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Long non-coding RNA/epithelial-mesenchymal transition axis in human cancers: Tumorigenesis, chemoresistance, and radioresistance

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ABSTRACT

Epithelial-to-mesenchymal transition (EMT) is a process that involves the transformation of polarized epithelial cells to attain a mesenchymal phenotype that presents an elevated migratory potential, invasiveness, and antiapoptotic properties. Many studies have demonstrated that EMT is a prominent event that is associated with embryogenesis, tumor progression, metastasis, and therapeutic resistance. The EMT process is driven by key transcription factors (such as Snail, Twist, ZEB, and TGF-β) and several long non-coding RNAs (lncRNAs) in many non-pathological as well as pathological conditions. In the present report, we have comprehensively discussed the oncogenic and tumor suppressor role of lncRNAs and their mechanism of action in the regulation of the EMT process in various cancers such as brain tumors, gastrointestinal tumors, and gynecological and urological tumors. We have also elaborated on the role of lncRNAs in the regulation of EMT-related transcription factors (such as Snail, Twist, ZEB, and TGF-β) and therapeutic response (chemoresistance and radioresistance). Lastly, we have emphasized the role of exosomal lncRNAs in the regulation of EMT, metastasis, and therapeutic response in the aforementioned cancers. Taken together, this review provides a detailed insight into the understanding of role of lncRNAs/exosomal lncRNAs in EMT, metastasis, and therapeutic response in human cancers.

Abbreviations: ATG12, Autophagy related 12; ceRNA, Competing endogenous RNA; CTNNB1, Catenin beta 1; DNMT3B, DNA methyltransferase 3B; EMT, Epithelial-mesenchymal transition; EMT-TFs, EMT-related transcription factors; EZH2, Enhancer of zeste homolog 2; FGFR3, Fibroblast growth factor receptor 3; FSCN1, Fascin actin-bundling protein 1; GI, Gastrointestinal; HMGB1, High mobility group box 1; HNRNPA1, Heterogeneous nuclear ribonucleoprotein A1; KRT18, Keratin 18; METTL14, Methyltransferase like 14; miRNA, MicroRNA; ncRNA, Non-coding RNA; PDCD4, Programmed cell death 4; PDGFRα, Platelet-derived growth factor receptor α; piRNA, piwi-interacting RNA; POU5F1B, POU class 5 homeobox 1B; PRC2, Polycomb repressive complex 2; SALL1, Spalt-like transcription factor 1; SOX4, SRY-related high-mobility-group box 4; STAT3, Signal transducer and activator of transcription 3; TGF-β, Transforming growth factor-β; YAP, Yes-associated protein; YY1, Yin Yang 1; ZEB, Zinc finger E-box-binding homeobox.

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1. Introduction

Metastasis is a process in which some tumor cells dislodge from the primary site of cancer and migrate to a different organ (secondary site) to form the tumors [1]. Metastasis is one of the most life-threatening pathological events that result in poor clinical outcomes. The process of metastasis is a complex multistep mechanism [2,3]. In the initial stages, a mass of cells disengage from the primary tumor and begin to migrate/invade the surrounding tissue. In the next step, these cells enter into blood circulation or lymph vessels through a process of intravasation. Then, tumor cells circulate in the body and exit from vessels through a process of extravasation to form a tumor at the secondary site [4]. Each of these steps is regulated by different molecular pathways through a complicated mechanism. The detachment of cancer cells from the primary site and invasion into surrounding tissue requires the degradation of cell-cell contacts and remodeling of cell-matrix adhesion sites [5,6]. These processes are specialized to physiological conditions meaning that they are also observed in non-pathological conditions such as developmental processes, embryogenesis, and tissue formation. However, cancer cells can exploit these processes for dissemination in the body and increase their malignancy [7]. Metastasis of cancer cells is one of the main reasons for death among patients [8,9].

The concept of metastasis in cancer revolves around a mechanism known as epithelial-mesenchymal transition (EMT). EMT is a process in which immobile epithelial cells attain the characteristics of mesenchymal cells to gain migratory and invasive potential [10,11]. EMT is observed in both vertebrates and invertebrates, and it has been implicated as a vital mechanism in morphogenesis [12,13]. It appears that the EMT mechanism is also important in adulthood as it is observed during wound healing. Currently, it has been more than 20 years since the first time that EMT was considered an important molecular mechanism in cancer [14]. Snail is the first transcription factor that was discovered to decrease E-cadherin levels and thereafter, many EMT-related transcription factors (EMT-TFs) were discovered [15,16]. EMT-TFs mainly include ZEB proteins, TGF-β, Snail, and Twist [17–19]. The role of EMT-TFs is increasing beyond tumor progression since they are expressed in various normal tissues [20,21]. Increasing evidence has shown that EMT-TFs not only elevate tumor metastasis, but also prevent apoptosis and senescence and can mediate cell cycle progression, radioresistance, and chemoresistance [22–25]. EMT is primarily considered as a phenotypic conversion of cells from epithelial phenotype to mesenchymal phenotype to mediate loss of cell junctions and polarity to generate mesenchymal cells with high migratory ability [26,27]. EMT-TFs are responsible for mediating molecular changes including downregulation of E-cadherin expression, and upregulation of N-cadherin and vimentin expression to stimulate EMT and thereby increase cancer progression and metastasis (Fig. 1) [28–30].

Over the past decades, the process of EMT has been under attention by researchers around the world to find pathways responsible for its regulation and subsequent targeting for modulating cancer metastasis [31–33]. For instance, Cartilage acidic protein 1 (a tumor suppressor protein) targeted Yin Yang 1 (YY1) protein to inhibit TGF-β signaling and subsequent EMT process in bladder cancer cells [34]. YY1 is a transcription factor that modulates the expression of EMT markers in bladder cancer by triggering the TGFβ cascade. The chaperonin protein containing TCP1–8 (CCT8) can prevent the nuclear translocation of WTp53 to increase the progression and metastasis of colorectal cancer cells [35]. Apart from studying signaling proteins in the EMT context, many researchers have also studied the role of non-coding RNAs (ncRNAs) in relevance to the regulation of EMT in cancers [36].

The human genome encodes approximately 2% of protein-coding DNA and 98% of non-protein-coding DNA. ncRNA is a class of RNA that is a product of the transcription of non-protein-coding segments of the genome [37]. Several ncRNAs have housekeeping functions and they include small nuclear RNA, transfer RNA, small nucleolar RNA, and ribosomal RNA that show expression in the majority of human cells. Other kinds of ncRNA molecules have a regulatory function and they are spatiotemporally expressed in human cells. Depending on the length, regulatory ncRNAs are classified into small ncRNA and long ncRNA (lncRNA). The ncRNA with a length lesser than 200 nucleotides is considered as small ncRNA (microRNA [miRNA] and piwi-interacting RNA [piRNA]) whereas ncRNA with a length greater than 200 nucleotides is termed lncRNA. Some studies have reported that about 68% of total transcripts in humans are contributed by lncRNAs [38]. LncRNAs display a high degree of resemblance with transcription and post-transcriptional modifications of mRNA. Like mRNA, lncRNA-coding genes are transcribed by RNA polymerase-II and also undergo modifications including 5′capping, splicing, and 3′polyadenylation [39,40]. The lncRNAs which are polyadenylated are processed by tRNA-modifying RNases to form a triple helical structure at 3′ to prevent themselves from degradation [41]. LncRNAs exert various biological functions in cells and they regulate gene expression via various mechanisms [42,43]. In the majority of the studies, lncRNAs are reported to function as competing endogenous RNA (ceRNA) where the lncRNA interacts with the target miRNA and blocks the binding of miRNA to its target mRNA [44,45]. In other words, miRNA is sponged by lncRNA, which permits the continuous expression of mRNA. For an instance, lncRNA SNHG16 sponges miR-4500. If miR-4500 is not sponged, it interacts with STAT3 mRNA to suppress its expression [46]. STAT3 is an oncogenic transcription factor that is overexpressed in human cancers and is involved in acceleration of cell proliferation, survival, metastasis, and tumor evasion [47–51]. LncRNAs can function as guides where they can bind to protein complexes and modulate the activity of target proteins. Scaffold lncRNAs act as a platform for the attachment of protein complexes and drive to specific genome locations [52,53]. LncRNA can also physically interact with target proteins to regulate their activity. LncRNA TPTEP1 physically interacts with the DNA binding domain of STAT3 and abrogates its transcriptional activity [54]. In contrast, lncSox4 was found to interact with STAT3 and direct STAT3 to the promoter region of Sox4 to promote the transcription of Sox4 [55]. These reports suggest that lncRNAs can function as a decoy for regulating gene induction or silencing via acting as a sink for transcription factors and repressors [56,57]. Additionally, lncRNAs can interact with target DNA to modulate gene expression. For example, Lnc-DILC was reported to interact with the IL-6 promoter to block the transcription of the IL-6 gene [58]. Research in the last decade

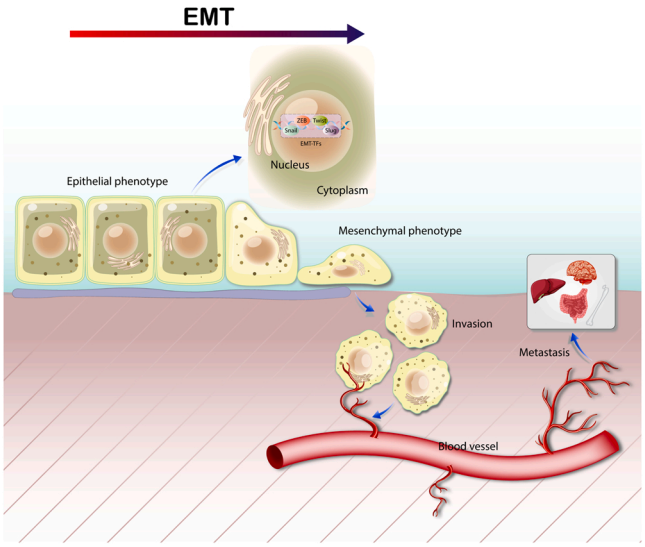

Fig. 1. : A summary of the EMT mechanism and related molecular pathways in cancer. During cancer progression, epithelial cells attain mesenchymal phenotype to acquire migration/invasive potential and spread to secondary organs through lymph nodes and circulation in a process of metastasis. The expression of EMT-TFs such as Snail, ZEB, and Twist are upregulated to promote EMT.

demonstrated that the altered expression of lncRNAs is observed in many pathological conditions including cancers. In the present article, we have focused on the role of lncRNAs in EMT, tumorigenesis, chemoresistance, and radioresistance in selected types of cancers.

