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Non-coding RNAs in epithelial-mesenchymal transition of renal cell carcinoma (Review)

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Abstract. Renal cell carcinoma (RCC) is a malignant tumor originating from the epithelial cells of the renal tubules. RCC has a high propensity for distant metastasis, complicating clinical management due to the paucity of effective post-metastatic therapeutic strategies and the associated poor prognosis. Epithelial-mesenchymal transition (EMT) is a biological process in which cells switch from epithelial to mesenchymal characteristics. RCC cells undergoing EMT exhibit a higher grade of malignancy with enhanced invasiveness and metastatic capabilities, thereby markedly promoting the tendency for distant metastasis. Non-coding RNAs (ncRNAs) are a group of functional RNAs that are not translated into proteins. ncRNAs serve key roles in RCC progression and one of the key mechanisms involved is through regulating the EMT process. The present study reviews the research on ncRNAs regulating EMT in RCC and their future clinical applications, highlighting their notable potential as novel diagnostic biomarkers and therapeutic targets to combat metastatic RCC in the future.

Contents

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1. Introduction

Renal cell carcinoma (RCC) is the 14th most frequently diagnosed cancer during 2022, Globally in 2022, RCC accounted for an estimated 434,000 newly diagnosed cases, corresponding to age-standardized incidence rates of 5.9 per 100,000 males and 3.0 per 100,000 females (1). A major clinical challenge in RCC is its high metastatic potential. It has been reported that ~30% of patients have distant metastasis at the time of the first diagnosis and the most common sites of metastasis are the lungs, bones, liver and brain (2). The prognosis for patients with metastatic RCC is generally unfavorable, therefore suggesting the key clinical importance of understanding the metastatic mechanisms in the development of effective therapeutic strategies for RCC in the future. RCC originates from the epithelium of the proximal convoluted tubule and accounts for 80-90% of kidney cancer cases (3). The etiology of RCC is not fully understood and the risk factors that can be identified include smoking, obesity, hypertension, chronic kidney disease and certain hereditary diseases, such as von Hippel-Lindau (VHL) disease and hereditary papillary renal carcinoma (4). Understanding these mechanisms is key for developing targeted therapies to improve patient outcomes.

The epithelial-mesenchymal transition (EMT) is a fundamental biological process, by which epithelial cells organized in tight junctions can transform into mesenchymal cells with increased motility and invasiveness. Through this process, RCC cells acquire mesenchymal stem cell-like features, which enhance their metastatic potential and invasive capacity, thereby facilitating entry into the bloodstream and colonization of distant organs to form secondary tumors. Furthermore, EMT has been implicated in drug resistance (5,6) and serves a key role in renal fibrosis (7), which is a common pathological manifestation of chronic kidney disease and is an independent risk factor for RCC. In summary, EMT is one of the primary mechanisms of distant metastasis in RCC and its activation is frequently associated with poor prognosis.

Non-coding RNAs (ncRNAs) are functional RNA molecules that do not encode proteins. Although a limited number of ncRNAs have recently been reported to encode peptides or proteins, the majority of these RNAs perform their biological functions through other functions (8,9). Major types of ncRNAs include microRNAs (miRNAs/miR), long ncRNAs (lncRNAs), circular RNAs (circRNAs), small interfering RNAs (siRNAs) and small nucleolar RNAs (snoRNAs). ncRNAs serve key roles in regulating gene expression and are involved in diverse biological processes, including growth, development, organ function and EMT. ncRNAs are reported to be associated with various human diseases such as cardiac hypertrophy and spinal motor neuron disease (10), particularly cancer, including RCC (11). Decades of research have reported that ncRNAs can regulate EMT and affect the occurrence, progression and metastasis of RCC through multiple pathways (12-15). For example, downregulation of the miR-200 family promotes EMT and enhances the invasive and metastatic potential of cancer cells (16).

