Cellular and Molecular Life Sciences (2024) 81:214
https://doi.org/10.1007/s00018-024-05236-w

REVIEW

Circular RNAs in EMT-driven metastasis regulation: modulation of cancer cell plasticity, tumorigenesis and therapy resistance

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Received: 5 December 2023 / Revised: 5 March 2024 / Accepted: 3 April 2024

Abstract
The non-coding RNAs comprise a large part of human genome lack of capacity in encoding functional proteins. Among various members of non-coding RNAs, the circular RNAs (circRNAs) have been of importance in the pathogenesis of human diseases, especially cancer. The circRNAs have a unique closed loop structure and due to their stability, they are potential diagnostic and prognostic factors in cancer. The increasing evidences have highlighted the role of circRNAs in the modulation of proliferation and metastasis of cancer cells. On the other hand, metastasis has been responsible for up to 90% of cancer-related deaths in patients, requiring more investigation regarding the underlying mechanisms modulating this mechanism. EMT enhances metastasis and invasion of tumor cells, and can trigger resistance to therapy. The cells demonstrate dynamic changes during EMT including transformation from epithelial phenotype into mesenchymal phenotype and increase in N-cadherin and vimentin levels. The process of EMT is reversible and its reprogramming can disrupt the progression of tumor cells. The aim of current review is to understanding the interaction of circRNAs and EMT in human cancers and such interaction is beyond the regulation of cancer metastasis and can affect the response of tumor cells to chemotherapy and radiotherapy. The onco-suppressor circRNAs inhibit EMT, while the tumor-promoting circRNAs mediate EMT for acceleration of carcinogenesis. Moreover, the EMT-inducing transcription factors can be controlled by circRNAs in different human tumors.

Keywords RNA transcripts · circRNAs · cancer malignancy · EMT · cancer cell plasticity · Drug resistance

Introduction

Since cancer mortality is associated with metastasis, it is essential to emphasize the role of factors that regulate tumor invasion [1]. Therefore, improving treatment and the survival of patients rely on reducing invasion and the malignancy of tumors. Metastasis is one of the hallmarks of tumor and was coined in 1829 by Jean Claude [2]. The word "metastasis" has Greek roots and means "displacement", with "meta" meaning next and "statis" meaning placement [3]. Metastasis refers to the process in which tumor cells migrate to another part of the body from their primary site to form new cancer cells, leading to death [4]. Cancer metastasis can be modulated via various mechanisms, such as EMT. Increasing evidence reveals that EMT mechanisms have a potential role in tumor invasion and drug insensitivity (Fig. 1).

EMT causes a loss of cell-cell and cell-extracellular matrix adhesion, causing cells with a mesenchymal phenotype to detach from their primary site and separate from surrounding tissues. The process of EMT is not only vital for cancer metastasis but is essential for embryogenesis, tissue fibrosis, and wound healing [6]. Upon EMT induction, the motility of cancer cells increases, and epithelial cells lose their apical-basal polarity in order to transform into mesenchymal cells [7]. The generation of adherens junctions by E-cadherin is vital for cell adhesion and polarity in epithelia and leads to cell-cell attachment and recruitment of signaling complexes [8, 9]. The earliest step in the process of EMT is the loss of E-cadherin levels. EMT-TFs mediate epithelial reorganization via changing and decreasing

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Published online: 11 May 2024

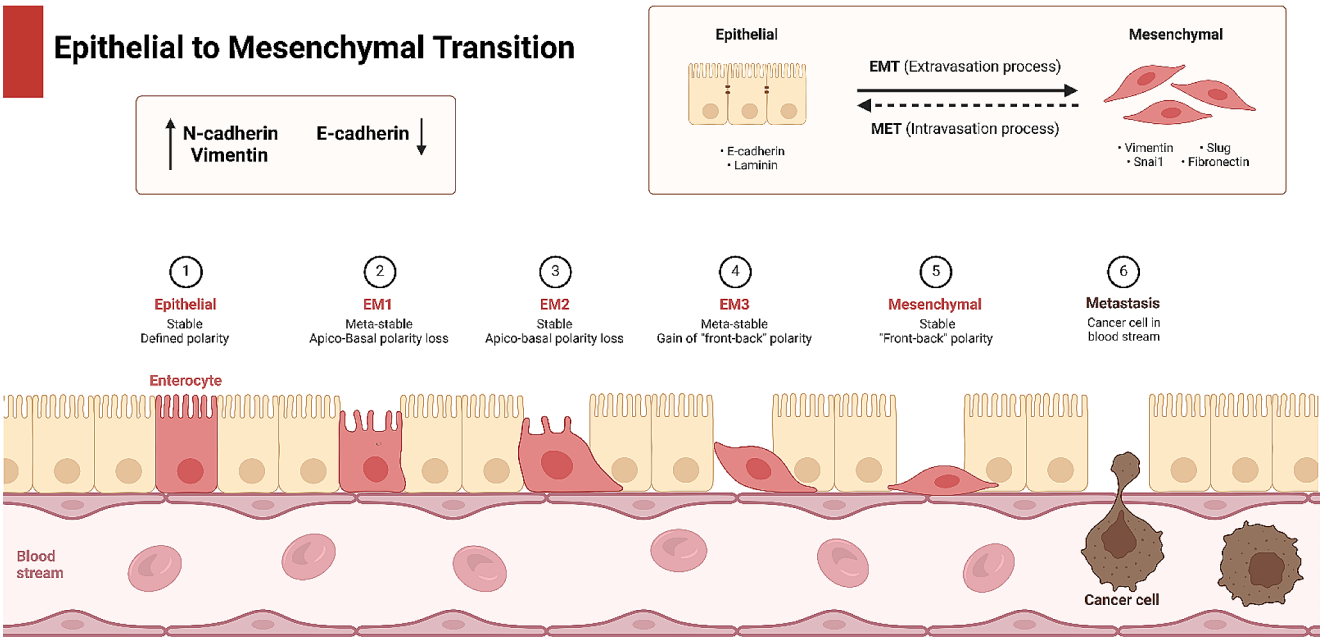

Fig. 1 A summary of EMT mechanism [5]. The EMT includes morphological and biochemical alterations that can occur simultaneously. The biochemical features include the downregulation of E-cadherin and upregulation of vimentin and N-cadherin that can participate in EMT induction. The epithelial cells are changed into mesenchymal cells during EMT that demonstrate high levels of Slug, Snail1, vimentin and fibronectin. The occurrence of EMT can result in escape of a number of cells from other population of colony that diffuse into blood steam to reach to a new site for the establishment of a new colony, participating in the metastasis and progression of tumor

E-cadherin levels [10, 11]. EMT is associated with epithelial-mesenchymal transitions, changes in EMT-TF expression levels, including ZEB proteins, TGF-β, Twist and Snail, as well as Wnt/β-catenin and Notch regulation. The induction of EMT and overexpression of PD-L1 by ERK signaling can cause drug resistance lung tumor. Suppressing PAR2 leads to inhibition of ERK-induced EMT to inhibit osimertinib resistance in lung cancer [12]. Also, Bakuchiol administration is critical for suppressing EMT and cancer invasion by downregulating TGF-β [13]. Low expression levels of ADRB2 by cardamonin are advantageous in inhibiting EMT and reducing the metastasis of colorectal tumor [14]. Besides, activation of Hedgehog signaling is vital for EMT induction in breast tumor [15]. Hence, the regulation of EMT in cancer occurs via various molecular pathways, and targeting inducers of EMT is therefore beneficial in reversing tumor invasion [16–18]. Interestingly, non-coding RNAs can control EMT mechanism [19], and the purpose of the present review is to shed some light on the function of circular RNAs (circRNAs) in regulating EMT and tumor invasion. The Figs. 2 and 3 demonstrate an overview of EMT-related pathways.

The function of EMT in tumorigenesis

Despite the valuable functions of EMT during the physiological and developmental stages, the function of EMT in cancer is oncogenic. Although EMT has been confirmed as a modulator of cancer migration, the increasing evidences have shown that EMT can also mediate the drug resistance [21, 22]. Therefore, the recent experiments have emphasized on highlighting the underlying mechanisms modulating EMT in human cancers. The androgen receptor has shown ability in increasing prostate cancer invasion. The androgen receptor stimulates eIF5A2 expression to enhance vimentin and N-cadherin levels for EMT induction in prostate tumor [23]. In pancreatic cancer, the induction of EMT can significantly increase cancer metastasis and mediate poor prognosis. The upregulation of MACC1 in nucleus and itsinteraction with SNAI1 as EMT regulator can significantly enhance the metastasis of pancreatic tumor [24]. The lncRNA NRON has been shown as an inducer of metastasis and progression in bladder tumor. LncRNA NRON can upregulate EZH2 to stimulate EMT for bladder tumor invasion [25]. Noteworthy, the induction of EMT can also participate in the immunosuppression in human cancers. The ZEB1 is an inducer of EMT in which can stimulate exocytotoic vesicular trafficking through release of Rab6A and Rab8A. Then, MMP14-mediated focal adhesion turnover occurs in lung cancer and induces CD8 + T cell exhaustion