2. LncRNAs in tumorigenesis

Numerous studies have suggested that deregulated expression of lncRNAs is observed in many types of human malignancies [59,60]. Deregulated expression of lncRNA was reported to contribute to uncontrolled proliferation, antiapoptosis, chemoresistance, radioresistance, EMT, and metastasis [61–63]. Expression of lncRNA A1BG-AS1 was upregulated in breast cancer tissues compared to their normal counterpart, whereas depletion of A1BG-AS1 suppressed the proliferation, migration, and invasion of breast cancer cells. In the breast cancer cells, it was found to sponge miR-485–5p (a tumor suppressor miRNA) to allow the expression of FLOT1 (cancer-promoting protein) [63]. LncRNA UCA1 can elevate the growth and metastasis of cervical tumor cells via sponging miR-299–3p [56]. Furthermore, lncRNAs can serve as markers of survival, prognosis, and clinical outcome in prostate cancer patients [64]. LncRNA TMCC1-AS1 stimulates the EMT mechanism to increase liver cancer progression and predicts unfavorable prognosis [65]. Increased expression of lncRNA CBR3-AS1 can be used as a sensitive biomarker for breast cancer prognosis [66]. LncRNA SNHG4 promotes lung cancer progression and its silencing decreases the survival rate of tumor cells [67]. In addition to regulating cancer hallmarks including growth and invasion [61,68], lncRNAs can affect the therapy resistance and metastasis of tumor cells (Table 1) [62]. In the following section, we have discussed the function of lncRNAs in the modulation of EMT in different cancers.

3. LncRNA/EMT axis in different cancers

3.1. Brain tumors

Glioma is the most common primary tumor of the brain and spinal cord which include astrocytomas, oligodendrogliomas, and ependymomas [69]. Surgical resection, chemotherapy, and radiotherapy are the therapeutic strategies used for the treatment of glioma. However, therapeutic resistance and metastasis can be often seen in gliomas [70]. LncRNAs play a significant role in regulation of the metastasis of glioma. Although lncRNAs can either be oncogenic or tumor suppressors, the majority of the so far discovered lncRNAs are reported to have oncogenic roles. LncRNA PART1 and SALL1 (Spalt-like transcription factor 1), a tumor suppressor protein, were found to be downregulated whereas miR-374b was overexpressed in glioma cells. Increased expression of PART1 targets miR-374b to accelerate the expression of SALL1, whereas depletion of miR-374b repressed proliferation and EMT of glioma cells through increasing the levels of SALL1 [71]. The overexpression of lncRNA NNT-AS1 was observed in glioma cells and it was positively correlated with their metastasis. MiR-582–5p is the target of NNT-AS1 and EZH2 (enhancer of zeste homolog 2) is the target of miR-582–5p. EZH2 is a histone-lysine N-methyltransferase and functional component of the polycomb repressive complex 2 (PRC2) that is associated with the promotion of metastasis by epigenetically silencing the tumor suppressor genes [72]. The sponging of miR-582–5p by NNT-AS1 permits the expression of EZH2 and subsequent progression of the disease [73]. The sponging of miRNAs by lncRNAs is the prevalent mechanism observed in the regulation of various biological processes including EMT process. For instance, lncRNA CCAT1 is overexpressed in glioma cells/tissue samples and its silencing prevented the EMT mechanism. LncRNA CCAT1 was found to promote tumor progression by sponging miR-181b, whereas the interaction site of miR-181b was found on 3′UTR of FGFR3 (fibroblast growth factor receptor 3) and PDGFRα (platelet-derived growth factor receptor α). Therefore, CCAT1-driven blockade of miR-181b results in increased expression of FGFR3 and PDGFRα to promote EMT induction and metastasis of glioma cells [74]. FGFR3 and PDGFRα are the oncogenic proteins that belong to the receptor tyrosine kinase family and are found to be upregulated in many types of human cancers including gliomas.

EMT regulation by SOX transcription factors, especially SOX4 (SRY-related high-mobility-group box 4) has been of interest in recent years. METTL14 (methyltransferase like 14), is an active component of the N6-methyltransferase complex that can mediate N6-methyladenosine modification of SOX4 mRNA. Depletion of METTL14 increases the stability of SOX4 mRNA to promote EMT and colorectal tumor progression [75]. Based on the study, it can be concluded that SOX4 is an oncogenic transcription factor that increases cancer metastasis via EMT induction and SOX4-targeting miRNAs (such as miR-30a and miR-195) can reverse these effects [76,77]. LncRNA XIST increased the EMT of glioma cells by blocking the miR-133a-mediated suppression of SOX4 expression [78]. Therefore, targeting the lncRNA/EMT axis can be used to impair the invasion and migration of glioma cells [79–81].

Many studies have also investigated the role of lncRNAs in the regulation of the EMT mechanism in glioblastoma. Chen and colleagues reported that malignant behavior including induction of EMT of glioblastoma cells was enhanced by lncRNA HOXA-AS3. It has been reported that HOXA-AS3 increases USP3 expression via sponging of miR-455–5p to promote EMT [82]. The PI3K/Akt pathway is one of the major signaling cascades that drive the EMT process in human cancers [83]. SAMMSON is an oncogenic lncRNA that is overexpressed in many types of human cancers, and silencing SAMMSON impeded the malignant behavior and EMT of glioblastoma cells by suppression of the PI3K/Akt pathway. The downregulation of SAMMSON resulted in the induction of apoptosis of glioblastoma cells indicating the crucial role of this lncRNA in relaying survival signals [84]. Therefore, it can be concluded that various signaling pathways are modulated by lncRNAs to regulate the EMT process in turn metastasis in brain cancers [85,86].

3.2. Gastrointestinal (GI) tumors

GI cancers is the umbrella term used to describe the cancers of the esophagus, stomach, liver, pancreas, colon, and rectum. Gastric cancer appears third in terms of global mortality rate as per 2020 statistics with the highest incidence rate in Asia and Southern America [87]. The high mortality of gastric cancer patients is due to metastasis, recurrence, and therapeutic resistance [88–91]. The overall survival rate of gastric cancer patients significantly reduces with the advancement of the disease. The current therapeutic strategies for gastric cancer include surgery, radiotherapy, chemotherapy, and neoadjuvant therapy [92]. There is a need for improvement of diagnostic and therapeutic strategies to enhance favorable prognosis of gastric cancer patients [93–95]. The huge number of lncRNAs in relevance to the GI cancer progression have been described. LncRNA SNHG11 was elevated in gastric cancer cells and it increased migration and invasion of gastric cancer cells. Autophagy induction by SNHG11 was found to be vital for EMT and the promotion of gastric cancer metastasis. By inhibiting miR-483–3p and miR-1276, SNHG12 promoted the expression of autophagy related 12 (ATG12) and catenin beta 1 (CTNNB1) expression and subsequent stimulation of EMT in increasing gastric cancer invasion [96]. In hepatocellular carcinoma, SNHG16 functions as a ceRNA to sponge miR-4500 which allows the STAT3 to aggravate tumorigenesis [97]. LncRNA CHRF was reported to be higher in gastric cancer tissue samples compared with the adjacent para-tumor samples and it was found to promote the progression of EMT to enhance the metastasis of gastric cancer cells [98]. Gao and colleagues demonstrated that lncRNA LINC02253 was found to be overexpressed in gastric cancer tissues and it was correlated with tumor size, lymph node metastasis, and worse five-year overall survival. Mechanistically, LINC02253 recruited METTL3 (methyltransferase-like 3), a catalytic subunit of m6A methyltransferase complex, to modify and stabilize KRT18 (Keratin 18) mRNA. KRT18 is a member of the intermediate filament family of the

Table 1
A summary of lncRNAs regulating EMT mechanism in different cancers.