Unlike previous reports that have only partially addressed the roles of individual ncRNA species in EMT (17) of miscellaneous cancer types like breast cancer (18) and colorectal carcinoma (19), to the best of our knowledge, the present review introduces the first integrated analysis of miRNAs, lncRNAs, circRNAs, transcribed-ultra conserved regions and pseudogenes specifically within RCC context By synthesizing evidence published until March 2025, the present review reports an updated regulatory landscape that highlights ncRNA crosstalk, most notably miRNA-lncRNA-circRNA axes, and clarifies how these interactions drive both EMT and emerging therapy resistance (20,21). Furthermore, the present review translates these mechanistic insights into clinically actionable prospects, notably evaluating the diagnostic accuracy of circulating ncRNA signatures and the therapeutic potential of circRNA-based vaccines together with exosome-directed interventions, aspects that previous reviews have, to the best of our knowledge, rarely contemplated (22,23).

Therefore, the present review comprehensively summarizes current advances in understanding how ncRNAs regulate EMT in RCC and explores their clinical potential as diagnostic biomarkers and therapeutic targets to improve the prognosis of patients with RCC in the future.

2. Literature search strategy

A systematic literature search was conducted using the PubMed database (https://pubmed.ncbi.nlm.nih.gov) to identify all relevant studies published up to March 2025. The search strategy was designed to encompass three key concepts: ncRNAs, RCC and EMT. Medical Subject Headings (MeSH; https://www.ncbi.nlm.nih.gov/mesh) terms were primarily used to ensure retrieval of high-quality, relevant studies.

The core search strategy that yielded the most comprehensive results was: ['RNA, Untranslated' (Mesh)] AND 'Carcinoma, Renal Cell'(Mesh) AND 'Epithelial-Mesenchymal Transition' (Mesh). This search returned 88 results. These results were sorted by publication date to prioritize the most recent evidence. To ensure comprehensiveness, a broader search without the EMT term ['RNA, Untranslated' (Mesh)] AND 'Carcinoma, Renal Cell' (Mesh) was also executed, which returned 1,501 results. Furthermore, a filter for systematic reviews was applied to the core search string, which returned 0 results, confirming the novelty of the synthesis approach in the present review. The reference lists of all retrieved articles and relevant reviews were manually screened to identify any additional publications that the electronic search might have missed.

Inclusion criteria for the studies were as follows: i) Original research articles or reviews focusing on ncRNAs regulating EMT in RCC; and ii) studies published in English.

The exclusion criteria were as follows: i) Studies not associated with RCC; ii) studies not investigating EMT or ncRNAs; and iii) conference abstracts, editorials and letters without original data.

Due to the predominantly mechanistic nature of the studies reviewed, which address molecular rather than clinical endpoints, an objective evidence hierarchy analogous to that employed in large-scale clinical research could not be rigorously applied; therefore, formal evidence grading akin to meta-analytical methodology was not feasible. Although the present review is structured as a narrative review rather than a systematic review or meta-analysis, the present review adopted a comprehensive search strategy with clearly defined exclusion criteria to minimize selection bias. The present analysis incorporated all relevant studies identified by the search, with the exception of retracted publications. Therefore, it can be considered that the potential for selection bias in the present review is minimal. However, the present review acknowledges that the scope and emphasis of the synthesis may be influenced by the current research focus within the field, which inherently shapes the available evidence.

3. Overview of EMT

EMT is a biological process in which epithelial cells undergo morphological and functional transformation into mesenchymal cells. EMT underlies key biological processes such as embryonic development and wound healing, and also serves a key role in the metastasis of malignant tumors (24).

Epithelial cells are usually present in the superficial layers of the skin or lumen, such as the small intestinal epithelium, lung epithelium and renal tubular epithelium. Common features of epithelial cells include abundant intercellular connections, intercellular communication through tight junctions and desmosomes and adhesion to each other and tightly latch onto the basement membrane (25). In cancer, epithelial cells lose their tissue structure and cell polarity, which suppress cancer malignancy by controlling asymmetric cell division and the integrity of the apical junctional complex (26). The main biomarkers of epithelial cells are E-cadherin, β-catenin and other key proteins for inter-epithelial cell junctions and epithelial cell adhesion molecule (27). By contrast, mesenchymal stem/stromal cells are extensively distributed in various types of tissues, including bone marrow, adipose and blood. These cells are non-polarized, often exhibit an irregular morphology and are loosely arranged with connections mediated by cytoplasmic protrusions. They also possess certain stem cell properties such as self-renewal (28), CSC-marker expression (29), multi-lineage potential (28) and enhanced tumorigenicity (30). The main markers of mesenchymal stromal cells include N-cadherin and vimentin (VIM) (31).