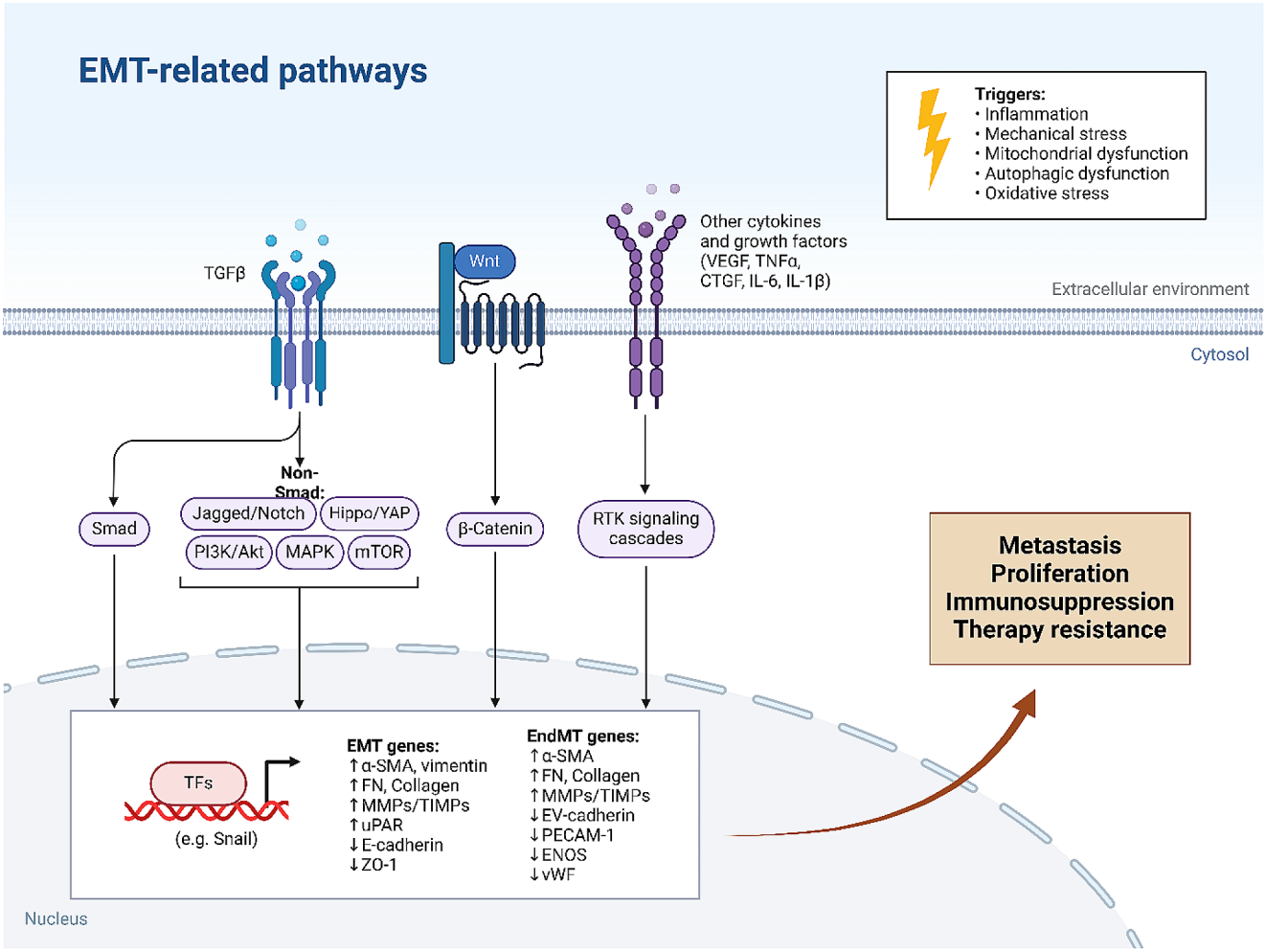

Fig. 2 An overview of a number of pathways regulating EMT. TGF-β, Wnt, PI3K/Akt, mTOR, YAP, MAPK and RTK are a number of molecular interactions contributing to the regulation of EMT. Such pathways are related to the proteins that finally translocate into the nucleus to regulate expression levels of EMT-related genes. The process of EMT is vital for carcinogenesis, since EMT participates in metastasis, therapy resistance and immunosuppression in human cancers. (Created by Biorender.com)

[26]. In cholangiocarcinoma, the upregulation of PLCB1 occurs to induce PI3K/Akt axis. Then, phosphorylation of GSK-3β occurs to increase Snail levels for induction of EMT and increasing cancer progression. However, miR-26b-5p suppresses EMT through PLCB1 downregulation [27]. These experiments provide the insight that EMT has a versatile function in tumorigenesis and it is not limited to metastasis, while it can affect therapy response and impair the immune system.

CircRNAs: an overview in oncology

More than four decades ago, a new kind of RNA molecule without the capability of protein coding was recognized as circular RNA (circRNA). The first circRNA was identified by Sanger and colleagues with a covalently closed loop structure in plant viroids [28]. After that, circRNAs were recognized in eukaryotic cells and viruses [29, 30]. In 1991, the first mammalian circular transcript from the DCC gene was identified in cancerous and non-cancerous cells. Nevertheless, circRNAs were not easily accepted after their discovery and were initially dismissed. They were believed to be by-products of erroneous splicing and transcription errors, and their function was called into question [31]. Progress and efforts on the identification of these RNA molecules were stopped until recently with the discovery of high-throughput sequencing technology and bioinformatic tools. A high number of circRNAs, 32,000 human exonic circRNAs, have been discovered to date [32]. As stable non-coding RNA molecules, circRNAs are mainly found in the cytoplasm of eukaryotic cells, although a number of them, such as intronic circRNAs, can be present in the nucleus [33]. Linear RNA molecules, such as lncRNAs and miRNAs, have a 5′ end cap and a 3′ end poly(A) tail, but circRNAs have a unique structure that lacks both 5′ and 3′

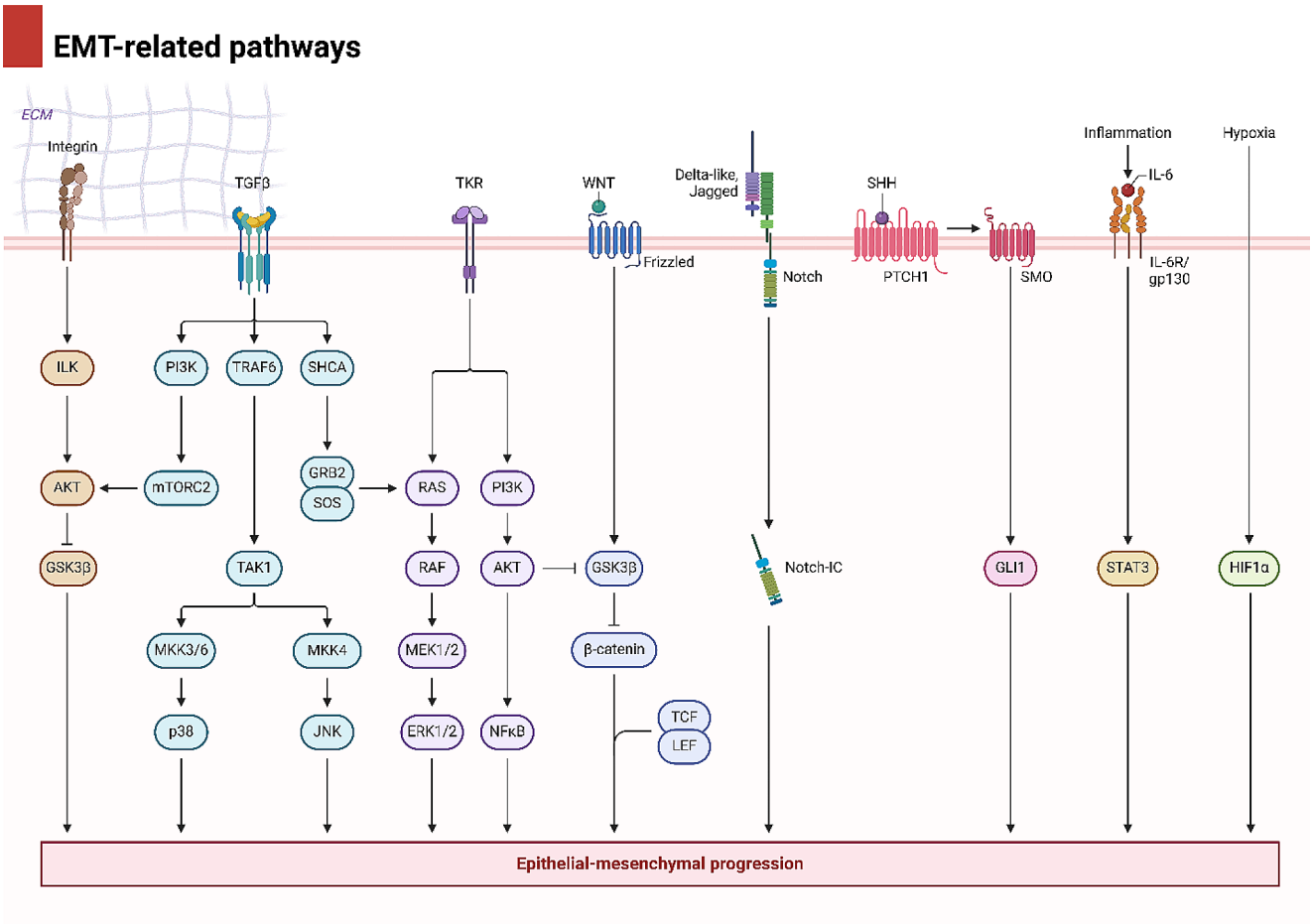

Fig. 3 The other mechanisms regulating EMT [20]. A number of these pathways demonstrate interaction in the regulation of EMT such as TGF-β that modulates mTORC2 and the integrin that regulates AKT. Finally, mTOCR2 can induce AKT. TKB, Wnt/β-catenin, Notch, GLI1, STAT3 and HIF-1α are among the other pathways regulating EMT. (Created by Biorender.com)

ends. Therefore, expression of circRNAs is stable, and their stability is high due to a lack of degradation by endonucleases [34]. CircRNAs are able to sponge miRNAs in the cytoplasm and accelerate the procedure of protein translation. Moreover, circRNAs regulate the transcription process by interacting with RBPs [35–37]. The action of circRNAs in affecting tumor progression is mainly performed via sponging miRNAs. For example, circCCDC85A sponges miR-550a-5p, increasing MOB1A levels and impairing breast tumor progression [38]. Tumor progression and proliferation are tightly regulated by the function of circRNAs [39]. Hsa-circ-0001013 upregulates TWSG1 via miR-136 inhibition, promoting gastric tumorigenesis [40]. The circMET contributes to tamoxifen resistance in breast tumor via increasing AHR level [41]. Furthermore, stabilization of ATP7A and upregulation of PHLPP2 by circPBX3 and circ-0001017, respectively, can lead to tumorigenesis [42, 43].