LncRNA	Molecular pathway	Cancer type	Remark	Ref
LINC00665	miR-424–5p/BCL9L	Cholangiosarcoma	EMT induction Gemcitabine resistance LINC00665 sponges miR-424–5p to enhance BCL9L expression	[299]
H19	–	Ovarian cancer	LncRNA H19 induces the EMT mechanism in triggering cisplatin resistance	[300]
SPRY4-IT1	MPZL-1/EMT	Non-small cell lung cancer	SPRY4-IT1 decreases MPZL-1 expression to inhibit EMT and overcome cisplatin resistance	[301]
CILA1	Wnt/β-catenin	Tongue cancer	CILA1 stimulates Wnt signaling in mediating drug resistance via EMT induction	[302]
NONHSAT101069	miR-129–5p/Twist1	Breast cancer	NONHSAT101069 stimulates epirubicin resistance and mediates the EMT mechanism via miR-129–5p sponging to increase Twist1 expression	[303]
MAFG-AS2	miR-3196/STRN4	Liver cancer	MAFG-AS2 promotes STRN4 expression via miR-3196 sponging to induce EMT in increasing cancer progression and metastasis	[304]
MALT1	–	Colorectal cancer	Chronic oxymatrine treatment promotes MALAT1 expression to induce EMT and increase cancer progression	[305]
BC087858	PI3K/Akt MEK/ERK EMT	Non-small cell lung cancer	BC087858 stimulates EMT, PI3K/Akt, and MEK/ERK pathways in increasing cancer metastasis and mediating drug resistance	[306]
XLOC-006753	PI3K/Akt/mTOR	Gastric cancer	XLOC-006753 stimulates the mTOR axis in EMT induction and increases cancer progression	[307]
UCA1	Akt/mTOR	Non-small cell lung cancer	UCA1 stimulates Akt/mTOR axis in EMT induction, increasing cancer progression and mediating drug resistance	[308]
HOTAIRM1	miR-17–5p/BTG3	Colorectal cancer	HOTAIRM1 promotes BTG3 expression via miR-17–5p sponging in EMT inhibition and enhancing 5-fluorouracil sensitivity	[309]
HNF1A-AS1	miR-30b-5p/EIF5A2	Gastric cancer	HNF1A-AS1 promotes EIF5A2 expression via miR-30b-5p sponging in triggering EMT and mediating drug resistance	[310]
SNHG6	miR-1297/Bcl-2	Gastric cancer	SNHG6 promotes Bcl-2 expression by miR-1297 inhibition in triggering cisplatin resistance	[311]
MALAT1	PI3K/Akt/mTOR	Oral cancer	MALAT1 stimulates PI3K/Akt/mTOR axis in triggering cisplatin resistance and EMT	[312]
SNHG7	miR-186	Breast cancer	SNHG7 promotes cisplatin resistance and stimulates EMT via miR-186 inhibition	[313]
CYTOR	miR-378a-5p/SERPINE1	Colon cancer	CYTOR promotes SERPINE1 expression via miR-378a-5p inhibition to induce the EMT mechanism	[314]
SNHG3	miR-128/CD151	Hepatocellular carcinoma	SNHG3 induces EMT mechanism and sorafenib resistance via miR-128 inhibition to upregulate CD151	[315]
GAS5	miR-221/SOCS3	Pancreatic cancer	GAS5 promotes SOCS3 expression via miR-221 inhibition in overcoming EMT	[316]
ATB	miR-200c/ZEB1	Breast cancer	LncRNA ATB promotes ZEB1 expression via miR-200c inhibition, leading to EMT induction and trastuzumab resistance	[317]
CYTOR	miR-1252–5p/miR-3148/LPP	Oral cancer	CYTOR promotes LPP expression via miR-1252–5p and miR-3148 inhibition EMT induction Drug resistance	[318]
DLX6-AS1	miR-199b-5p/Paxillin	Breast cancer	DLX6-AS1 promotes paxillin expression via miR-199b-5p inhibition in EMT induction	[319]
CHRF	miR-10b/STAT3	Ovarian cancer	CHRF induces STAT3 signaling via miR-10b inhibition to mediate EMT	[320]
ST7-AS1	PI3K/Akt	Gastric cancer	ST7-AS1 induces PI3K/Akt signaling in EMT induction and enhances cisplatin resistance	[321]
LINC01116	–	Lung adenocarcinoma	LINC01116 induces EMT and cisplatin resistance	[322]
POIR	miR-182–5p/EMT	Hepatocellular carcinoma	POIR induces EMT mechanism via miR-182–5p sponging in mediating sorafenib resistance	[323]
MALAT1	PI3K/Akt	Prostate cancer	Quercetin downregulates MALAT1 expression to inhibit PI3K/Akt signaling in EMT inhibition and prevent tumor progression	[324]
MALAT1	–	Esophageal cancer	Dexmedetomidine downregulates MALAT1 expression in EMT inhibition	[325]
UCC	miR-143–3p/SOX5	Non-small cell lung cancer	UCC promotes SOX5 expression via miR-143–3p sponging in EMT induction	[326]
NR2F2-AS1	miR-545–5p/c-Met	Non-small cell lung cancer	NR2F2-AS1 increases c-Met expression via miR-545–5p sponging in inducing AVR/ATF-2 induction for EMT stimulation	[327]
ELFN1-AS1	miR-497	Non-small cell lung cancer	EMT induction and poor prognosis by ELFN1-AS1 via miR-497 sponging	[328]
MCF2L-AS1	miR-105–5p/RAB22A	Colorectal cancer	MCF2L-AS1 increases RAB22A expression via miR-105–5p inhibition for EMT induction	[329]
DARS-AS1	miR-188–5p/KLF12	Lung adenocarcinoma	DARS-AS1 increases KLF12 expression via miR-188–5p inhibition in EMT induction	[330]
FGD5-AS1	miR-454–3p/ZEB1	Non-small cell lung cancer	Thalidomide decreases FGD5-AS1 expression to upregulate miR-454–3p expression, leading to ZEB1 inhibition and subsequent EMT inactivation	[331]
HCG11	miR-1270/PTEN	Ovarian cancer	HCG11 sponges miR-1270 to induce PTEN signaling, leading to Akt suppression and EMT inhibition	[332]
SNHG6	miR-944/EMT	Pituitary adenoma	SNHG6 stimulates the EMT mechanism via miR-944 inhibition	[333]
LINC01857	miR-19a-3p/SMOC2	Pancreatic cancer	LINC01857 increases SMOC2 expression by miR-19a-3p inhibition in EMT induction	[334]
PCAT1	ZNF217/MTA2/MTA3/Snai1/E-cadherin	Colorectal cancer	PCAT1 positively cooperates with ZNF217 to increase MTA2 and MTA3 expression levels in upregulating Snai1, resulting in E-cadherin downregulation	[335]
RBM5-AS1	Wnt/β-catenin	Breast cancer	RBM5-AS1 induces Wnt signaling to mediate EMT and increase cancer metastasis	[336]
SND1-IT1	miR-124/COL4A1	Gastric cancer	SND1-IT1 sponges miR-124 to overexpress COL4A1 in EMT induction	[181]
MAFG-AS1	NFKB1/IGF1	Ovarian cancer	MAFG-AS1 induces NFKB1/IGF1 axis in EMT induction and mediates the malignant phenotype of tumor cells	[337]
MAFG-AS1	miR-3196/SOX12	Lung cancer	MAFG-AS1 increases SOX12 expression via miR-3196 sponging in increasing lung cancer progression	[338]
RP11–10A14.5	–	Lung cancer	EMT induction by lncRNA and mediating poor prognosis	[339]
MBNL1-AS1	miR-424–5p/Smad7	Gastric cancer	MBNL1-AS1 promotes Smad7 expression via miR-424–5p sponging in EMT inhibition	[340]
PSMB8-AS1	miR-1299/ADAMTS5	Colorectal cancer	PSMB8-AS1 sponges miR-1299 to increase ADAMTS5 expression in EMT induction	[341]
NR2F2-AS1	miR-320b/PDCD4	Gastric cancer	NR2F2-AS1 sponges miR-320b to increase PDCD4 expression in EMT inhibition	[342]
SNHG1	miR-497/FGFR1	Pancreatic cancer	SNHG1 stimulates EMT via miR-497 sponging and subsequent overexpression of FGFR1	[343]
MEG3	DNMT1/MEG3/Notch1	Breast cancer	DNMT1 mediates demethylation of MEG3 promoter to inhibit Notch1 signaling, leading to EMT inhibition	[344]

(*continued on next page*)

Table 1 (*continued*)

LncRNA	Molecular pathway	Cancer type	Remark	Ref
ELVCR1-AS1	miR-23a-5p/SLC7A11	Cervical cancer	FLVCR1-AS1 promotes SLC7A11 expression via miR-23a-5p sponging in EMT induction	[345]
LINC00659	SP1/LINC00659/miR-370/AQP3	Gastric cancer	SP1 increases LINC00659 expression to induce EMT mechanism via mir-370 sponging and upregulation of AQP3	[346]
MIR9–3HG	miR-138–5p/TAF15	Lung cancer	MIR9–3HG sponges miR-138–5p to recruit TAF15 for overexpressing LIMK1 mRNA, leading to EMT induction and an increase in cancer metastasis	[347]
PCAT6	miR-326/KLF1	Non-small cell lung cancer	PCAT6 promotes KLF1 expression via miR-326 sponging in mediating M2 polarization of macrophages and EMT induction	[348]
CYTOR	HNRNPC/ZEB1	Oral cancer	CYTOR interacts with HNRNPC for increasing the stability of ZEB1, resulting in EMT induction	[349]
LINC00924	miR-6755–5p/NDRG2	Hepatocellular carcinoma	LINC00924 promotes NDRG2 expression via miR-6755–5p sponging in EMT induction	[350]
DLEU2	PI3K/Akt	Gastric cancer	knock-down of DLEU2 inhibits PI3K/Akt axis in EMT inhibition	[351]
OGFRP1	miR-423–5p/CTCF	Colorectal cancer	OGFRP1 increases CTCF expression via miR-423–5p sponging in EMT induction	[352]
HCG18	miR-29a/b/TRAF4/TRAF5	Ovarian cancer	HCG18 accelerates cancer progression and EMT induction via miR-29a/b sponging and subsequent overexpression of TRAF4/5	[353]
LGALS8-AS1	miR-125b-5p/SOX12	Breast cancer	LGALS8-AS1 increases SOX12 expression via miR-125b-5p sponging in EMT induction	[354]
SNHG16	miR-124–3p/MCP-1	Colorectal cancer	SNHG16 increases MCP-1 expression by miR-124–3p inhibition in EMT induction	[355]
GAS6-AS1	miR-370–3p/miR-1296–5p/TRIM14	Colorectal cancer	GAS6-AS1 sponges miR-370–3p and miR-1296–5p in increasing TRIM14 expression and mediating EMT	[356]
ZNF674-AS1	miR-181a/SOCS4	Thyroid cancer	ZNF674-AS1 promotes SOCS4 expression via miR-181a inhibition in suppressing the EMT mechanism	[357]
H19	Wnt/β-catenin	Gastric cancer	LncRNA H19 induces Wnt/β-catenin signaling for EMT induction	[358]
OIP5-AS1	miR-147a/IGF1R	Cervical cancer	OIP5-AS1 increases IGF1R expression via miR-147a sponging in EMT induction	[359]
CATIP-AS1	miR-515–5p/EMT	Thyroid cancer	CATIP-AS1 induces EMT mechanism via miR-515–5p sponging in increasing cancer progression	[360]
CYTOR	YAP1/EMT	Colorectal cancer	ENO2 increases the expression level of CYTOR to mediate YAP1-induced EMT	[361]
H19	EMT	Breast cancer	Curcumin prevents H19-mediated EMT in cancers	[362]
NNT-AS1	miR-186/HMGB1	Cervical cancer	NNT-AS1 increases HMGB1 expression by miR-186 inhibition in EMT induction and mediating cisplatin resistance	[363]
XIST	miR-125b-2–3p/Wee1	Colorectal cancer	XIST promotes Wee1 expression by miR-125b-2–3p inhibition in EMT induction	[364]
HOXA-AS3	HOXA3	Non-small cell lung cancer	HOXA-AS3 downregulates mRNA levels of HOXA3 in EMT induction	[365]
MALAT1	–	Ovarian cancer	MALAT1 increases the progression and malignant phenotype of cancer cells via EMT induction	[366]