The EMT process in tumors typically does not occur spontaneously but is triggered by various internal and external factors, including growth factors such as fibroblast growth factor (FGF), epidermal growth factor and hepatocyte growth factor. Furthermore, several signaling pathways, including the TGF-β, Wnt/β-catenin, NF-κB, Notch and PI3K-AKT pathways, can regulate EMT (32). The regulatory network of EMT is highly complex, involving multiple transcription factors [for example, Twist, Snail and zinc finger E-box binding homeobox (ZEB)], ncRNAs and epigenetic factors such as EZH2 (33) and HOTAIR. Numerous studies have demonstrated that ncRNAs serve a notable role in regulating the EMT process in cancer (8,10,11).

During EMT, epithelial cells detach from the basement membrane and acquire a partial mesenchymal phenotype to varying degrees, entering an intermediate state between epithelium and mesenchyme. This transition endows cells with enhanced invasive and migratory capabilities. Throughout this process, cells undergo multiple changes, including cytoskeletal remodeling and downregulation of adhesion molecules. Morphologically, epithelial cells transform from a homogeneous, tightly packed structure to various irregular shapes, such as spindle-like and elongated forms. The apical-basal polarity of cells is lost and the cytoskeleton shifts to be dominated by VIM, a wave-like protein. These changes confer a stronger capacity for locomotion and migration, facilitating entry into the bloodstream and subsequent colonization of distant organs (34). However, there is ongoing debate regarding the necessity of the EMT process for tumor metastasis. Some studies suggest that EMT may not be key to metastasis but can markedly enhance chemoresistance. For instance, research using spontaneous breast-to-lung metastasis models and genetically engineered mouse models of pancreatic ductal adenocarcinoma has indicated that EMT is not a prerequisite for metastasis but can contribute to drug resistance in tumor cells (5,35). These findings highlight the complex role of EMT in tumor biology, where its primary function may extend beyond facilitating metastasis to enhancing therapeutic resistance. The resistance mechanisms associated with EMT are considered to involve increased drug efflux, reduced cell proliferation and the evasion of apoptosis signaling pathways (36). Furthermore, numerous clinical studies have reported that EMT is associated with immunosuppression within the tumor microenvironment (TME), with immune cells in the TME facilitating the progression of EMT in tumor cells (37-39). EMT transcription factors (EMT-TF) such as Twist, Snail and ZEB are activated, leading to the accumulation of immunosuppressive cells within the TME (40). Furthermore, EMT-TF inducers, including TGF-β, also contribute to the immunosuppressive milieu of the TME (41). Therefore, it is widely recognized that the EMT process enables cancer cells to acquire stem cell-like properties, which not only promote the proliferation of metastatic foci but also increase resistance to targeted therapies and immunotherapy (42). The major regulatory mechanisms governing EMT and the functional roles of the ncRNAs highlighted in this review are schematically depicted in Fig. 1.

Therefore, the EMT process represents a key mechanism by which cancer cells gain increased invasiveness and metastatic potential. Numerous studies have demonstrated that the cell populations in advanced epithelial tumors and metastatic cancer exhibit varying degrees of mesenchymal characteristics when compared with early-stage cancer (24,43), suggesting that epithelial-to-mesenchymal transition is a key step and hallmark event in cancer metastasis. Furthermore, EMT is a reversible process and cells can undergo reversion to an epithelial phenotype through the mesenchymal-to-epithelial transition (MET). This MET process after metastasis may facilitate the colonization of tumors in distant organs (7).

4. Regulatory mechanisms of ncRNAs

There are various types of ncRNAs, such as miRNAs, lncRNAs, circRNAs, siRNAs, transfer RNAs, ribosomal RNAs, snoRNAs and small nuclear RNAs. However, due to the extensive research on the regulatory roles of miRNAs, lncRNAs and circRNAs in RCC, the present review primarily focused on their roles. As shown in Fig. 2, several ncRNAs influence the progression of renal cancer by regulating the EMT process. miRNAs constitute the hub of this regulatory network; all other ncRNAs exert their effects principally by modulating these miRNAs, whereas select circRNAs and lncRNAs can additionally regulate the EMT programme directly in the absence of a downstream miRNA intermediate.

miRNAs. miRNAs are a family of single-stranded ncRNA molecules, ~22 nucleotides in length. These small RNAs are ubiquitously present in eukaryotes and primarily function in regulating gene expression in plants, animals and humans. Dysregulation of miRNAs has been observed in nearly all types of cancer cells such as A549 (44) and 786-O (45), highlighting their key role in cancer pathogenesis (46).