There are three subcategories of circRNAs based on the distribution and biogenesis [44]. The first subclass is exonic circRNAs (ecRNAs) that are generated through back-splicing of the 5′ splice site (splice donor site) to a 3’ splice site (splice acceptor site) [45, 46]. The second subclass is intronic circRNAs (ciRNAs) that are originated from the intronic lariat precursoes escaping from the debranching step of canonical linear splicing [47]. The third subclass is exon-intron circRNA (ElciRNAs) that increase the expression of parental genes in *cis* through circularizing with the retained intronic sequences among circularized exosones [48]. Moreover, a new kind of circRNAs have been recognized known as mitochondria-encoded circRNAs (mecciRNA) that their biogenesis occurs through a splicing-idependent pathway and can function as molecular chaperons to accelerate the mitochondrial entry of nuclear-encoded proteins [49]. The biogenesis of circRNAs has been highlighted somehow and there are still many unknown aspects. The circRNAs have been shown to be derived from pre-mRNAs and they undergo canonical spliceosomal machinery [50]. The back-splicing reactions in circRNAs require the covalent linking of the 3′ splice site with the 5’ splice site, occurring during biogenesis of circRNAs and can be

accelerated through reverse complementary Alu repeats flanking the circularized exon [51].

The function of circRNAs occurs through four distinct mechanisms [52]. For influencing the expression of genes, the circRNAs affect the parental gene mRNA mediated through interaction with RNA binding proteins [53–55]. Notably, the function of circRNAs is also related to acting as ceRNAs to spong miRNAs [56–58]. Moreover, the circRNAs have been shown to regulate the immune responses [59–61]. Although circRNAs are mainly believed as non-coding RNA factors, a variety of circRNAs have been shown to exert their function through encoding proteins [62–64]. The circRNAs are considered as potential factors in carcinogenesis. The circ-403,658 increases LDHA expression to induce glycolysis in bladder tumor [65]. Moreover, circ-103,809 facilitates the tumorigenesis of hepatocellular carcinoma through acting as tumor-promoting factor [66]. Table 1 summarizes the function of circRNAs in tumors. Table 2 summarizes the role of circRNAs in the controlling EMT.

Function of circRNAs as biomarkers

The distinct biochemical characteristics of circRNAs has led to the application of circRNAs as potential cancer biomarkers. The circRNAs possess high stability and they have cell-, tissue- and developmental-stage-specific paradigms of expression [90]. Moreover, the circRNAs are demonstrated to be highly conserved among the species and resistant to RNase R activity. The enrichment of circRNAs in exosomes can occur and they are found in body fluids including saliva, plasma and blood. The RNA sequencing has led to the recognition of high number of circRNAs in human peripheral whole blood cell [91]. In high number of cases, the level of circRNAs is higher compared to the corresponding linear RNA isoform [91]. According to this fact, a variety of experiments have emphasized on application of circRNAs as biomarkers in various human cancers [92]. The circ-002059 has a poor expression in gastric tumor compared to the healthy tissues and can influence the distal metastasis and TNM stage, highlighting its function as biomarker in gastric tumor [93]. The circRNA-PVT1 has upregulation in gastric tumor that can affect the overall survival and disease-free survival of patients and through sponging miR-125 family, it functions as tumor-promoting factor [94]. In addition to gastric tumor, the circRNAs have been considered as biomarkers in other kinds of tumors. The circ-0005075 has differential expression between hepatocellular carcinoma and health tissues and its expression can increase tumor size [95]. Moreover, the circ-0001649 has differential expression and shows low expression in hepatocellular carcinoma

Table 1 A summary of circRNAs function

CircRNA	Cancer type	Remark	Reference
Hsa_circ_0136666	Gastric cancer	Sponging miR-375-3p to increase PRKDC expression and enhance PD-L1 levels in immune evasion	[67]
Hsa_circ_0006401	Colorectal cancer	Downregulation of circRNA decreases growth and invasion of tumor cells	[68]
Circ_0004140	Lung adenocarcinoma	Circ_0004140 sponges miR-1184 to upregulate CCL22 in tumorigenesis	[69]
Hsa_circ_0000437	Gastric cancer	Increasing lymph node metastasis through HSPA2/ERK axis regulation	[70]
Hsa_circ_0003258	Prostate cancer	Sponging miR-653-5p and complexation with IGF2BP3 to enhance invasion	[71]
Circ_0000235	Bladder cancer	Downregulation of miR-330-5p to stimulate glycolysis	[72]
Circ_0042881	Breast cancer	EIF4A3 increases circ-0042881 levels to stimulate RAS pathway in tumorigenesis	[73]
Hsa_circ_0060467	Breast cancer	Hsa_circ_0060467 inhibits miR-1205 and mediates complexation with eIF4A3 to enhance liver invasion	[74]
Circ-hnRNPU	Gastric cancer	Suppression of NONO-mediated c-Myc transactivation and mRNA stabilization vital for glycolysation and tumorigenesis	[75]

[96]. Circ-100,876 has high expression in lung cancer and mediates lymph node metastasis and tumor staging, acting as prognostic factor [97].

CircRNA/EMT axis in cancer metastasis

In this section, we discuss the function of the circRNA/EMT in regulating the invasion of tumor. Based on the role of circRNAs, the interaction of circRNAs and EMT in cancers mediates metastasis. Oncogenic circRNAs induce EMT to increase tumorigenesis, while onco-suppressor circRNAs reduce cancer invasion via EMT inhibition. The field of biology and next-generation sequencing enables the identification of new circRNAs with important functional roles in cancer. The first complexity that arises from circRNAs is that their function in cancer varies and is context-dependent. For instance, circ-0008305 increases the progression of hepatocellular carcinoma via promoting TMED2 level and miR-186 inhibition [43]. Circ-0008305, on the other hand, acts as an oncosuppressor in lung cancer by regulating EMT. Circ-0008305, also known as circPTK2, interacts with miRNAs and EMT regulators such as TGF-β in lung tumor. TGF-β induced EMT in lung tumor promotes tumor cell progression and invasion. Notably, TIF1γ deficiency is required for TGF-β-associated EMT induction in lung tumor [98]. According to these studies, as circRNA induces EMT, it may be capable of suppressing EMT in other cancers.

The expression of certain factors can significantly promote the metastasis, and IGF2BP3 is one of them. USP11 promotes the stability of IGF2BP3 to increase the colorectal cancer metastasis [99]. The upregulation of IGF2BP3 by linc 01305 can lead to overexpression of HTR3A at the mRNA level, which elevates the progression of esophageal tumor [100]. Hence, IGF2BP3 upregulation also increases invasion [101, 102]. IGF2BP3 is the target of circRNAs in regulating the EMT. CircIGHG elevates the malignancy of oral tumor via EMT induction. CircIGHG increases IGF2BP3 level via miR-142-5p inhibition to elevate the progression of oral cancer via an EMT mechanism [103]. Although IGF2BP3 is a target of circRNAs in increasing cancer metastasis, it is not the only mechanism. For instance, the function of circ-0003258 in prostate tumor has been shown to be oncogenic as it induces EMT to elevate cancer metastasis. Circ-0003258 affects two distinct molecular pathways to increase prostate tumor metastasis via EMT. Initially, circ-0003258 sponges miR-635-5p to upregulate ARHGAP5 expression, which then elevates cancer metastasis. Subsequently, circ-0003258 interacts with IGF2BP3 to upregulate HDAC4 and to induce ERK along with EMT [71].

Circ-0001666 impairs breast carcinogenesis via sponging miR-620 to upregulate WNK2 [104]. However, circ-0001666 also enhances the progression of lung and thyroid cancers via regulating ETV4 and AGO1, among others [105, 106]. Circ-0001666 acts as an onco-suppressor to regulate the EMT mechanism in colorectal cancer.

"Once miR-576-5p is synthesized in the nucleus, it's shuttled into the cytoplasm via Exportin5, where it acts to diminish PCDH10 expression, consequently promoting the progression of colorectal cancer. In contrast, the back-splicing event between exon 2 and exon 4 in FAM120B pre-mRNA leads to the creation of circ-0001666. This particular circRNA elevates PCDH10 levels by inhibiting miRNA-576-5p. The outcome is a decrease in the 'stemness' of colorectal cancer cells due to the suppression of EMT, which is facilitated by hindering Wnt/β-catenin signaling pathways." [79]. Circ-0001017 is another example of circRNAs with onco-suppressor function in gliomas, which reduce let-7 g-3p level to upregulate NDST3, suppressing EMT [107]. Drawing from these studies, it becomes clear that the circRNA/EMT axis serves as a key regulatory mechanism in cancer metastasis (Table 3; Fig. 4).