cytoskeletal protein, which is essential for tissue integrity and it is found to be aberrantly expressed in various human malignancies and correlated with clinical progression and prognosis [99]. Therefore, LINC02253 accelerated gastric cancer growth, migration, invasion, and metastasis by promoting METTL3-mediated mRNA stability of KRT18 [100].

LncRNA HCP5 mediated cisplatin resistance in gastric cancer cells by sponging miR-519d and HMGA1 was identified as the direct target of miR-519d. [101,102]. Similarly, HCP5 was found to accelerate the proliferation of gastric cancer and the EMT process via the miR-186–5p/WNT5A axis under hypoxia conditions [103]. In contrast, HCP5 was found to block miR-106b-5p to allow the expression of p21 (a cyclin-dependent kinase inhibitor) to inhibit gastric cancer progression [104]. LncRNA SNHG1 blocks miR-15b to increase DCLK1 expression, leading to Notch1 signaling induction and EMT activation in increasing gastric cancer invasion [105]. During hypoxia, the expression level of lncRNA PCGEM1 enhances and promotes SNAI1 expression to promote EMT and gastric cancer metastasis [106]. Therefore, lncRNAs regulating the EMT mechanism are potential targets in gastric cancer therapy [107–110].

Colorectal cancer often appears in the top five list of cancers that contributes to the highest mortality and it is one of the prominent type of cancers with a global death rate of 862,000 in 2018 [111]. The five-year survival rate of colorectal cancer patients is about 90% and in patients with lymph node metastasis or distal metastasis, the 5-year survival rate decreases to 70.4% or 12.5%, respectively [112]. Despite therapeutic advancements, most of the patients are diagnosed with the disease at advanced stages [113–115]. Many lncRNAs are discovered in colorectal cancers in relevance to their role in the promotion of EMT and metastasis. Some lncRNAs can play dual roles such as guiding the target protein to interact with the genome and functioning as ceRNA to sponge to target miRNA. In one such distinct mechanism, overexpression of lncRNA CASC21 occurs in colorectal cancer and CASC21 has been reported to have dual roles. CASC21 was reported to bind to transcription factor POU5F1B (POU class 5 homeobox 1B) and recruit it to the promoter of HGH1 to activate the transcription of HGH1 in the nucleus of colon cancer cells. In parallel, CASC21 functioned as a ceRNA and sponged miR-485–5p. If miR-485–5p is left free, it inhibits interaction with HGH1 mRNA to block its translation in the cytoplasm of colorectal cancer cells [116]. LncRNA ADAMTS9-AS1 stimulates EMT to increase metastasis of colorectal cancer and is correlated with unfavorable prognosis [117]. Upon hypoxia, an increased expression level of HIF-1α is observed that mediates autophagy, and EMT induction and increases colorectal cancer progression. However, lncRNA CPS1-IT1 prevented the activation of HIF-1α-driven autophagy, leading to EMT suppression and a decrease in metastasis of colorectal tumor cells [118].

Another malignancy of the gastrointestinal tract is hepatocellular carcinoma in which metastasis and chemoresistance are the major problems [119–121]. We have comprehensively discussed the role of STAT3 targeting lncRNAs in hepatocellular carcinoma in our previous review article [53]. LncRNA miR503HG was identified as an inhibitor of angiogenesis and EMT in hepatocellular carcinoma, but it is underexpressed. LncRNA miR503HG can interact with miR-15b to allow the expression of PDCD4 (programmed cell death 4). PDCD4 is a tumor suppressor that modulates apoptosis [122]. LncRNA DRHC also functions as an onco-suppressor factor where it suppresses MEK/ERK signaling to promote EMT inhibition and decrease hepatocellular carcinoma metastasis [123]. Similarly, lncRNA WWOX-AS1 sponged miR-20b-5p to increase WWOX expression and reduce EMT in hepatocellular carcinoma [124]. On the other hand, some lncRNAs are capable of inducing the EMT mechanism for promoting hepatocellular carcinoma progression [125]. These lncRNAs mainly sponge miRNAs in EMT induction and increasing cancer metastasis. Therefore, targeting both lncRNAs and miRNAs can be used for EMT inhibition [126–128]. Furthermore, induction of EMT by lncRNAs can mediate poor prognosis in GI cancers [129].

3.3. Urological tumors

Three main urological cancers include cancers of the bladder, prostate, and kidney which contribute to high mortality and morbidity worldwide [130,131]. Many therapeutic strategies implemented in the treatment of urological cancers have limited efficacy [132]. Therefore, the prognosis of patients is still unfavorable and these cancers are still under attention for the development of new therapeutics [133,134]. LncRNAs can regulate the advancement of urological cancer cells by affecting the EMT mechanism [135]. In bladder cancer, lncRNA SNHG7 is overexpressed and its silencing stimulated apoptosis and blocked invasion and metastasis of tumor cells. SNHG7 promoted the expression of N-cadherin, vimentin, and Snail, while it decreased the expression of E-cadherin in enhancing the metastasis of bladder cancer cells [136]. Similar to other types of tumors, lncRNAs regulate miRNA to affect the EMT mechanism in bladder cancer. LncRNA H19 sponged miR-29b-3p to allow the expression of DNMT3B (DNA methyltransferase 3B) to increase EMT and pulmonary metastasis of bladder cancer cells [137]. LncRNA TP73-AS1 was found to suppress EMT by abrogating the expression of vimentin, Snail, MMP-2, and MMP-9 in bladder cancer cells. The expression of TP73-AS1 was significantly low in bladder cancer tissues and cells in comparison with adjacent non-tumor tissues. It was also reported that patients with low TP73-AS1 expression had shorter overall survival and progression-free survival than those with high TP73-AS1 expression [138]. Activation of the Wnt/β-catenin axis is of importance for increasing metastasis of bladder tumor cells. LncRNA DLX6-AS1 stimulates the EMT mechanism via the Wnt/β-catenin axis in promoting bladder cancer metastasis [139]. Cancer-associated fibroblasts in the tumor microenvironment secrete TGF-β1 that upregulated the levels of lncRNA ZEB2NAT in EMT induction and enhances bladder cancer metastasis [140].

Prostate cancer ranks second in terms of occurrence in men and 1414,259 new cases were diagnosed with a death rate of 375,304 throughout the globe in 2020 [141]. In prostate cancer, lncRNA PAINT is associated with aggressive behavior of tumor cells via increasing Slug and vimentin levels to induce the EMT mechanism [142]. Preclinical experiments have revealed the role of lncRNAs in regulating EMT in prostate cancer. LncRNA PVT1 is associated with EMT induction in prostate cancer and its downregulation impairs tumor metastasis. PVT promoted KIF23 (kinesin family member 23) expression via sponging of miR-15a-5p to induce EMT and prostate cancer progression [143]. KIF23 is a crucial protein associated with cell division and is upregulated in various types of human cancers. LncRNA ZFAS1 sponges miR-135a-5p to induce EMT in prostate cancer cells [144]. LncRNA MNX1-AS1 is an oncogenic factor in prostate cancer, and depletion of MNX1-AS1 decreased the levels of proliferating cell nuclear antigen, PH-3, vimentin, and N-cadherin [145]. LncRNA SNHG1 was found to be dominantly present in the nuclei of prostate cancer cells and it was elevated in the samples derived from prostate cancer patients. Its expression was positively correlated with tumor metastasis and patient survival. Mechanistically, SNHG1 competitively bound with hnRNPL (heterogeneous nuclear ribonucleoprotein L) to interfere with the translation of E-cadherin and subsequent activation of EMT and metastasis [146]. hnRNPL is a ribonucleoprotein that is involved in the advancement of cancers though mediating alternative splicing of precursor mRNA, strengthening mRNA stability, and regulating mRNA translation. In another study, SNHG17 sponged miR-339–5p to induce STAT5A signaling and enhanced SNORA71B expression [147]. Similarly, overexpression of lncRNA SNHG3 is associated with EMT induction in prostate cancer. SNHG3 promotes SMURF1 expression via miR-577 sponging to accelerate EMT [148]. Therefore, lncRNAs are potent regulators of the EMT mechanism in prostate cancer and can be employed as biomarkers [149]. Some lncRNAs that are involved in the regulation of EMT in renal cancer have also been studied. Overexpression of lncRNA ATB promoted EMT and invasion of renal cancer cells which was correlated with metastasis [150]. Kulkarni and colleagues demonstrated that lncTCL6 is reduced in renal cancer tissues compared with its normal counterpart and its overexpression showed good antiproliferative properties. The overexpression of lncTCL6 blocked miR-155 by directly interacting with it. Also, lncTCL6 interacted with STAU1 protein to mediate the degradation of Src mRNA and subsequent reduction of the Src-dependent signaling network to suppress EMT [151]. STAU1 is a double-stranded RNA-binding protein, that binds within the translationally active target mRNAs. More studies are essential to understand the role of lncRNAs in regulating the EMT mechanism in renal cancer.