The primary biological function of miRNAs is to regulate post-transcriptional gene expression. A single miRNA can regulate multiple mRNAs, while several miRNAs can target the expression of a single mRNA, creating a 'many-to-many' relationship. miRNAs interact with argonaute and other functional proteins to form the miRNA-induced silencing complex, which is key to their function (47). miRNAs can influence mRNA translation through several mechanisms. If a miRNA is complementary to its target mRNA, it will induce direct cleavage of the transcript. This mechanism is common in plants but rarely occurs in animals and humans, as the complementarity between miRNAs and target mRNAs is often insufficient. In animals and humans, miRNAs typically exert their effects by binding to sequences in the 3'-untranslated region of mRNAs, thereby preventing ribosome-mediated translation or promoting mRNA destabilization (48). Occasionally, miRNAs directly enter the nucleus and enhance the expression of target genes. In addition, miRNAs can interact with other ncRNAs, such as circRNAs, lncRNAs and other miRNAs (49).

lncRNAs. lncRNAs are a class of ncRNAs typically longer than 200 nucleotides. Most of the lncRNAs possess an mRNA-like structure, including a 5'-end cap, a poly(A) tail and exon-intron

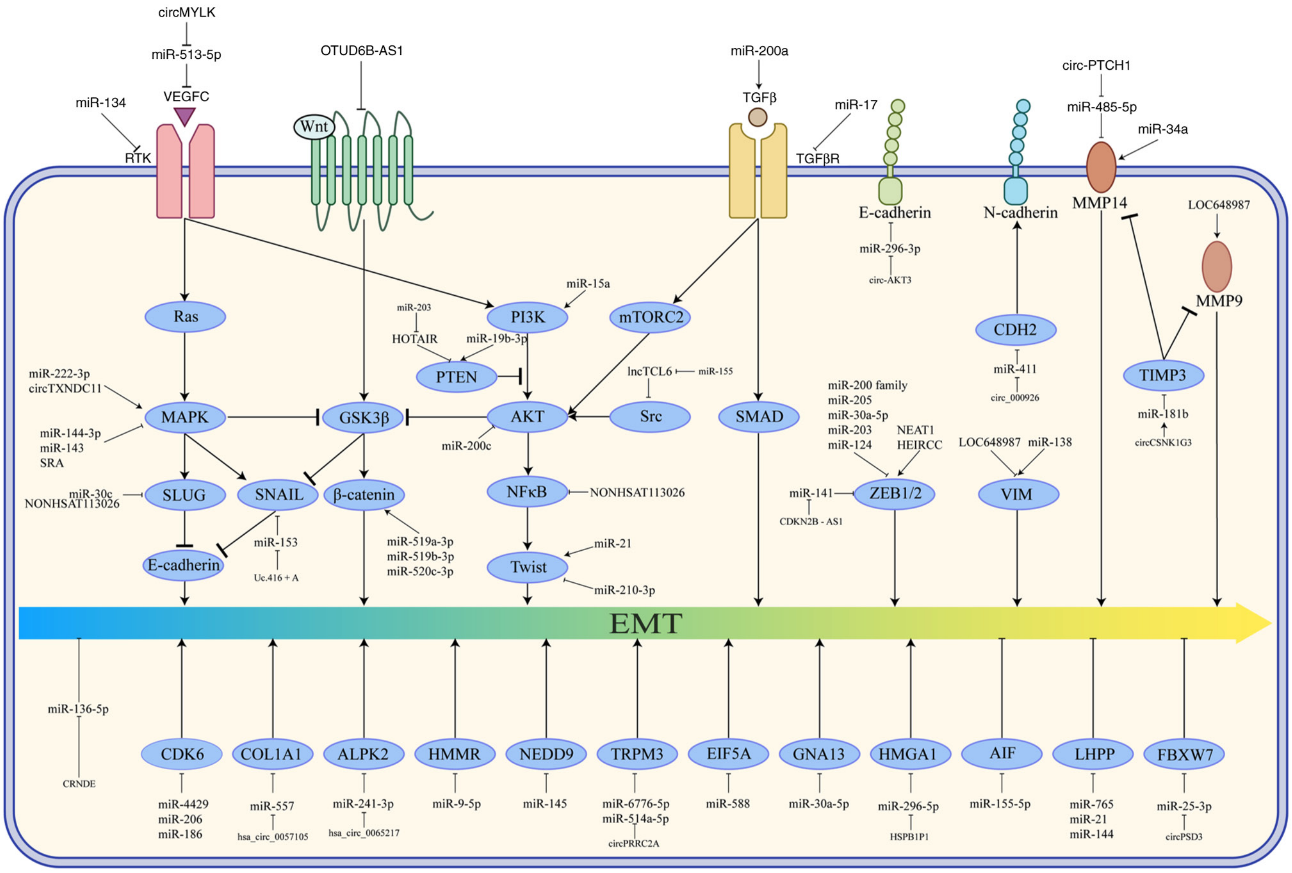

Figure 1. Regulatory mechanisms of EMT progression associated with ncRNA in RCC. A complex regulatory network of ncRNAs modulates EMT in cancer cells through selective activation or inhibition of key signaling pathway components. →, promotion; ⊥, inhibition; EMT, epithelial-mesenchymal transition; ncRNA, non-coding RNA; RCC, renal cell carcinoma; miRNA, microRNA; circRNA, circular RNA; HOTAIR, HOX transcript antisense intergenic RNA; NEAT1, nuclear enriched abundant transcript 1; SNHG, small nuclear RNA host gene; CDKN2B-AS1, CDK inhibitor 2B-antisense RNA 1; OTUD6B, ovarian tumor domain deubiquitinase 6B.