CircRNA/EMT axis in chemoresistance and radioresistance

Chemoresistance is an intriguing concept and can develop in two ways, including intrinsic and acquired chemoresistance. Although understanding drug resistance is a key focus in the past decade, the failure of therapy has not been appropriately solved. Non-coding RNAs are regulators of tumorigenesis, and interestingly, circRNAs can determine therapy response in cancer patients. Hsa-circ-0007883 interacts with FUS to increase the FOXR2 stability in developing paclitaxel resistance in ovarian cancer [114]. Exosomal circ-SFMBT2 upregulates TRIB1 via miR-136-5p sponges to induce docetaxel resistance in prostate cancer [115]. Therefore, the association of circRNAs with downstream targets can change the chemotherapy response in cancer [116].

Paclitaxel is an inhibitor of tumor progression and increases polymerization of microtubules to disturb their stability in inhibiting proliferation. COL5A1 upregulation causes paclitaxel resistance [117]. KHDRBS3 increases MIR17HG level to stimulate glycolysis and paclitaxel insensitivity in ovarian tumor [118]. Upregulation of gp96 and HIF-1α can also result in paclitaxel resistance in cancer [119, 120]. Overexpression of circ-0007534 in endometrial tumor results in paclitaxel resistance. The circ-0007534 elevates ZEB2 level via miR-625 inhibition to accelerate EMT and accelerate paclitaxel insensitivity [121]. Docetaxel functions similarly to paclitaxel and prevents the depolymerization of microtubules to suppress cancer. Upregulation of circ-CRIM1 in nasopharyngeal cancer is

Table 2 The circRNAs-associated EMT control

CircRNA	Effect on EMT	Cancer type	Remarks	References
Hsa_circ_0094606	Induction	Prostate cancer	Hsa_circ_0094606 attaches to PRMT1 to mediate M2 polarization of macrophages EMT induction	[76]
Hsa_circ_0013561	Induction	Ovarian cancer	Hsa_circ_0013561 upregulates ANXA2 through miR-23b-3p suppression in EMT induction	[77]
Circ_0087429	Suppression	Cervical cancer	EIF4A3 inhibits circ-0087429 to mediate EMT	[78]
Hsa_circ_0001666	Suppression	Colorectal cancer	Hsa_circ_0001666 increases PCDH10 level through miR-576-5p disruption to inhibit EMT	[79]
Hsa_circ_0006732	Induction	Colorectal cancer	Hsa_circ_0006732 downregulates miR-127-3p to increase Rab3D levels in EMT induction	[80]
Circ_0000799	Induction	Colorectal cancer	Sponging miR-647	[81]
Hsa_circ_0000497 and hsa_circ_0000918	Induction	Ovarian cancer	Hsa_circ_0000497 and hsa_circ_0000918 regulate miRNAs to induce EMT in ascites	[82]
Circ_0001589	Induction	Cervical cancer	Circ_0001589 sponges miR-1248 to upregulate HMGB1 in EMT induction	[83]
Circ-OXCT1	Suppression	Gastric cancer	Circ-OXCT1 increases SMAD4 expression to promote N-cadherin and vimentin levels and reduce E-cadherin levels	[84]
Circ_0003221	Induction	Cervical cancer	Circ_0003221 increases S100A14 level by miR-139-3p inhibition	[85]
CircRNA circ_0001666	Induction	Pancreatic cancer	Downregulation of circRNA circ_0001666 increasing miR-1251 level, while it reduces SOX4 level to impair EMT	[86]
Circ_0058106	Induction	Hypopharyngeal squamous cell carcinoma	miR-185-3p downregulation to induce Wnt2b/β-catenin/c-Myc axis	[87]
Circ-STK39	Induction	Pancreatic cancer	Circ-STK39 inhibits miR-140-3p to increase TRAM2 levels	[88]
Hsa_circ_0009092	Suppression	Colorectal cancer	Hsa_circ_0009092 sponges miR-665 to elevate NLK levels and impairing Wnt/β-catenin axis	[89]

a positive indicator of docetaxel resistance in tumor cells. miR-422a decreases FOXQ1 level to inhibit the EMT and mediate docetaxel sensitivity. However, when expression of circ-CRIM1 increases, it sponges miR-422a to upregulate FOXQ1, induce EMT, and increase the docetaxel resistance [122]. The docetaxel potential in prostate tumor therapy increases upon upregulation of circ-Foxo3 and is related to Foxo3 and EMT suppression, thereby reducing the malignancy of cancer cells [123].

Circ-0003998 is another regulator of tumor progression and can enhance proliferation and invasion in lung tumor via miR-326 inhibition [124]. The function of circ-0003998 in triggering chemoresistance has been evaluated in hepatocellular carcinoma. Circ-0003998 stimulates the EMT to promote tumorigenesis. Additionally, Circ-0003998 reduces miR-218-5p level, which upregulates EIF5A2 [125].Circ-0007022 is present on chromosome 19 and is formed as a result of back-splicing. Circ-0007022 suppresses miR-338-3p to cause radioresistance. Following the inhibition of miR-338-3p by circ-0007022, the levels of NRP1 increased. Two molecular pathways, including PI3K/Akt and EMT, are activated to increase tumor progression and mediate radioresistance [126]. However, only one experiment investigated the function of the circRNA/EMT axis in radioresistance, and more research is required to confirm and expand on the current findings (Fig. 5).

CircRNA/miRNA/EMT axis

Linear RNA molecules do not encode proteins with a length of less than 24 nucleotides, best known as microRNAs (miRNAs). MicroRNAs sequester mRNA to downregulate gene [127]. The expression level of miRNAs changes during cancer progression and can be used as biomarkers. Furthermore, miRNAs can be sponged by lncRNAs and circRNAs [128, 129]. miRNAs demonstrate dysregulation in tumorigenesis and are biomarkers. The malignancy of cervical tumor depends on the high level of circ-000322, a driver of tumor progression via EMT induction. Upregulation of S100A14 leads to EMT induction and cervical cancer progression. The role of circ-0003221 in enhancing cervical tumorigenesis is related to sponging miR-139-3p to stimulate EMT mechanisms via S100A14 upregulation. Knocking down the expression of circ-0003221 is beneficial for impairing cervical cancer progression via EMT suppression [85]. miR-370 is inhibited by SNHG15 in ovarian cancer to increase the progression of tumor cells [117]. miR-370 overexpression elevates the response of ovarian tumor to cisplatin chemotherapy [130].

Restoring expression of miR-185-5p is beneficial in suppressing osteosarcoma malignancy, as miR-185-5p reduces CTSE expression [131]. PCAT6 downregulation of miR-185-5p in osteosarcoma can result in TGF-β signaling activation and tumor cell progression [132]. Circ-001569 is capable of sponging miR-185-5p in osteosarcoma, and this interaction results in upregulation of FLOT2, a factor involved in triggering EMT in cancer cells and thus enhancing tumor progression [133]. In esophageal cancer, the interaction of circRNA and miRNA is beneficial in determining the progression. Hsa-circ-0000277 undergoes overexpression in esophageal cancer, and by reducing miR-4766-5p expression, it paves the way for upregulation of LAMA1 to induce EMT [134]. However, not all circRNAs sponge miRNA to induce EMT and tumor metastasis. Sometimes, circRNAs sponge oncogenic miRNAs to suppress EMT mechanisms. Hsa-circ-001988 reduces miR-197-3p level to suppress EMT and the progression of gastric tumor [135]. Moreover, miR-503-5p overexpression can result in EMT in oral cancer as circ-0072387 inhibits miR-503-3p to decrease its expression, disrupt EMT, and minimize tumor progression [136]. More importantly, the interaction of circRNAs and miRNAs can be affected by upstream mediators in cancer. The biogenesis of circ-DOCK5 is inhibited in esophageal cancer by ZEB1. To prevent circ-DOCK5 biogenesis in esophageal cancer, ZEB1 downregulates EIF4E3 and DOCK5 mRNA levels to affect back-splicing between exon 49 and exon 50. When circ-DOXK5 is inhibited, miR-527-3p expression decreases, resulting in decreased TGF-β secretion. TGF-β overexpression then forms a positive feedback loop with ZEB1 to elevate esophageal cancer EMT induction and progression [137]. Table 4; Fig. 6 summarize the function of circRNA/miRNA interactions in the control of EMT mechanisms.