3.4. Gynecological tumors

Ovarian cancer is the third most common type of gynecological cancer worldwide in 2020 and the five-year survival rate of ovarian cancer patients at an advanced stage is merely 17% [152,153]. Most ovarian cancer patients demonstrate relapse and recurrence after 2 years which contributes to a high mortality rate [154,155]. Elevated levels of lncRNA SRA were noted in ovarian cancer cells and it was found to promote EMT through modulation of the Notch signaling pathway [156]. Silencing lncRNA HOTTIP showed a beneficial effect in impairing the progression and metastasis of ovarian cancer cells. HOTTIP stimulated MEK/ERK axis to accelerate EMT induction and metastasis [157]. PI3K/Akt pathway is one of the best-studied pathways in relevance with the EMT process. Activation of PI3K/Akt further triggers the activation of a cascade of proteins that promote the expression of EMT-related genes. LncRNA PSMA3-AS1 stimulated the activation of the PI3K/Akt axis by sponging miR-378a-3p and thereby increased the growth and invasion of ovarian cancer cells [158]. LncRNA MALAT1 has been implicated in enhancing the progression of EMT in ovarian cancer by modulating PI3K/Akt signaling cascade [159].

Cervical cancer ranks fourth in terms of frequency of diagnosis and the fourth leading cause of cancer death in women, with an estimated 604,000 new cases and 342,000 deaths worldwide in 2020 [160]. WHO proposed a global initiative to eliminate cervical cancer which involves three strategies including vaccination of girls (at least 90% population within the age of 15 years) against human papillomaviruses, screening 70% of women by 35 years of age, and again by 45 years of age, and treating at least 90% of identified precancerous lesions and invasive cancers [161]. Although screening is successful, metastasis of tumor cells is a threatening factor [162,163]. Initiation of an EMT program is vital for metastasis of cervical cancer cells and altered expression of some lncRNAs is commonly seen.

LncRNA AL592284.1 sponged miR-30a-5p to induce the vimentin/EMT axis to facilitate metastasis of cervical cancer cells [164]. Overexpression of lncRNA UCA1 is associated with poor prognosis in cervical cancer and it induced EMT by sponging miR-155 [165]. Similarly, lncRNA SNHG7 promoted the expression of EMT markers such as N-cadherin and vimentin with a parallel decline in the expression of E-cadherin in cervical cancer cells [166]. Taken together, these studies highlighted that EMT regulation by lncRNAs, not only regulates the metastasis of cervical cancer cells, but also affects the overall survival and prognosis of patients (Fig. 2) [167,168].

4. LncRNAs regulating EMT-TFs

4.1. TGF-β

TGF-β signaling is one of the most prominent pathways in the regulation of the EMT process in various types of human malignancies [169–171]. The role of lncRNAs in the regulation of TGF-β signaling to modulate cancer progression and EMT has been studied widely in recent years [44,172]. Some lncRNAs have presented a differential role in different cancers. For an instance, lncRNA ANCR accelerated metastasis of hepatocellular carcinoma by interacting with and upregulating the levels of HNRNPA1 (heterogeneous nuclear ribonucleoprotein A1) [173]. In contrast, ANCR functioned as a tumor suppressor in which its

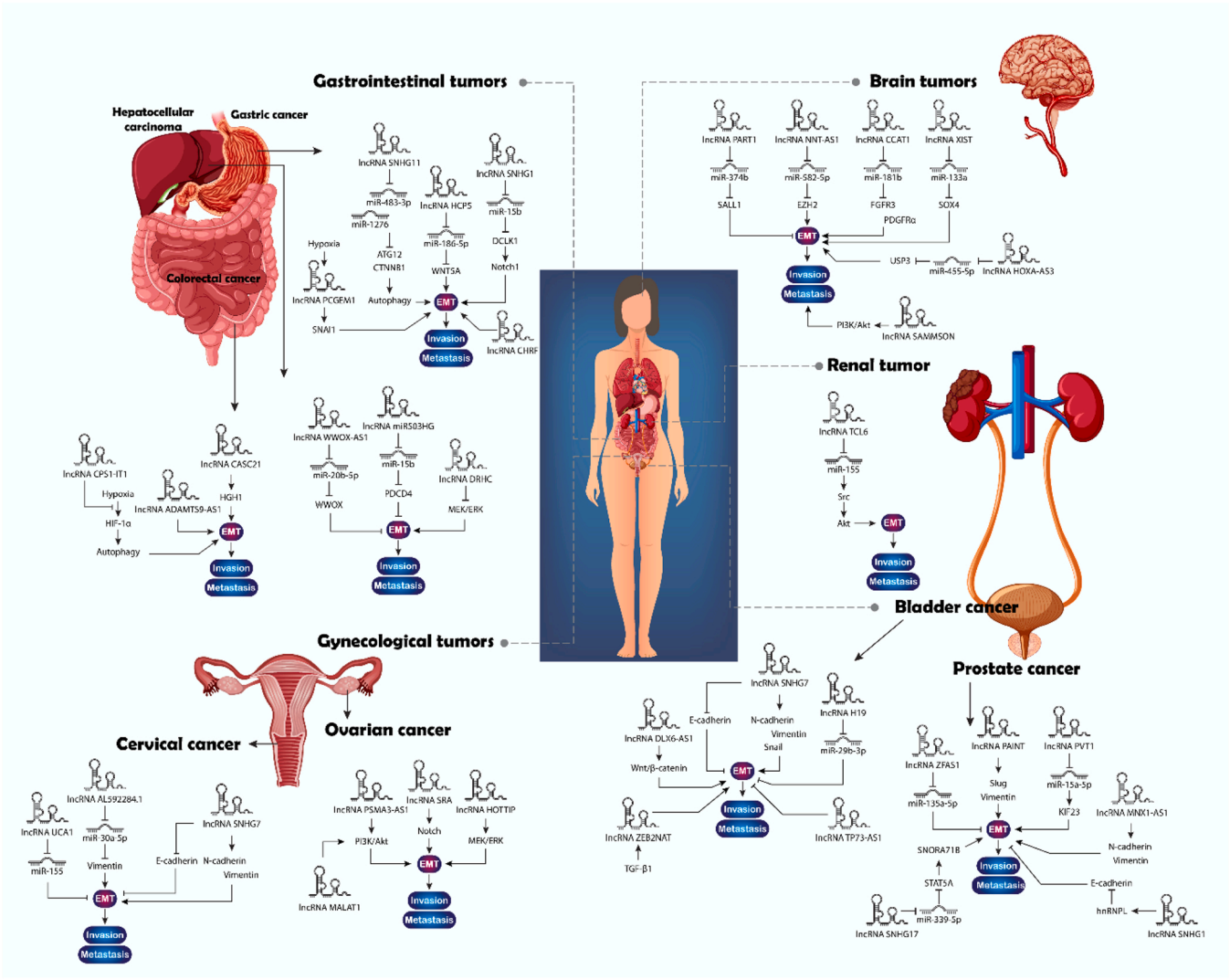

Fig. 2. : LncRNA/EMT axis in various tumors. This axis accounts for the increase in invasion and metastasis of various malignancies including cancers of the kidney, ovary, bladder, prostate, and stomach. Therefore, effective treatment of these tumors and impairing their malignancy are dependent on targeting the lncRNA/EMT axis. BioRender software was used to generate figures.

reduction promoted TGF-β-driven EMT and metastasis in breast cancer [174]. In TGF-β signaling, TGF-β binds to cell surface TGF-β receptors and drives the activation of downstream proteins (SMAD2 and SMAD3) [175]. Thereafter, SMAD2-SMAD3 forms complexes with SMAD4, and then, they translocate into the nucleus to transcribe the target genes which are involved in the progression of EMT and cancer metastasis [175–178]. LncRNA CASC9 was upregulated in bladder cancer and positively correlated with metastasis of tumor cells. CASC9 sponged miR-758–3p to induce the EMT mechanism in bladder cancer cells whereas miR-758–3p in the unbound form, it interacts with the 3′UTR of TGF-β2 [179]. CASC9 levels are often upregulated in colorectal cancer tissues and CASC9 forms a complex with CPSF3 via RNA-protein interaction to activate TGF-β pathway and subsequent EMT program [180]. Upon TGF-β1 stimulation, lncRNA SND1-IT1 sponged miR-124 in gastric cancer cells to permit the expression of COL4A1 which initiates EMT process. If miR-124 is not sponged, it binds to 3′UTR of COL4A1 mRNA to abrogate the expression [181].

LncRNA PLAC2 is an antitumor factor that elevates the levels of miR-663, which results in a reduction of TGF-β1 levels and cell motility in bladder cancer cells [182]. LncRNA LINC01451 induced the EMT program by regulating the LIN28/TGF-β/SMAD axis in bladder cancer cells [183]. LncRNA KIF9-AS1 regulated TGF-β and autophagy signaling pathways to elevate chemoresistance in renal cancer cells [184]. LncRNA linc00645 promoted the TGF-β-driven EMT process by sponging miR-205–3p, permitting the expression of ZEB1, whereas depletion of linc00645 displayed the opposite effects in glioma [185]. Similarly, lncRNA H19 functioned as a ceRNA to block miR-370–3p to promote EMT in ovarian cancer cells [186]. Taken together, TGF-β is a critical inducer and regulator of EMT in different cancers, and lncRNAs indirectly regulate TGF-β signaling to modulate EMT-mediated metastasis in human cancers [187–190].