organization. However, they generally lack open reading frames of sufficient length to encode proteins, representing a fundamental distinction between lncRNAs and mRNAs. Despite their inability to be translated into proteins, several lncRNAs still exert notable biological functions. lncRNAs are involved in nearly all stages of gene expression, including transcription, post-transcriptional regulation and epigenetic modifications. In cancer cells, lncRNAs regulate genes with specific functions, thereby influencing biological processes such as proliferation, invasion and metastasis. The mechanisms underlying these actions are complex and diverse, including miRNA sponging, RNA-protein scaffolding, recruitment of specific proteins, chromatin remodeling and the production of micropeptides (50,51). lncRNAs can function as competing endogenous RNAs (ceRNAs) when they contain specific miRNA binding sites. Therefore, lncRNAs inhibit the activity of their target mRNAs by sequestering miRNAs (52). Furthermore, lncRNAs modulate transcriptional activation or repression by influencing chromatin topology. Certain lncRNAs can recruit various chromatin-modifying enzymes such as PRC2 and G9a to specific loci or directly bind to chromatin structural proteins (53), thereby altering chromatin structure and influencing gene expression at those sites. A subset of lncRNAs is transcribed from cis-regulatory elements, such as promoters and enhancers, and regulate the expression levels of downstream genes (50).

circRNAs. circRNAs are a class of ncRNAs that form covalently closed continuous loops, with covalent bonds at both ends, thus lacking 3'- and 5'-ends (54). This unique structure grants circRNAs higher stability and makes them more resistant to degradation by ribonuclease R (55,56). Initially, circRNAs were considered byproducts of transcriptional errors, but recent studies have revealed their notable regulatory functions as ncRNAs.