CircRNAs regulating EMT-TFs in cancers

ZEB proteins

The ZEB family of proteins, which includes ZEB1 and ZEB2, is one of the best-known modulator of EMT. Upregulation of ZEB1 in cancer can lead to tumor metastasis. YTHDF3 increases the expression of ZEB1 and promotes its stability at the mRNA level to enhance breast cancer invasion [146]. Induction of PI3K/Akt signaling by BAG4 leads to an increase in cancer metastasis via ZEB1 overexpression [147]. Furthermore, when the expression of ZEB1 increases, it represses E-cadherin to enhance the mobility of tumor cells [148]. Similarly, ZEB2 functions as an oncogenic factor. ZEB2 down-regulation by miR-518a-5p leads to inhibition of breast cancer progression [149]. Paeonol increases the expression level of miR-126-5p to downregulate ZEB2, thereby decreasing the invasion of lung

Table 3 CircRNA/EMT axis in cancers

CircRNA	Molecular pathway	Cancer type	Remark	Ref
Circ-0082182	miR-411/miR-1205/Wnt	Colorectal cancer	Circ-0082182 stimulates Wnt/β-catenin signaling via miR-411 and miR-1205 sponging in carcinogenesis	[108]
Circ-0001666	miR-1251/SOX4/EMT	Pancreatic cancer	Circ-0001666 upregulates SOX4 via miR-1251 inhibition in EMT acceleration	[86]
Circ-0087429	miR-5003-3p/OGN	Cervical cancer	Circ-0087429 overexpression occurs by EIF4A3 to increase OGN level by miR-5003-3p inhibition in EMT suppression	[78]
Circ-0004913	miR-184/HAMP	Hepatocellular carcinoma	Circ-0004913 increases HAMP level via miR-184 inhibition in suppressing tumor metastasis	[109]
Circ-0089153	miR-2467-3p/E2F6	Breast cancer	Circ-0089153 upregulates E2F6 via miR-2467-3p inhibition in accelerating tumorigenesis	[110]
Circ-GLIS2	GLIS2	Hepatocellular carcinoma	Circ-GLIS2 increases GLIS2 expression in reducing invasion and decreasing levels of EMT-related markers	[111]
Circ-0006732	miR-127-5p/RAB3D	Colorectal cancer	Circ-0006732 increases RAB3D via miR-127-5p inhibition in EMT induction	[112]
Circ-FOXM1	FOXM1/Wnt	Osteosarcoma	Circ-FOXM1 sponges miR-320a and – 320b Upregulation of FOXM1 in Wnt signaling induction Inducing EMT	[113]

tumor cells [150]. Therefore, both ZEB1 and ZEB2 proteins are inducers of cancer metastasis, and notably, their expression level is controlled by circRNAs in cancer [151]. Circ-VANGL1 upregulation is in favor of enhancing the metastasis of thyroid cancer cells as it affects ZEB1 expression. Depleting circ-VANGL1 with siRNA is advantageous in reducing the metastasis of tumor cells and decreasing their malignancy. Circ-VANGL1 acts as a ceRNA, decreasing miR-194 expression while increasing ZEB1 expression. As EMT-TFs, ZEB1 stimulates EMT to promote the progression and metastasis of thyroid cancer cells [152]. The expression level of ZEB1 is tightly regulated by miRNAs in cancer. miR-429 is a negative regulator of ZEB1, leading to inhibition of hepatocellular carcinoma cells. In contrast, MAPKAPK5-AS1 increases ZEB1 via adsorption of miR-429 to elevate tumor progression [153]. Moreover, miR-144-3p reduces ZEB1 expression to interfere with lung cancer invasion [154]. Therefore, miRNAs and ZEB1 closely interact to regulate cancer metastasis [155].

However, there are studies demonstrating that circRNAs can suppress ZEB1. Circ-ACAP2 is an inhibitor of EMT in head and neck cancer. Circ-ACAP2 sponges miR-21-5p to suppress STAT3 signaling in cancers, lowering ZEB1 expression and impairing EMT [156]. In addition, ZEB2 is regulated by circRNAs in cancer. Circ-0007534 stimulates EMT in endometrial cancer and, in this way, promotes the progression of tumor cells to mediate paclitaxel resistance. Circ-0007534 increases ZEB2 expression via miR-625 inhibition to trigger the EMT mechanism and paclitaxel resistance [121]. According to these studies, circRNAs regulate ZEB1 and ZEB2, and more research is needed to understand ZEB2 regulation by circRNAs in cancers.

Slug and Snail

Upregulation of Slug or Snail has been shown to be a driver for the progression and metastasis of cancer cells. Upon overexpression of Snail in cancer, EMT is induced to enhance metastasis. An experiment has shown that upregulation of circ-0023642 can result in a significant enhancement of metastasis in gastric cancer. Circ-0023642 promotes tumor invasion by increasing N-cadherin, vimentin, and Snail expression while decreasing E-cadherin expression [157]. As a result, circRNAs are regulators of snail and slug EMT mechanisms in cancer.

TGF-β

TGF-β is another important regulator of cancer progression, and abnormal expression can influence cancer metastasis and malignancy. Smad3 is one of the key players of TGF-β signaling. LHPP inhibits phosphorylation of Smad3 to impair

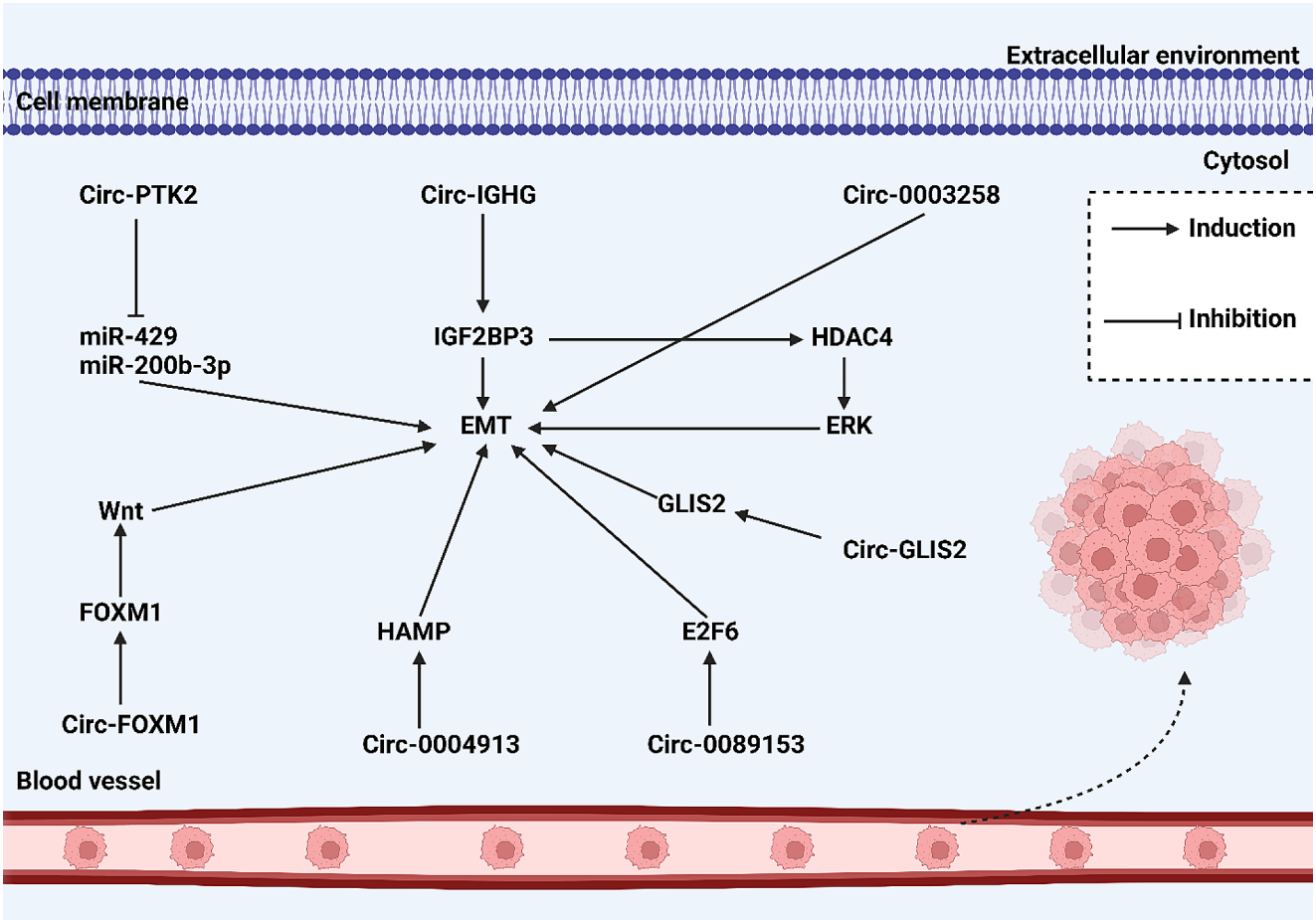

Fig. 4 CircRNA/EMT axis in modulating cancer invasion and metastasis. The circRNAs mainly induce EMT in increasing progression of tumor cells. In some cases, including circ-GLIS2, circ-0089153 and circ-0004913, the circRNAs affect the proteins to regulate EMT. However, in other cases, such as circ-PTK2, the circRNAs sponge miRNAs to affect EMT.

the progression and invasion of colorectal cancer [158]. Furthermore, overexpression of TGF-β has been implicated in inhibiting apoptosis in tumor cells and increasing their survival rate [159]. TGF-β and c-Myc signaling pathways are both involved in gastric tumor cell progression and the induction of EMT mechanisms. The expression levels of TGF-β and c-Myc increase in gastric cancer. Notably, circ-CCDC66 stimulates EMT and accelerates the progression of gastric tumors by promoting TGF-β and c-Myc [160].

Circ-VANGL1 interacts with TGF-β to modulate tumorigenesis. miR-150-5p is an inhibitor of TGF-β signaling to prevent EMT mechanism in melanoma. Circ-VANGL1 sponges miR-150-5p to enhance TGF-β expression, resulting in EMT induction and enhancement of melanoma metastasis [161]. Furthermore, TGF-β can regulate expression of circRNAs to affect EMT mechanism. Activation of TGF-β signaling and phosphorylation of Smad2/3 can result in upregulation of circ-Akt1 which in turn increase Akt1 expression via miR-942-5p inhibition to then promote cancer metastasis and EMT induction [162]. Moreover, TGF-β2 promotes the expression level of circ-PRDM5 to enhance COL1A2 expression via miR-92b-3p inhibition, thereby triggering EMT mechanisms and elevating cancer invasion [163].

