298]
miR-30a	BAY11-7082 impairs miR-30a/NF-κB/Snail to suppress EMT mediated by M2 macrophages in bladder cancer progression	[299]
miR-125a-5p	FUT4 suppression in EMT inhibition	[300]
miR-942-3p	Presence of positive feedback loop between TAZ and miR-942-3p in regulation of cancer progression	[301]
miR-20a-5p	NR4A3 suppression to increase invasion and metastasis	[302]
miR-433	c-Met/Akt/GSK-3β/Snail inhibition to impair EMT	[303]
miR-655	VIM-AS1 sponges miR-655 to induce EMT through ZEB1 upregulation	[304]
miR-203a	SIX4 downregulation in EMT inhibition	[305]
miR-200	TGF-beta1 reduces miR-200b expression to induce EMT and increase MMP-16 expression	[306]
miR-199a-5p	CCR7 downregulation to suppress EMT and metastasis	[307]
miR-485-5p	HMGA2 downregulation to disrupt EMT and invasion	[308]
miR-429	E-cadherin upregulation to overcome EMT	[309]
miR-15	PI£K/Akt downregulation to impair BMI1 expression and suppress EMT	[310]
miR-7-5p	Gli3 inhibition to reverse EMT	[311]
miR-221	STMN1 inhibition to accelerate EMT	[312]
miR-323a-3p	Downregulation of MET and SMAD3 to reduce SNAIL expression in EMT suppression	[313]

sponge miRNAs in affecting EMT mechanism in cancer. The function of miRNA/EMT axis is not only related to progression and metastasis of gastric cancer cells, and based on studies, miRNA/EMT can determine response of gastric tumor cells to chemotherapy and radiotherapy. Therefore, manipulation of miRNAs regulating EMT mechanism should be considered as a promising approach in improving prognosis of gastric cancer patients.

The miRNA/EMT axis has been also evaluated in bladder cancer and the message of studies is that miRNA/EMT axis regulates the progression of bladder cancer from metastasis and even to the proliferation of cancer cells, since their malignancy increases. The miRNA/EMT axis has been evaluated in bladder cancer mainly in terms of biological aspect and emphasis on the molecular interactions. The regulation of EMT by miRNAs, and the lncRNAs and circRNAs modulating miRNA/EMT axis have been understood in bladder cancer. However, there are still some gaps that require more investigation including control of EMT-TFs by miRNAs in bladder cancer, the regulation of miRNA/EMT axis by pharmacological compounds and the response of tumor cells to chemotherapy. The clinical implication of current paper for patients is that if the discussed molecular pathways regulating gastric and bladder cancers progression are evaluated more and the therapeutics are developed based on them, the treatment of patients will be improved. Moreover, a number of miRNAs with highest dysregulation in gastric and bladder cancers can be utilized to develop signatures for understanding the prognosis of patients.

Credit author statement

The authors of this paper have contributed to different stages from first draft preparation, to edition and responding to the reviewers in revision time. All the authors have confirmed the last version of the current paper for submission to the journal. Ameer S. Sahib, Amjid Fawzi, Rahman S. Zabibah, Nisar Ahmad Koka and Shaymaa Abdulhameed Khudair Faris wrote the first draft of paper and depicted the figures. Anad Muhammad and Doaa A. Hamad edited the paper, collected studies and focused on tables of paper.

Declaration of Competing Interest

The authors declare no conflict of interest.

Data availability

No data was used for the research described in the article.

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