The main mechanisms of circRNA action are as follows: i) circRNAs can inhibit miRNA activity by binding large numbers of miRNAs. A single circRNA may contain multiple miRNA binding sites, allowing it to sequester numerous miRNAs. Once bound, these miRNAs are unable to exert their regulatory effects, thereby influencing their downstream targets. CircRNAs are often referred to as 'molecular sponges' due to this function (57). Since miRNAs typically exert their functions by binding to mRNAs, circRNAs act as ceRNAs, competing with mRNAs for miRNA binding and thereby indirectly regulating gene expression (58). This is the predominant mechanism by which circRNAs function (22).

ii) In addition to miRNA binding, circRNAs can also function as 'protein sponges'. By binding to RNA-binding proteins, circRNAs prevent the proper functioning of these proteins (59). Furthermore, recent studies indicated that certain circRNAs bind to proteins and form circRNA-protein

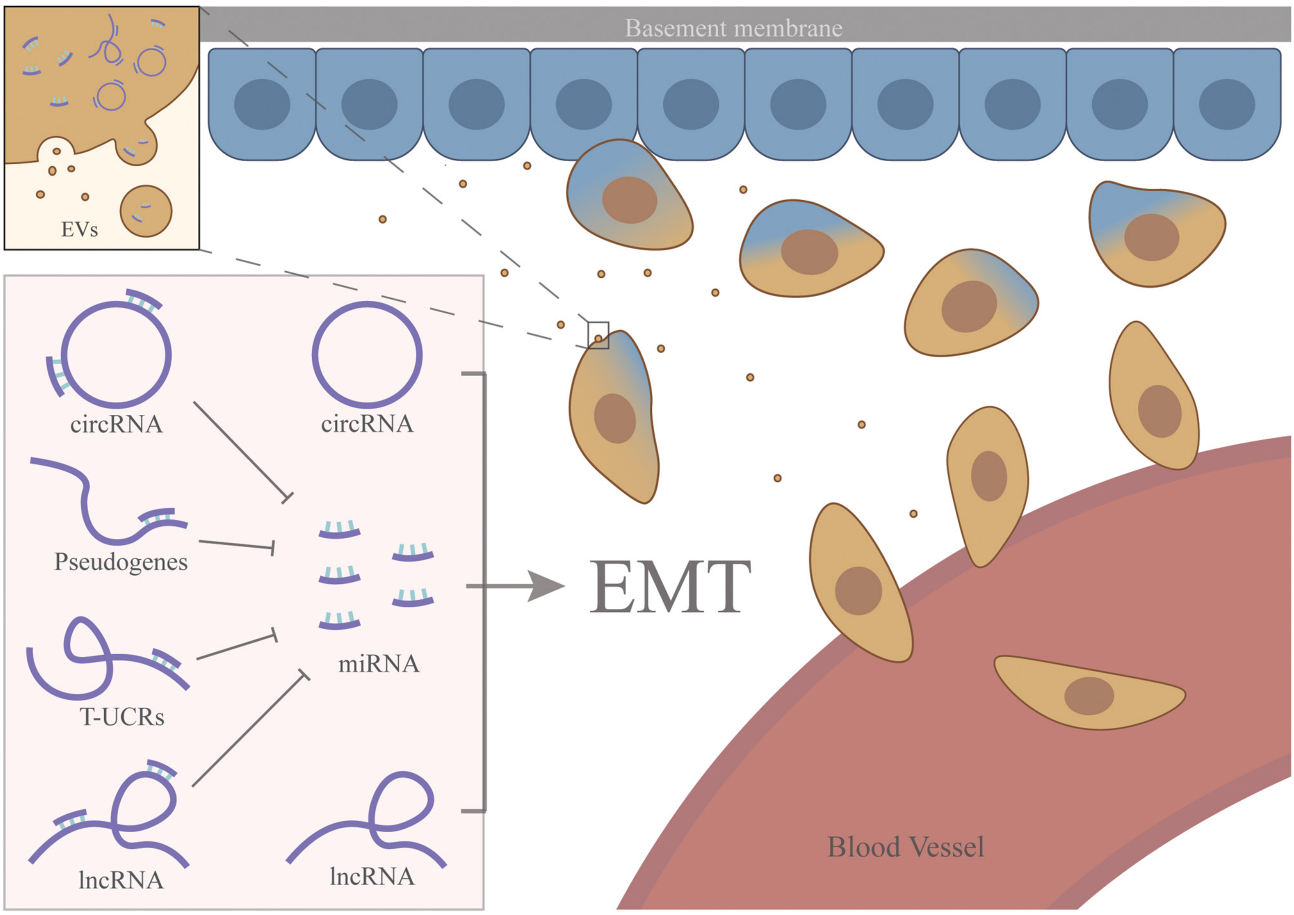

Figure 2. ncRNAs regulate EMT in RCC. ncRNAs regulating the EMT progression and miRNAs are the center of this system. Pseudogenes, circRNAs, lncRNAs and T-UCRs can exert their downstream effects by sequestering miRNAs, which establishes miRNAs as the central hub of this regulatory network. However, certain circRNAs and lncRNAs may also regulate EMT directly, independent of the miRNA pathway. RNAs can be located in the cytoplasm and extracellular vesicles of RCC. Certain tumor cells release various EVs, including exosomes and microparticles containing ncRNAs, which further promote the EMT process and facilitate tumor metastasis. After EMT, the carcinoma cells become more invasive and spread to distant organs through the circulation. EMT, epithelial-mesenchymal transition; ncRNA, non-coding RNA; RCC, renal cell carcinoma; EVs, extracellular vesicles; miRNA, microRNA; circRNA, circular RNA; T-UCRs, transcribed-ultra conserved regions; lncRNA, long non-coding RNA.

complexes (60,61). These complexes can serve as scaffolds facilitating interactions between proteins and mRNAs or other proteins or participate in subcellular protein trafficking. The various ways in which circRNAs interact with proteins warrant further research (19,62).

iii) Although most circRNAs do not encode proteins, a small subset of circRNAs has been reported to serve a role in biological functions through translation into proteins (63).

5. miRNAs in EMT of RCC