Twist

Another important regulator of the EMT mechanism is Twist. Upregulation of Twist can lead to the induction of cancer metastasis via EMT. Silencing EGFR leads to suppression of tamoxifen resistance in breast cancer via reducing Twist expression to impair the EMT mechanism [164]. Twist expression decreases when METTL14 is inhibited, resulting in a reduction in lung cancer progression and invasion [165]. Notably, non-coding RNA molecules can regulate Twist-mediated EMT in cancer [166]. CircRNAs are effective Twist regulators in cancer EMT mechanisms. CircRAB3IP increases the migration and invasion of osteosarcoma cells. miR-580-3p is an inhibitor of Twist1, which reduces the malignancy of osteosarcoma cells. However,

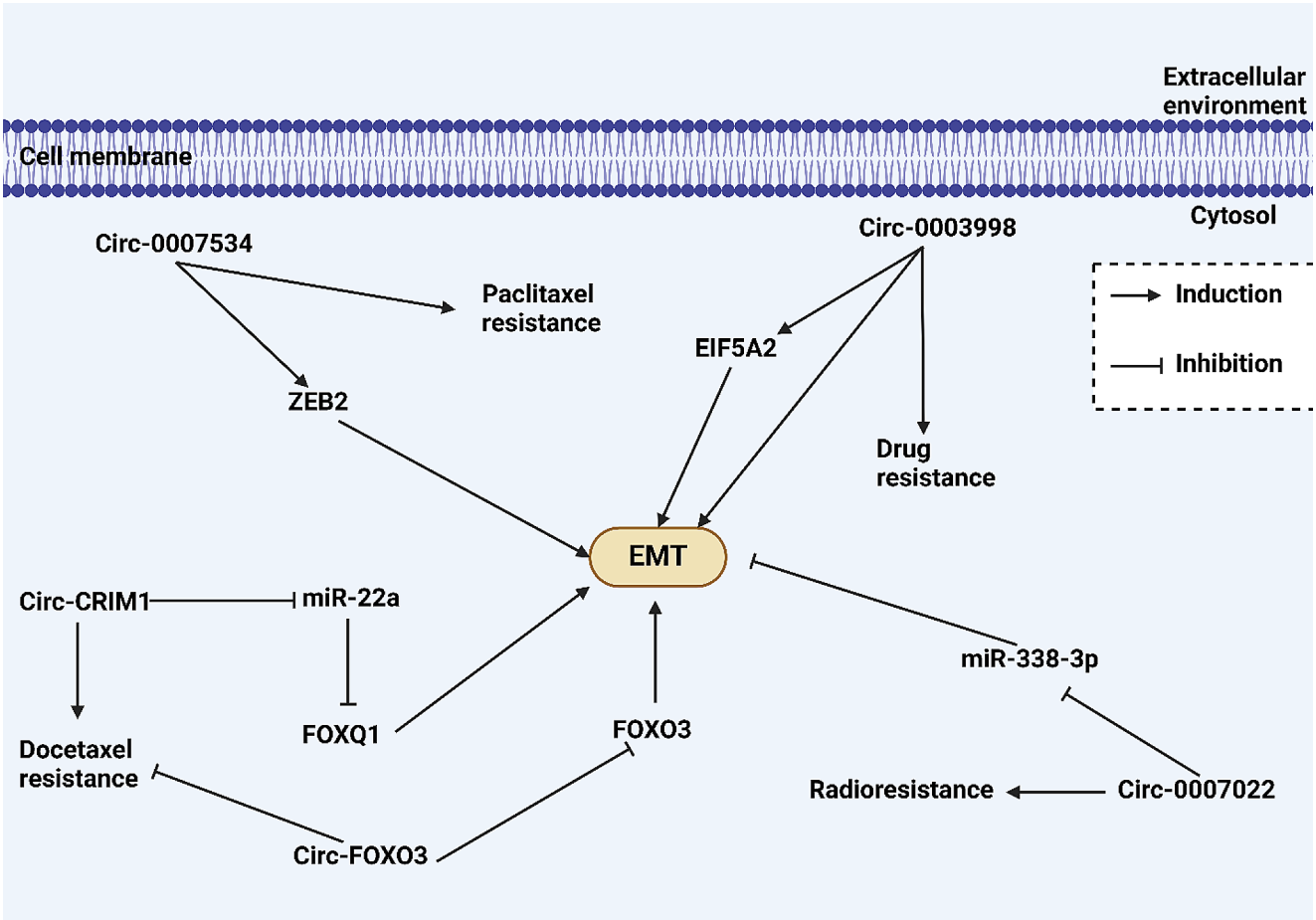

Fig. 5 CircRNA/EMT axis in drug resistance and radio-resistance. The upregulation of ZEB2 by circ-0007534 can induce EMT to mediate paclitaxel resistance. Moreover, circ-0003998 increases EIF5A2 levels to mediate EMT-induced drug resistance. The circ-0007022 inhibits miR-338-3p to mediate EMT-induced radioresistance. The sponging of miR-22a by circ-CRIM1 can induce docetaxel resistance

circRAB3IP reduces miR-580-3p expression to upregulate Twist1 and promote osteosarcoma malignancy [167]. CircRNA PVT1 is upregulated in cancers and stimulates the Wnt4/β-catenin axis to increase carcinogenesis [168]. Silencing PVT1 is advantageous for reducing the progression of lung cancer and enhancing sensitivity to cisplatin [169]. Reducing the expression level of oncogenic circRNAs is beneficial in impairing tumorigenesis. Upregulation of circ-0001681 results in Twist1 overexpression to enhance thyroid cancer metastasis. Silencing circ-0001681 impairs tumor invasion via EMT inhibition. Mechanistically, circ-0001681 increases Twist1 expression via miR-942-5p sponging to induce EMT and cancer invasion [170]. The interesting point is that the expression level of circRNAs can be increased by Twist during cancer. Circ-10,720 overexpression can lead to EMT induction in hepatocellular carcinoma. Twist1 increases the expression level of circ-10,720 to upregulate vimentin, trigger EMT, and enhance cancer invasion [171]. These studies highlight the fact that EMT-TFs are regulated by circRNAs in cancer, and interconnected molecular pathways need to be highlighted in the near future.

CircRNA/EMT axis in different cancers

Brain cancers

One of the malignancies of the central nervous system is glioma, and due to its aggressive nature, the survival rate of patients is 12–14 months. Furthermore, other challenges, including resistance to therapy and recurrence, prevent effective strategies for treatment [172, 173]. Increasing evidence demonstrates the role of circRNAs in regulating the progression of gliomas. Circ-0000215 promotes glioma progression by activating the EMT mechanism, which mediates metastasis. Circ-0000215 reduces the expression level of miR-495-3p to upregulate CXCR2, induce EMT, and pave the way for glioma metastasis [174]. miR-599 is an inhibitor of EMT in esophageal cancer that reduces the progression of

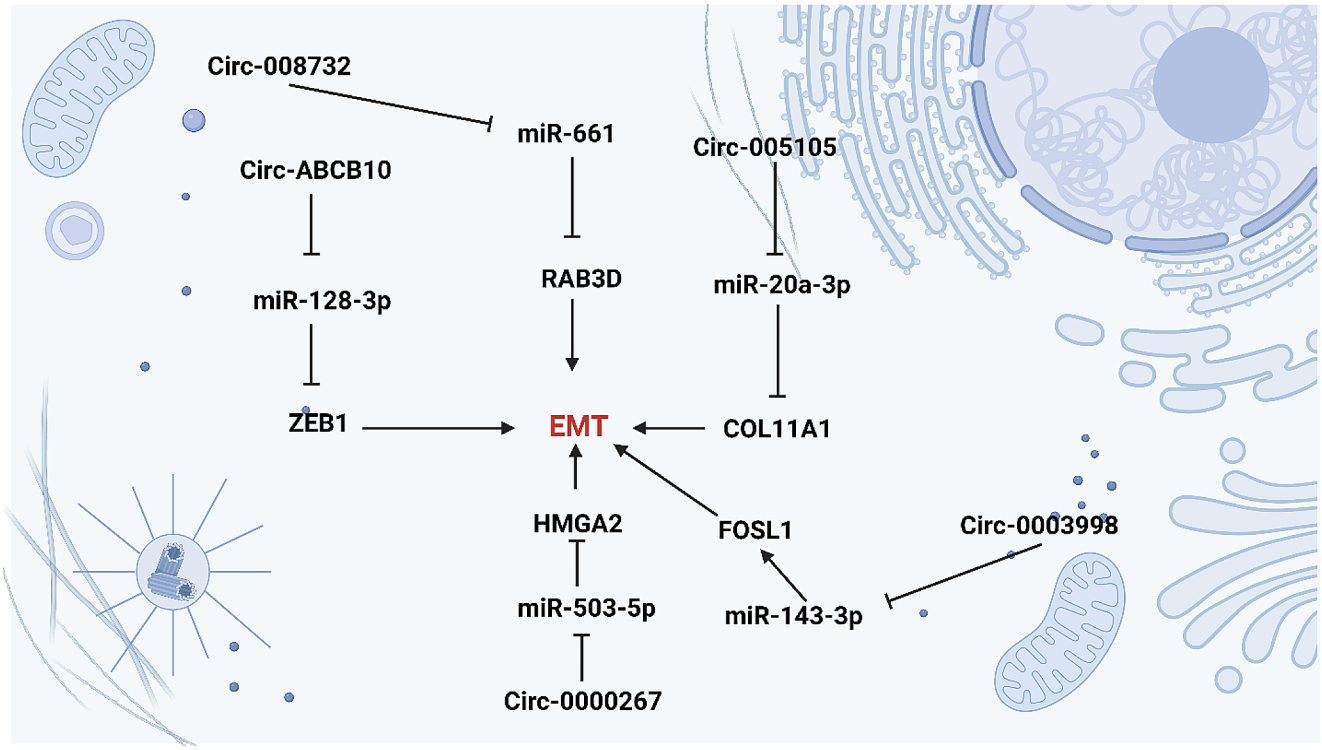

Fig. 6 CircRNA/miRNA/EMT axis in human cancers. The circRNAs mainly function as ceRNA to sponge miRNAs in the control of carcinogenesis. The circ-008732 sponges miR-661 to upregulate RAB3D in EMT induction. Moreover, circ-ABCB10 sponges miR-128-3p to stimulate EMT via ZEB1 overexpression. The circ-0000267 suppresses miR-503-5p to increase HMGA2 levels in EMT. Finally, circ-0003998 stimulates EMT through miR-143-3p inhibition