4.2. *Snail and Slug*

Snail belongs to the class of zinc finger transcription factors which were initially identified in *Drosophila melanogaster* and subsequently discovered in humans and other organisms. Three variants of Snail have been described so far, namely, Snail (Snail1 or Snai1), Slug (Snail2 or Snai2), and Smug (Snail3 or Snai3) [191]. Snail plays a prominent role in the regulation of EMT in embryo development. However, Snail also mediates the EMT process in pathological conditions including cancer. Therefore, Snail family proteins are identified as key transcription factors involved in EMT and metastasis of various types of human cancers [192,193]. Some lncRNAs modulate the expression/activity of Snail

family proteins to modulate the EMT process in human cancers.

LncRNA PTENP1 is a tumor suppressor RNA that sponged miR-106b and thereby allowed the expression of PTEN in cervical cancer cells. Overexpression of PTENP1 reduced the levels of Snail, ZEB1, and vimentin and abrogated the EMT process in cervical cancer cells [194]. PTEN is a well-known tumor suppressor protein that is often downregulated in many types of cancers. LncRNA HOTAIR was found to mediate the physical interaction between Snail and EZH2 which resulted in the recruitment of this complex to the regulatory sites of genes coding for E-cadherin and HNF4α to repress their expression and thereby promoting mesenchymal features in hepatocellular carcinoma cells [195]. This study was validated by producing a mutant variant of the HOTAIR to impede Snail function in EMT [196].

Most of the lncRNAs affect the expression of Snail in tumor cells via affecting upstream mediators or sponging Snail-targeting miRNAs [197]. For example, lncRNA SNHG7 promoted cell motility by sponging miR-34a and modulating the miR-34a-Snail-EMT axis in gastric cancer cells [198]. In a similar line, SNHG1 sponged miR-376a and in turn allowed the expression of FOXK1 (Forkhead box protein K1). FOXK1 is a transcription factor that has been known to upregulate the expression of Snail. Therefore, sponging of miR-376a allowed the expression of FOXK1 with a subsequent increase of Snail levels which contributed to the progression of EMT, tumor growth, and metastasis in HCC [199]. Zhong and colleagues demonstrated that lncRNA DGCR5 isoform-1 could sequester miR-211–5p which leads to the increase of Snail expression and subsequent increase in the proliferation and migration of renal cancer cells [200]. LncRNA RP11–422N16.3 is an inhibitor of the EMT mechanism in hepatocellular carcinoma. It acts by sponging miR-23b-3p and reducing the expression of Snail, ZEB1, and vimentin to inhibit EMT and impair metastasis [201]. Wnt signaling is a critical regulator of the EMT mechanism in cancers. Activation of Wnt signaling is in favor of enhancing EMT and metastasis of tumor cells [202–204]. LncRNA H19 increases metastasis of colorectal tumor cells via EMT induction. LncRNA H19 promotes PGRN expression via miR-29b-3p downregulation to induce Wnt signaling, leading to Snail overexpression and stimulation of the EMT mechanism [197]. LncRNA RHPN1-AS1 enhanced proliferation, migration, and invasion of glioma cells by directly interacting with miR-625–5p and increasing the expression of EMT-TFs including Snail [205].

LncRNA PVT1 is considered a new emerging target in cancer and its overexpression is associated with metastasis, radioresistance, and chemoresistance in cancers [206]. LncRNA PVT1 modulates the activity of YAP (Yes-associated protein) to induce the EMT mechanism in gastric cancer [207]. PVT1 promoted the EMT of gastric cancer cells by sponging miR-30a, whereas if miR-30a is not sponged, it directly targets and reduces Snail expression [208]. In addition to Snail, PVT1 has the capacity of targeting Slug in gastric tumor cells. Therefore, targeting lncRNA PVT1 is a promising approach to suppressing the progression and metastasis of gastric cancer cells. PVT1 showed overexpression in gastric cancer and it increased the aggressive behavior of tumor cells. PVT1 physically interacted with STAT3 and facilitated the recruitment of STAT3 to the promoter of the Slug gene to enhance the expression of Slug and subsequent EMT mechanism in gastric cancer cells [209]. Jiang and colleagues demonstrated that lncRNA SNHG15, which is overexpressed in colon cancer, physically interacts with the C-terminal zinc finger domain of Slug and blocks its ubiquitin-mediated degradation to promote colon cancer [210]. LncRNA NOAT113026 was reduced in renal cancer tissues compared to their non-tumor counterparts and its overexpression impeded the proliferation and EMT by interacting with 3′UTR of NF-κB/p50 and Slug in renal cancer cells [211]. It was noticed that miR-124–3p availability is antagonized by lncRNA MALAT1 to promote Slug-driven metastasis in hepatocellular carcinoma [212]. Human papillomavirus 16 E6/E7 was found to regulate the expression of lncRNA SNHG12 and subsequently, SNHG12 facilitated EMT through ERK/Slug/E-cadherin pathway in cervical cancer cells [213]. Overall, these reports suggest that Snail family proteins play a crucial role in the regulation of EMT and the expression and activity of these proteins are tightly regulated by lncRNAs in GI and urological tumors.

4.3. ZEB proteins

ZEB (Zinc finger E-box-binding homeobox) proteins are transcription factors that are involved in the modulation of expression of genes associated with the EMT process [214]. ZEB family comprises two members namely ZEB1 and ZEB2 (SIP1) and both of them possess zinc finger clusters which allows them to directly interact with the promoter sequence of target genes to modulate transcription. ZEB proteins promote EMT by directly repressing the epithelial genes associated with cellular adhesion and cytoskeleton organization, with a parallel elevation in the expression of genes responsible for mesenchymal phenotype [215]. Deregulated expression of ZEB proteins is often seen in some types of malignancies which results in EMT and metastasis. The role of lncRNAs in the regulation of the expression of ZEB proteins in cancers has been studied. LncRNA ZEB1-AS1 increased YAP1 expression by sequestering miR-205 and thereby facilitating colorectal tumor progression [216]. ZEB1-AS1 increased the expression of TRIB2 via sponging miR-505–3p to enhance pancreatic cancer progression [217]. Furthermore, ZEB1-AS1 has been implicated in triggering paclitaxel and cisplatin resistance in ovarian cancer [218]. Silencing lncRNA ZEB1-AS1 blocked the metastasis in esophageal cancer via EMT inhibition. ZEB1-AS1 promoted ZEB1 expression to increase cancer metastasis [219]. LncRNA XIST drives pancreatic cancer progression by antagonizing miR-429 thereby permitting the expression of ZEB1 to trigger EMT and metastasis [220]. Hypoxia is an important factor to enhance the progression of pancreatic cancer [221]. During hypoxia, overexpression of lncRNA BX111 was observed which upregulated the expression of ZEB1 with a decline in E-cadherin levels and potentiating pancreatic cancer metastasis [222]. Overexpression of lncRNA HOTTIP served as a marker of poor prognosis in glioma patients. HOTTIP sequestered miR-101 which resulted in elevated expression of ZEB1 and EMT process under hypoxia conditions [223].

Besides ZEB1, ZEB2 is also regulated by lncRNAs in affecting EMT and metastasis in cancers. LncRNA DDX11-AS1 overexpression can significantly increase the metastasis of esophageal cancer cells. LncRNA DDX1-AS1 sponged miR-30d-5p to increase the expression of ZEB2 in triggering EMT and metastasis [224]. The increased expression of ZEB2 in cervical cancer resulted in the tumor progression [225]. LncRNA CTS is an inducer of metastasis in cervical cancer and it sponged miR-505 to overexpress ZEB2 and triggered EMT [226]. The expression of ZEB2 and lncRNA UCA1 was enhanced, while miR-498 was decreased in esophageal cancer cells. It has been shown that UCA1 upregulated ZEB2 expression by inhibiting miR-498 to enhance EMT [227]. LncRNA TUG1 levels are upregulated in bladder cancer cells and TUG1 was found to sponge miR-142 and in turn, allowed the expression of ZEB2 (a downstream target of miR-142) to encourage the growth of bladder cancer cells [228]. Hence, targeting ZEB1/2 proteins or related lncRNAs is important in suppressing the metastasis of cancer cells. Several other studies have also demonstrated the effect of lncRNAs in the regulation of ZEB proteins to modulate EMT in various types of human cancers [229–233].

4.4. Twist

Twist is a major transcription factor that regulates the process of EMT by activating the expression of target genes. High expression of Twist is frequently associated with various human malignancies and it significantly contributes to the disease progression and metastasis. Some miRNAs can interact with Twist mRNA to regulate their expression [234, 235]. LncRNA SNHG3 accelerated EMT in gastric cancer cells by blocking miR-326 and promoting Twist expression [236]. LncRNA DANCR is another non-coding RNA with regulatory functions on EMT in cancers [237]. LncRNA DANCR induced EMT in cervical cancer cells by

sponging miR-335–5p and thereby elevating the levels of ROCK1 [238]. LncRNA GHET1 was elevated in bladder cancer tissues compared to adjacent normal tissues and inhibition of GHET1 reversed the EMT process in bladder cancer cells and decreased EMT-TFs including Twist [239]. LncRNA LINC00339 induced the formation of vasculogenic mimicry by sequestering miR-539–5p in glioma whereas Twist1 was identified as the direct target of miR-539–5p [240]. Vasculogenic mimicry significantly hampers the therapeutic efficacy of anti-angiogenic tumor therapy for glioma patients. In cholangiosarcoma, lncRNA DANCR sponged miR-345–5p to enhance the expression level of Twist1 and the subsequent EMT process [241]. In lung tumor cells, overexpression of lncRNA SNHG4 stimulates EMT and increases cancer metastasis. Mechanistically, SNHG4 downregulates miR-98–5p expression to overexpress Twist in EMT induction and increase lung cancer metastasis [12]. Based on these studies, it can be concluded that lncRNAs can modulate Twist expression and subsequent EMT process in human cancers (Fig. 3) [242,243].