Among all ncRNAs, miRNAs are the most extensively studied class, with several regulatory processes of EMT involving the participation of miRNAs. Based on their roles in the EMT process of RCC, miRNAs can be broadly classified into several categories: One category includes miRNAs that are downregulated during EMT, typically functioning as tumor suppressors (6,12,13,64-88). Another category comprises miRNAs that are upregulated during EMT, generally promoting cancer progression. There are also miRNAs with more complex mechanisms of action, which can simultaneously exert both pro-tumor and antitumor effects; these will be discussed separately. Based on the extant literature accessible to date, the preponderance of reported miRNAs fall into the first category.

Tumor suppressor miRNAs. Numerous miRNAs are closely associated with EMT, with the earliest identified miRNA being the miRNA-200 family (miR-200a, miR-200b, miR-200c, miR-141, miR-429 and miR-205) (16,64-66). The roles of the miR-200 family in various cancer types such as lung adenocarcinoma (LUAD) (89), endometrial cancer (EC) (90) and RCC (16) have been extensively documented and they are among the most well-established miRNAs associated with EMT. This family can be categorized into two groups based on the chromosomal regions where it is located: miR-200b/c/429 and miR-200a/141 (91).

It has been observed that all six of the aforementioned miRNAs are markedly downregulated in RCC cells. Reintroducing miRNA clusters consisting of these miRNAs inhibits EMT development. These findings suggest a strong association between these miRNAs and the EMT process (16,64-66). Mechanistically, these miRNAs inhibit the expression of ZEB1/ZEB2 genes, which are direct targets of miR-200c and miR-200b, respectively. ZEB1/2 functions to downregulate E-cadherin and β-catenin expression by reducing inter-epithelial cell adhesion and the interaction between epithelial cells and the basement membrane, thereby promoting EMT (64,66). Under normal conditions, miR-200a, miR-200b and miR-205 work synergistically to suppress ZEB1/2 expression (64,67). The underlying mechanism may be associated with chromosome instability triggered by telomere shortening (92).

It is worth noting that RNAs from this family may have distinct roles in different cancer types. For instance, miR-200c expression is upregulated in pancreatic cancer and non-small cell lung cancer, although the exact mechanism remains to be elucidated. High expression of miR-144 in prostate cancer may also indicate a relatively poor prognosis (93). Numerous other miRNAs exhibit similar behaviors, performing different functions across various tumors, for example, miR-106b-5p is oncogenic in gastric cancer (GC), hepatocellular carcinoma (HCC), and RCC, yet tumor-suppressive in non-small cell lung cancer (NSCLC) and colorectal cancer (CRC) (94). However, in RCC, this family is still considered oncogenic.