tumor cells. Circ-0030018 is an oncogenic factor in esophageal cancer and sponges miR-599 to increase the expression of ENAH. The positive association of circ-0030018 with ENAH expression is vital for inducing EMT and increasing tumor cell invasion and metastasis [175]. Like glioma, EMT induction poses a treatment challenge in glioblastoma. MICAL2 promotes glioblastoma progression by inducing EMT mechanisms via TGF-β upregulation [176]. GRP78 stabilization by UBE2T can lead to EMT induction, thereby increasing the invasion of glioblastoma cells [177]. Anticancer agents such as Eriodictyol have been used to reduce ZEB1 expression to suppress EMT in glioblastoma [178]. EMT is commonly induced in glioblastoma. Circ-0001801 stimulates EMT to increase glioblastoma progression. Circ-0001801 enhances the expression level of HMGB3 via miR-628-5p sponging to induce EMT in favor of glioblastoma malignancy [179]. Circ-0067934 also induces EMT in glioblastoma metastasis by inducing PI3K/Akt signaling to mediate EMT and enhance tumor invasion [180].

Gastrointestinal cancers

- Gastric cancer is a life-threatening disease and is the third leading cause of death [181]. Gastric tumor cells show little response to chemotherapy and radiotherapy and manifest a metastatic nature. The malignancy of gastric cancer cells can be enhanced by circRNAs. An experiment has shown that upregulation of circ-101,882 is beneficial in promoting malignancy and the progression of gastric tumor cells. Circ-101,882 prevents apoptosis and enhances invasion of cancer cells. For this purpose, circ-101,882 promotes vimentin, N-cadherin, and Snail levels while decreasing E-cadherin expression to stimulate EMT [182]. One of the changes in the tumor microenvironment that can increase gastric cancer progression is hypoxia, which promotes CD36 expression to mediate peritoneal invasion [183]. The expression level of non-coding RNAs changes under hypoxia in gastric cancer [184, 185]. Hypoxia induces EMT in gastric cancer and promotes the progression of tumor cells. Circ-0081143 enhances the expression level of EGFR via miR-497-5p inhibition. Since miR-497-5p suppresses EMT, it reduces gastric cancer progression. Conversely, down-regulation of circ-0081143 can lead to EMT induction [186].
- The malignancy of the colon or rectum is known as colorectal cancer, which has high mortality rates [187–189]. The prognosis of colorectal cancer patients is poor despite advances in treatment [190, 191]. miR-338-5p

Table 4 Modulation of EMT mechanism by circRNA/miRNA axis in tumors

CircRNA	Molecular pathway	Cancer type	Remark	Ref
Circ-0088732	miR-661/RAB3D	Glioma	Circ-0088732 upregulates RAB3D via miR-661 sponging in EMT induction	[138]
Circ-ABCB10	miR-128-3p/ZEB1	Cervical cancer	Circ-ABCB10 upregulates ZEB1 by miR-128-3p inhibition in accelerating tumorigenesis and EMT	[139]
Circ-0000267	miR-503-5p/HMGA2	Gastric cancer	Circ-0000267 upregulates HMGA2 via miR-503-5p suppression in EMT stimulation	[140]
Circ-0000144	miR-217/EMT	Gastric cancer	Circ-0000144 sponges miR-217 in triggering EMT mechanism	[141]
Circ-CORO1C	miR-138-5p/KLF12	Gastric cancer	Circ-CORO1C upregulates KLF12 via miR-138-5p inhibition in EMT	[142]
Circ-03955	miR-3662/MTDH	Osteosarcoma	Circ-03955 promotes MTDH level via miR-3662 suppression in EMT induction	[143]
Circ-006100	miR-195/GPRC5A	Gastric cancer	Circ-006100 upregulates GPRC5A via miR-195 downregulation in EMT	[144]
Circ-0058106	miR-185-3p/Wnt2b/β-catenin/c-Myc	Hypopharyngeal cancer	Circ-0058106 sponges miR-185-3p in inducing Wnt2b/β-catenin/c-Myc in EMT induction	[145]

expression increases the progression of colorectal cancer and induces EMT. The expression level of circ-0137008 decreases in colorectal cancer samples, which leads to significant increases in the progression of tumor cells. Circ-0137008 suppresses EMT mechanisms in colorectal cancer via miR-338-5p down-regulation [192]. Silencing circ-0026416 can be considered an impediment to the progression of colorectal cancer. Circ-0026416 increases the progression of colorectal cancer via EMT induction. Circ-0026416 reduces miR-545-3p expression, which subsequently leads to an increased expression level of MYO6 to promote tumor metastasis [193].

Gynecological cancers

Cervical cancer is a gynecological malignant tumor with high incidence and death rates [194, 195]. The number of cervical cancer cases in developing countries is higher and comprises up to 85% of the global burden [196]. CircRNAs are considered key players in the progression of cervical cancer and the development of therapy resistance [197, 198]. Both proliferation and invasion of cervical tumor cells are enhanced by circ-MYBL2. However, the function of circ-MYBL2 in increasing cervical cancer metastasis is based on regulating EMT mechanisms. Circ-MYBL2 reduces miR-361-3p expression via sponging to enhance lymph node metastasis in cervical tumors [199]. On the other hand, miR-449a overexpression in cervical cancer can impair the progression of tumor cells. Notably, circ-CDK6 is an onco-suppressor factor, and by reducing miR-449a expression, it suppresses EMT in cervical tumors [200]. Due to the aggressive behavior of ovarian cancer cells and the unfavorable prognosis of patients, patients manifest higher death rates compared to cervical and endometrial cancers [201]. Similar to cervical cancer, the function of circRNAs in regulating the progression of ovarian cancer has been well-documented as they affect various molecular pathways [202–204]. A recent experiment has revealed the role of circ-0001756 in regulating ovarian cancer metastasis via affecting EMT mechanisms. Circ-0001756 promotes the expression level of RAB5A by inducing IGF2BP2 expression. Then, RAB5A stimulates the EGFR/MAPK axis to mediate EMT and increasing the progression and metastasis of ovarian tumor cells [205]. Similar to other tumor types, circRNAs regulate miRNA expression by affecting the progression of ovarian cancer. miR-361-5p is an inhibitor of ovarian cancer progression and reduces the expression levels of c-Met to inhibit the Akt/mTOR axis [206]. Circ-0061140 enhances the progression of ovarian cancer and induces EMT mechanisms. Circ-0061140 decreases miR-361-5p expression to promote RAB1A, which in turn

Table 5 The role of circRNA/EMT axis in regulating progression of cancers

CircRNA	Molecular pathway	Cancer type	Remark	Ref
Circ-0084904	miR-802/MAL2	Cervical cancer	Circ-0084904 promotes MAL2 expression by miR-802 inhibition in EMT induction	[229]
Circ-UBAP2	miR-361-3p/SOX4	Cervical cancer	Circ-UBAP2 sponges miR-361-3p to promote SOX4 expression in EMT stimulation	[230]
Circ-NFATC3	miR-9-5p/SDC2	Cervical cancer	Circ-NFATC3 promotes SDC2 expression by miR-9-5p inhibition in cancer progression development	[231]
Circ-OXCT1	miR-136/SMAD4	Gastric cancer	Circ-OXCT1 increases SMAD4 expression via miR-136 inhibition in EMT stimulation	[84]
Circ-0049447	miR-324-5p/EMT	Gastric cancer	Circ-0049447 inhibits EMT via miR-324-5p sponging in reducing tumor progression	[232]
Circ-0005230	miR-1299/RHOT1	Gastric cancer	Circ-0005230 increases RHOT1 expression by miR-1299 inhibition in triggering EMT mechanism	[233]
Circ-104,916	-	Gastric cancer	Low expression of circ-104,916 in gastric cancer Circ-104,916 inhibits EMT via E-cadherin upregulation and N-cadherin down-regulation	[234]
Circ-0029803	miR-216b-5p/SKIL	Colorectal cancer	Circ-0029803 increases SKIL expression via miR-216b-5p spongin in EMT induction	[235]
Circ-0053277	miR-2467-3p/MMP-14	Colorectal cancer	Circ-0053277 promotes MMP-14 expression via miR-2467-3p inhibition in increasing cancer progression and EMT induction	[236]
Circ-0000395	miR-432-5p/MYH9	Colorectal cancer	Circ-0000395 enhances MYH9 expression via miR-432-5p inhibition in EMT induction	[237]
Circ-0056618	miR-411-5p/PRRG4	Colorectal cancer	EMT induction by Circ-0056618 via miR-411-5p sponging and upregulating PRRG4 expression	[238]
Circ-0065378	miR-4701-5p/TUSC1	Colorectal cancer	Circ-0065378 reduces miR-4701-5p expression to upregulate TUSC1 expression in impairing EMT	[239]
Circ-0001459	miR-6165/IGF1R	Hepatocellular carcinoma	Circ-0001459 increases IGF1R expression via miR-6165 inhibition in EMT induction	[240]
Circ-0101145	miR-548c-3p/LAMC2	Hepatocellular carcinoma	Circ-0101145 increases LAMC2 expression by miR-548c-3p inhibition in triggering EMT	[241]
Circ-0003528	miR-421/MMP-3	Hepatocellular carcinoma	Circ-0003528 increases MMP-3 expression via miR-421 inhibition in EMT induction	[242]
Circ-PRKAR1B	miR-361-3p/FZD4	Osteosarcoma	EIF4A3 promotes Circ-PRKAR1B expression to sponge miR-361-3p in upregulating FZD4 expression and mediating EMT mechanism	[243]
Circ-ITCH	miR-199a-5p/Klotho	Gastric cancer	Circ-ITCH promotes Klotho expression via miR-199a-5p inhibition in impairing EMT	[235]
Circ-HIPK3	miR-326	Breast cancer	Circ-HIPK3 sponges miR-326 in increasing expression level of EMT markers for cancer progression	[244]