5. LncRNA/EMT axis in therapeutic response

5.1. Chemoresistance

A wide variety of anticancer agents have been/are being developed to induce cell death, inhibit the proliferation of cancer cells, and improve the prognosis and survival of cancer patients [244,245]. Therapeutic resistance (radioresistance and chemoresistance) is one of the biggest hurdles in the treatment of cancer patients. Chemoresistance can be intrinsic or extrinsic which differ in terms of exposure time and activation of oncogenic pathways as well as hyperactivation of drug efflux transporters [131,246]. LncRNAs have been implicated in mediating drug resistance in cancers. LncRNAs can modulate chemoresistance by interfering with the activity of some miRNAs or downstream target proteins. Furthermore, lncRNAs can be used as a biomarker for predicting the response of tumor cells to chemotherapy [247–250]. The current section focuses on the role of lncRNAs in the regulation of the EMT mechanism and their association with chemotherapeutic response.

LncRNA PVT1 was found to form a complex with EZH2 with subsequent recruitment of this complex to the promoter region of miR-195 to increase trimethylation of lysine 27 of histone 3 (H3K27me3). In parallel, PVT1 was also found to sponge miR-195 and modulate the chemoresistance of cervical cancer cells to paclitaxel [168]. As discussed earlier, EZH2 is a methyltransferase enzyme and a component of the polycomb repressive complex 2 that methylates particular lysine residues in the histone proteins to repress transcription [251]. LncRNA HOTAIR was reported to trigger chemoresistance in gastric cancer. HOTAIR downregulated PTEN expression via miR-17–5p to mediate EMT and increase chemoresistance [252]. The regulation of PTEN signaling by lncRNAs is also of importance in affecting therapeutic response in cervical cancer. PTEN negatively regulates PI3K/Akt signaling and impairs the proliferation and metastasis of various tumors [253,254]. HOTAIR is vital for increasing the growth and metastasis of cervical cancer cells. It has been shown that HOTAIR interfered with the activity of miR-29b to induce PI3K/Akt signaling via PTEN inhibition in mediating resistance to cisplatin, paclitaxel, and docetaxel in cervical cancer cells [255]. It has been shown that overexpression of lncRNA UCA1 in breast cancer cells increases tumor cell viability and mediates doxorubicin resistance. Noteworthy, TGF-β promoted the expression of UCA1 to stimulate EMT and mediate chemoresistance [256].

One of the hallmarks of the tumor microenvironment is the presence of hypoxia and hypoxia is responsible for providing plasticity and heterogeneity in many solid tumors [257,258]. The hypoxic tumor microenvironment contributes to mediating drug resistance and unfavorable prognosis in cancer [259–261]. Hypoxia in the tumor microenvironment also increases vasculogenic mimicry in cancers [262]. A recent experiment has shown that hypoxia in colorectal cancer leads to EMT, drug

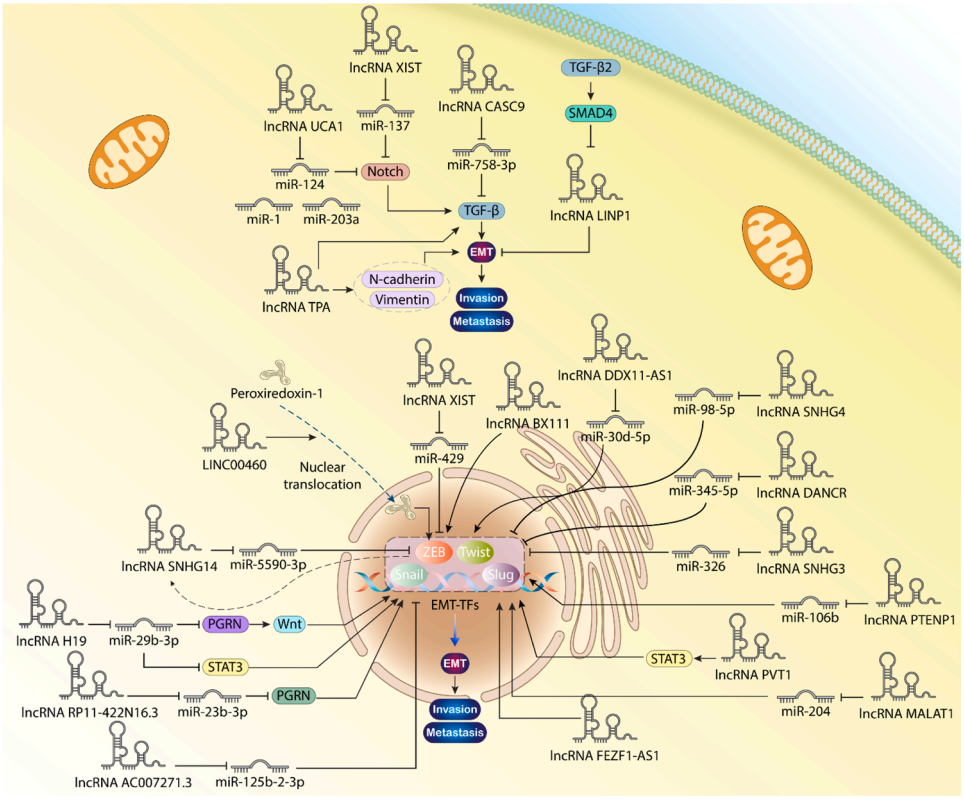

Fig. 3. : LncRNAs regulating EMT-TFs in different cancers. Slug, Twist, ZEB, and Snail are EMT-TFs and their expression levels are regulated by lncRNAs.

resistance, and vasculogenic mimicry. Overexpression of lncRNA NORAD occurs in hypoxic colorectal tumor cells and NORAD sponges miR-495–3p to upregulate HIF-1α for EMT induction, increasing vasculogenic mimicry and mediating drug resistance [263].

Sorafenib is a multikinase inhibitor that has been widely prescribed for the treatment of hepatocellular carcinoma patients [264]. Although sorafenib has been successful in improving the survival rate of HCC patients, its frequent application results in resistance to sorafenib chemotherapy [265]. The expression of lncRNA LIMT was found to be inversely correlated with sorafenib resistance in hepatocellular carcinoma cells [266]. Low expression of LIMT was observed in hepatocellular carcinoma tumor tissue samples and LIMT was found to target miR-665 (a miRNA that favors sorafenib resistance). The authors concluded that LIMT contributes to sorafenib resistance through the modulation of miR-665 and EMT in hepatocellular carcinoma cells [266]. Elevated expression of lncRNA DLEU1 was observed in glioma tissues compared to its normal counterpart and associated with a dismal prognosis. Depletion of DLEU1 resulted in the suppression of EMT and sensitized glioma cells to temozolomide, a primary drug used for the treatment of glioma patients [267]. The abundance of lncRNA PCAT6 was upregulated in cervical cancer tissues in comparison with that of corresponding normal tissues. PCAT6 contributed to the chemoresistance of cervical cancer cells to cisplatin by sponging miR-543, whereas ZEB1 was identified as the direct target of miR-543 [268]. Based on these studies, it can be concluded that overexpression of oncogenic lncRNAs that drive the EMT can increase chemoresistance, while onco-suppressor lncRNAs that inhibit EMT can sensitize cancer cells to standard therapeutic agents.

5.2. Radioresistance

Radiotherapy is the age-old and cost-effective strategy used for the treatment of many types of human cancers. Some tumors do not effectively respond to radiation therapy as they adapt some survival mechanisms which results in radioresistance. Radioresistance is also one of the major problems in the treatment of several types of cancers [269, 270]. Although the combination of radiotherapy and chemotherapy is being implemented in cancer treatment, resistance to radiotherapy remains an issue that needs to be addressed. Many of the studies have demonstrated the roles of lncRNAs in the development of radioresistance in various types of malignancies. LncRNA SNHG6, which is overexpressed in cervical cancer cells, increased the proliferation and radioresistance of cervical cancer cells by interacting with miR-485–3p [271]. LncRNA TUG1, which was elevated in bladder cancer tissues compared to the normal corresponding tissues, enhanced radioresistance in bladder cancer cells by elevating the expression of HMGB1 (High mobility group box 1) protein, whereas the knockdown of TUG1 displayed opposite effects [272]. TPTEP1 inhibited stemness and radioresistance of glioma in cell-based assays and preclinical models by sponging miR-106a-5p, thus allowing activation of the P38 MAPK signaling pathway [273]. Similarly, an inverse relationship was found between the expression of lncRNA OIP5-AS1 and miR-34a, and a direct relationship between the expression of OIP5-AS1 and Snail inferring that OIP5-AS1 sponges miR-34a to elevate the expression of Snail in ovarian cancer cells [274]. OIP5-AS1 was demonstrated to contribute to the radioresistance of colorectal cancer cells by interacting with miR-369–3p [275]. Silencing lncRNA RET increased the radiosensitivity of cancer cells. LncRNA RET sponges miR-3179 to induce Slug expression (a repressor of PTEN transcription), leading to EMT induction and subsequent resistance to radiation therapy [276]. LncRNA ROR is an oncogenic factor that triggers radioresistance in hepatocellular carcinoma. LncRNA ROR sponged miR-145 to increase the expression of RAD18, thus promoting cancer metastasis via EMT induction and radioresistance [277] (Fig. 4). These reports suggest that lncRNAs play a crucial role in the development of radioresistance in many types of cancers, and mechanism of resistance is majorly mediated through the sponging of target miRNAs.

6. Exosomal lncRNAs regulating EMT mechanism

Exosomes are small membrane vesicles of endocytic origin with sizes varying between 30 and 100 nm [278–280]. They are involved in the transportation of miRNAs, lncRNAs, mRNAs, DNA fragments, and proteins between the donor and recipient cells. Exosomes mediate communication between donor and recipient cells. Mounting evidence has suggested that exosomes play a key role in relaying the signals between cancer and surrounding cells in the tumor microenvironment to create a conducive environment for disease progression. They can mediate either local or systemic cell-to-cell communications [281]. Exosomes are the derivatives of endosomal compartments in which cytoplasmic RNAs and some proteins are encapsulated, further leading to the fusion with the plasma membrane and subsequent release to the extracellular environment. These exosomes are taken by the target cells depending on the presence of transmembrane proteins as discussed in previous articles [281–283]. Exosomes released from tumor cells are termed tumor-derived exosomes and they promote cell proliferation, chemoresistance, angiogenesis, and activate fibroblasts in the tumor microenvironment whereas creating a premetastatic niche and promoting immunosuppression in the systemic environment.

Recent studies have demonstrated that lncRNAs of tumor-derived exosomes play a key role in the regulation of growth, metastasis, and response to therapeutic agents [284–290]. Resistance to cisplatin treatment is frequently seen in gastric cancer. The transfer of lncRNA HOTTIP by exosomes has been implicated in mediating chemoresistance. Clinically, elevated expression of exosomal HOTTIP in the serum of gastric cancer patients is positively correlated with the low response to cisplatin chemotherapy. Mechanistically, exosomal lncRNA HOTTIP promoted HMGA1 expression via sponging miR-218 to cause cisplatin resistance in gastric cancer [291]. M1 and M2 are the two phenotypes of activated macrophages in which M1 is responsible for offering immunity against infections and tumor cells whereas M2 is endowed with tumor-promoting functions. Xin and colleagues demonstrated that lncRNA HCG18 is overexpressed in exosomes derived from gastric cancer cells. Further, exosomal HCG18 was found to facilitate the polarization of M2 macrophage by sponging miR-875–3p, thus allowing the expression of KLF4 [290]. Overexpression of miR-875–3p in macrophages blocked M1 to M2 polarization indicating the tumor derived

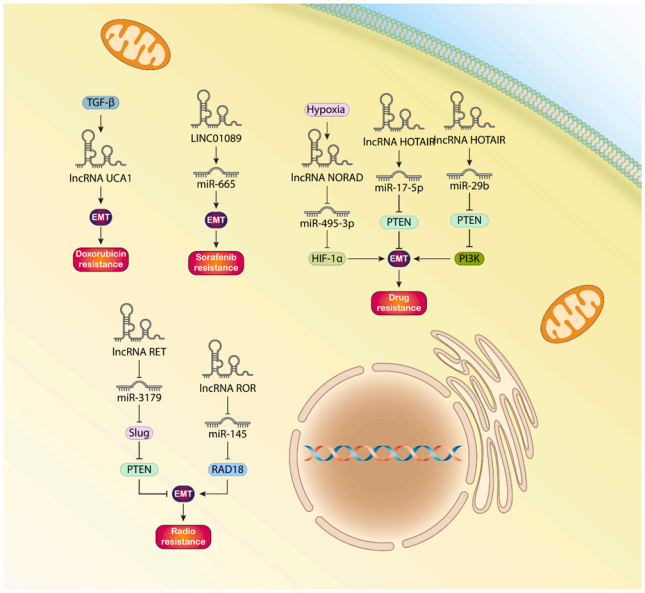

Fig. 4. : LncRNA/EMT axis contributes to the chemoresistance as well as radioresistance by various molecular mechanisms in cancer cells.

lncRNAs modulate the tumor microenvironment to have a conducive environment for the disease progression. Similarly, an exosome lncRNA LINC01711 derived from esophageal cancer accelerated the growth and invasion of tumors in mice model and LINC01711 was found to block miR-326 to permit the expression of FSCN1 (fascin actin-bundling protein 1).

Exosomes isolated from glioma tissues displayed a higher concentration of lncRNA ROR1-AS1 in comparison with adjacent normal tissues, and exosomal-ROR1-AS1 significantly promoted the proliferation of glioma cells by interacting with miR-4686 [292]. LncRNA-ATB in glioma cell-derived exosomes activated astrocytes by silencing miR-204–3p which in turn significantly elevated the invasion of glioma cells [293]. Exosomal lncRNA MALAT1 accelerated angiogenesis and predicts dismal prognosis in ovarian cancer. Also, high levels of exosomal MALAT1 were positively correlated with the metastatic phenotype of ovarian cancer [294]. LncRNA UCA1 was found to promote cisplatin resistance by regulating the miR-143/FOSL2 axis in ovarian cancer. Notably, UCA1 was increased in serum exosomes from cisplatin-resistant patients, indicating that exosome-derived lncRNAs may contribute to chemoresistance [295]. In a similar study, lncRNA lncARSR facilitated sunitinib resistance and served as a marker of poor response in renal cancer patients. Interestingly, lncARSR could be loaded into exosomes and transmitted to sunitinib-sensitive cells to disseminate sunitinib resistance [296]. Overall these studies propose that lncRNAs loaded in the tumor-derived exosomes play a pivotal role in tumor progression, chemoresistance, EMT, and metastasis, and blocking the transmission of exosomes could be an ideal strategy to prevent tumor progression (Fig. 5).

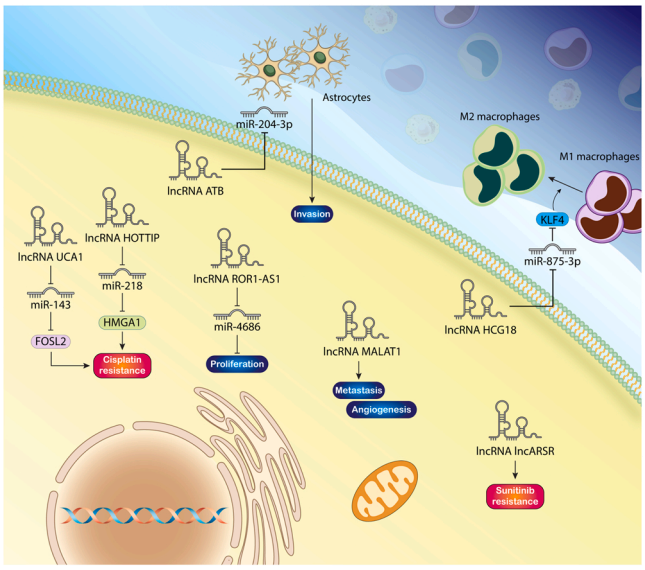

Fig. 5. : The role of exosomal lncRNAs in the regulation of the EMT mechanism. The transition of macrophages from M1 to M2 phenotype in the tumor microenvironment can be modulated by exosomal lncRNAs. Notably, exosomal lncRNAs regulating the EMT mechanism can affect the proliferation, metastasis, and therapy response of cancer cells.

7. Conclusion and remarks

The understanding of the concept of cancer has significantly advanced in recent years due to the continuous and intense efforts of many researchers worldwide [297,298]. Despite significant efforts in developing therapeutics for cancer, the prognosis and overall survival of patients are still low which demands more attempts to find alternative ways or new therapies. In recent years, a vast amount of ncRNAs (miRNA, lncRNA, and circular RNA) have been discovered and demonstrated to have a significant role in the maintenance of homeostatic conditions. The dysregulation of ncRNAs is often seen in various types of human diseases including cancers.

The role of lncRNAs in oncogenesis, chemoresistance, EMT, and metastasis has been widely explored in the last decade. LncRNAs can perform paradoxical functions as they can either promote or suppress tumor progression. Often, lncRNAs function as a ceRNA to sponge target miRNAs and make the miRNA unavailable to perform its functions. In homeostatic conditions, a delecate balance is maintained between the expression of oncogenic and tumor suppressor factors (miRNAs and lncRNAs). In cancers, tumor suppressor lncRNA/miRNA levels are reduced with a parallel increase in the oncogenic lncRNA/miRNA levels, and this imbalance results in the aggressiveness of cancers. Subsequently, overexpression of oncogenic lncRNAs often results in the promotion of EMT and metastasis. Therefore, targeting the lncRNA/EMT axis impairs the progression and metastasis of these tumors and improves the survival rate of patients. LncRNAs are critical regulators of EMT-TFs including TGF-β, Twist, Snail, and ZEB proteins, showing that different molecular interactions can occur among them. Furthermore, the lncRNA/EMT axis can regulate the response of tumor cells to chemotherapy and radiotherapy, confirming the role of this axis beyond cancer metastasis. Recent studies have also demonstrated that lncRNAs can be transferred from cancer cells to neighboring cells in the tumor microenvironment or they can be transferred to cells that are present in distant sites systemically with the aid of exosomes. The studies of Qu and colleagues demonstrated that chemosensitive cells were transformed into chemoresistant cells by transferring lncRNAs through exosomes [296]. Importantly, synthetic mimics of some tumor suppressor miRNAs are being evaluated in clinical trials against cancers. For instance, miR-34 is a major tumor suppressor that mediates the silencing of CDK4/6, SIRT1, and SOX2. MRX34 is a liposomal nanoparticle containing a synthetic mimic of the miR-34a and it was evaluated in the phase-I clinical trial in patients with advanced solid tumors (NCT01829971). In addition, some miR-based therapeutic approaches (miR-31–3p and miR-31–5p in colorectal cancers; miR-21 and miR-200 in oral cancers) have advanced to phase-III/IV of the clinical trials, indicating that ncRNAs are the future drugs. Although lncRNAs have not been successfully implemented in clinics so far, they may be implemented as therapeutic agents with advancements in research. All these reports suggest that the role of lncRNAs either in the maintenance of homeostatic conditions or in disease progression is much more complex than present-day understanding and demands many more studies to completely dissect the underlying molecular mechanisms. In this report, we have attempted to provide a holistic view of the involvement of lncRNAs in EMT, metastasis, chemoresistance, and radioresistance in various types of human cancers including brain tumors, gastrointestinal tumors, gynecological cancers, and urological cancers.

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CRediT authorship contribution statement

MH, SH, and CDM were involved in drafting and revising of the manuscript under the supervision of KSR, AT, and ME. All others were involved in conceptualization and revising the manuscript.

Declaration of 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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