triggers EMT-mediated ovarian cancer invasion [207]. Based on these studies, circRNAs are important regulators of EMT in gynecological cancers.

Urological cancers

The lives of men are commonly threatened by a malignant disease known as prostate cancer, which causes 300,000 deaths annually [188]. Many deaths in prostate cancer patients result from metastasis [208]. Patients with metastasis have an overall survival of 42 months [209], whereas patients with progressive metastatic prostate cancer have a survival of 27 months [210]. New technologies have been developed for the treatment of prostate cancer patients, such as nanoplatforms, but prostate cancer is still an incurable disease. CircRNAs are potential regulators of prostate cancer progression, affecting various molecular pathways [71, 210, 211]. Furthermore, accumulating data emphasizes the role of EMT as an inducer of prostate cancer invasion [212]. The function of circ-0004296 significantly reduces the metastasis of prostate cancer cells. Since EMT is an inducer of prostate cancer invasion, it is regulated by circ-0004296. EIF4A3 interacts with circ-0004296 to suppress nuclear translocation of ETS1, leading to impairment of prostate cancer invasion via EMT suppression [213]. Overexpression of circ-0030586 in prostate cancer can lead to induction of EMT, which enhances the invasion of tumor cells [214]. On the other hand, induction of Akt signaling can result in an increase in the progression of prostate cancer [215, 216]. Circ-0030586 stimulates PI3K/Akt signaling to induce EMT and enhance the invasion and metastasis of prostate tumor cells. This is mediated by E-cadherin downregulation and Twist upregulation [214]. Therefore, the circRNA/EMT axis is a regulator of prostate cancer invasion. The delineation of molecular pathways that can be targeted for treatment of this malignant disease warrants further research [217, 218].

Another malignancy of the genitourinary tract is bladder cancer, with increasing morbidity and mortality around the world [201]. Despite using chemotherapy, radiotherapy, and surgery, the 5-year survival rate of bladder cancer patients is low and has a high economic burden [219, 220]. New therapeutic approaches such as nanotheranostics have been developed for bladder cancer. However, it is highly recommended to focus on the underlying molecular pathways involved in bladder cancer progression. The expression level of circRNAs changes during bladder cancer development and progression. Besides, the metastasis of bladder cancer cells is highly dependent on the activation of the EMT mechanism [221–223]. The interaction of circRNAs with EMT in bladder cancer is important. Circ-BIRC6 is involved in enhancing the progression and metastasis of bladder tumor cells, and its depletion is key in reducing tumor malignancy. Circ-BIRC6 increases the expression level of XBP1 by inhibiting miR-495-3p to enhance the metastasis of bladder cancer cells via EMT induction. As a result, silencing circ-BIRC6 is advantageous in reversing EMT in bladder tumors [224]. In fact, the malignant behavior of bladder cancer cells is mediated via EMT induction. Circ-0006948 contributes to the progression of bladder tumor cells by reducing E-cadherin and increasing N-cadherin, vimentin, and β-catenin levels to stimulate EMT [224]. One of the key inducers of the EMT mechanism in cancer is HMGA2. HMGA2 stimulates Wnt/β-catenin signaling is activated by HMGA2 to mediate EMT and promote the progression of gastric tumor cells [225]. In bladder cancer, upregulation of HMGA2 leads to EMT induction, which enhances the progression of tumor cells. Notably, circ-0000658 promotes the expression level of HMGA2 via miR-498 inhibition to facilitate tumorigenesis in bladder cancer [226]. Therefore, the circRNA/EMT axis is a promising target in bladder cancer therapy (Table 5) [227, 228].

Conclusion and remarks

Cancer metastasis involves the migration of tumors from their original location to different organs, where they establish new growths. This journey necessitates breaking away from adjacent tissue and entering the circulatory system. Elevated motility and aggressiveness in cancer cells correspond to heightened rates of metastasis. One of the problems of metastasis is related to the diffusion of cancer cells into distant parts of body, challenging eradication of cancer cells. EMT induction is one mechanism facilitating this spread. As detachment of a number of cancer cells from other parts of colony is required for metastasis, the EMT can increase motility of tumor cells to facilitate this process. This paper delves into the influence of EMT-associated pathways in cancer, particularly highlighting the role of epigenetic factors such as circRNAs in modulating EMT. The dysregulation of epigenetic factors in cancer is a common feature and the researchers have focused on understanding the association between epigenetic alterations and EMT in context of cancer progression and EMT. EMT significantly boosts the migratory capabilities of tumor cells, a fact supported by studies across various types of cancers such as those affecting the brain, gastrointestinal tract, reproductive system, urinary system, and blood. It should be noted that function of EMT in cancer is versatile and it is beyond regulation of metastasis and can affect cancer therapy resistance and mediate immunosuppression. Most crucially, circRNAs serve as powerful modulators of EMT pathways in these diverse cancer types. Targeting EMT directly or adjusting

the expression levels of circRNAs emerge as two effective approaches for cancer treatment, with the potential to reduce metastatic spread and improve both patient survival rates and prognoses. Since EMT is a reversible process, targeting related circRNAs can significantly change the progression of cancer cells. In exploring the relationship between circRNA and the EMT axis in cancer, two crucial dimensions emerge: metastasis and responsiveness to treatment. On one hand, circRNAs have the ability to either trigger or suppress EMT processes, thus influencing the invasive capabilities of cancer cells. On the other hand, the regulation of EMT by circRNAs plays a key role in determining how cancer cells react to therapeutic interventions. When circRNAs promote EMT, they essentially bolster the malignant properties of tumors, setting the stage for resistance to treatment. Conversely, suppressing EMT through circRNAs can increase a tumor sensitivity to both drug and radiation therapies. Yet, circRNAs are not confined to modulating EMT directly; they can also affect other signaling pathways. A primary function of circRNAs in this context is their ability to sponge miRNAs, thus affecting EMT processes in cancer. Consequently, the circRNA/EMT axis serves as a promising target for therapeutic interventions. EMT-related transcription factors such as ZEB proteins, TGF-β, Twist, and Slug can also be influenced by circRNAs, impacting both the metastasis and severity of cancer. Preliminary studies suggest that circRNAs are pivotal in controlling EMT in cancer, and future research may well center on their potential as biomarkers for treatment outcomes and long-term prognosis in cancer patients. Although significant efforts have been made in understanding the function of circRNAs in regulating EMT in cancers, there are still some limitations to be explored in the future studies. A number of anti-cancer compounds have shown potential in the inhibition of EMT. However, the studies should focus on the compounds regulating circRNA/EMT axis. Moreover, the genetic tools, specially CRISPR/Cas9 system should be introduced for circRNA/EMT axis regulation in human cancer therapy. One of the most promising limitations is lack of emphasizing on nanoparticles for targeting circRNA/EMT axis to impair metastasis and invasion of cancer cells.

The pre-clinical studies provide the valuable insights regarding the metastasis of tumor cells mediated by EMT and then, the function of circRNAs in the modulation of EMT-associated metastasis. Based on the estimates, up to 90% of cancer-related deaths in patients are due to the metastasis. In fact, the metastasis allows the tumor cells to diffuse into various parts of body and develop new colonies that further can proliferate and improve the survival of tumors. Therefore, the modulation of metastasis can be of high importance in clinical level. Since circRNAs can mainly affect metastasis through EMT regulation and their stability is high, they can be utilized as diagnostic and prognostic tools in patients. The changes in the circRNAs in serum or exosomal serum can provide a non-invasive method for the metastasis prediction in patients. In addition to prognostic and diagnostic tool, the circRNAs regulating EMT mechanism can be considered as valuable targets in cancer therapy. However, the drugs have poor ability in the regulation of circRNA regulation and therefore, it is suggested to apply the genetic tools to regulate circRNA expression in cancer therapy.

Author contributions M.A and M.Z developed the idea, designed outline and collected papers. P.T, N.N, M.T, M.Z and M.A wrote the paper and prepared the first draft. A.R.A critically edited the paper. J.D revised the paper, drew the figures and improved English editing.

Declarations

Conflict of interest The authors declare no conflict of interest.

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