In addition to the classical ZEB pathway, other mechanisms of action for the miR-200 family have been identified through studies in RCC. In RCC, the miR-200 family can also modulate the PI3K/AKT pathway by regulating AKT proteins, which in turn influences the production of E-cadherin, thereby affecting the EMT process (66). miR-429 can directly target B-cell-specific Moloney murine leukemia virus integration region 1 (BMI1) and E2F transcription factor 3, leading to their downregulation. BMI1 inhibits E-cadherin expression and the reduced levels of miR-429 in RCC result in the loss of its inhibitory effect, thus promoting EMT (68). A previous study on disease-free survival and overall survival in patients with clear cell RCC (ccRCC) suggested that low miR-429 levels are associated with a relatively poor prognosis (69). In the context of RCC, miR-200a directly targets TGF-β2 to inhibit RCC progression (65). miR-141 has been reported to reverse the EMT process and enhance the sensitivity of tumor cells to hypoxia. Furthermore, miR-141 promotes resistance to sunitinib in tumor cells (6).

Another miRNA family markedly associated with EMT is the miR-30 family (miR-30a, miR-30b, miR-30c, miR-30a-5p, miR-30a-3p, miR-30e and miR-30e-3p), which is also notably downregulated in renal tumors (95). Low expression level of miR-30a-5p, which targets ZEB2, is associated with poor patient survival and, under normal conditions, this miRNA markedly reduces ZEB2 expression. Furthermore, this miRNA may be regulated by lncRNA-deleted in lymphocytic leukemia 2, although this requires further verification (70). Compared with normal renal tissues, miR-30b-5p is downregulated in both RCC cell lines and tissue samples. Upregulation of miR-30b-5p *in vitro* markedly inhibits the proliferation and metastasis of RCC cells. Mechanistically, miR-30b-5p directly targets and inhibits the expression of guanine nucleotide-binding protein α 13, which is upregulated in RCC and promotes tumor cell proliferation and metastasis; its tumorigenic role has been validated in a variety of other cancer types (71). miR-30c is typically an oncogenic miRNA, serving a key role in various cancer types, including endometrial, ovarian and breast cancer (96). In RCC, the downregulation of miR-30c expression reduces its inhibitory effect on Snail family transcriptional repressor 2 (SLUG), leading to increased SLUG expression and excessive production of E-cadherin, which triggers the EMT process. The decrease in miR-30c expression is induced by hypoxia, a process dependent on hypoxia inducible factor (HIF) and VHL deficiency in RCC hampers HIF degradation, resulting in excessive HIF accumulation (97).

Similar to the aforementioned RNAs, miRNAs with inhibitory effects on cancer are typically downregulated in RCC and a notable proportion of them decrease with the progression of tumor stage. Specifically, their expression is lower in advanced and metastatic cancer types compared with early-stage and primary cancer types (6,12,13,64-88). The specific RNA names and targets are presented in Table I.

Certain miRNAs can influence EMT through multiple pathways. An example of this is a study by Han *et al* (72), in which miR-203, previously described as targeting FGF2, was reported to inhibit the EMT process by another mechanism: Inactivation of the PI3K/AKT/mTOR signaling pathway via the inhibition of caveolin-1 (CAV1).

In addition to acting individually, miRNAs can cooperate with each other. Multiple miRNAs can work together to regulate a common target, as seen in the case of miR-124 and miR-203. miR-124 is a key miRNA that targets CAV1 and flotillin 1 to promote ccRCC invasiveness and its downregulation can be a predictor of relatively poor prognosis (98). miR-203 targets FGF2 and reduces tumor invasiveness (99); it is regulated by lncRNA snRNA host gene (SNHG) 14 and HOX transcript antisense intergenic RNA (HOTAIR) and is also considered an oncogene and indicator of poor prognosis in certain studies (13). Both miR-124 and miR-203 have been identified to be downregulated in RCC cell lines, where they have a synergistic effect in regulating EMT, with ZEB2 being their direct target. When miR-124 and miR-203 were overexpressed in RCC cell lines, ZEB2 expression was reduced by 11 and 27%, respectively. Co-overexpression of both miRNAs resulted in a 45% reduction in ZEB2 expression. Co-transfection of miR-124 and miR-203 inhibited the invasion and metastasis of RCC cells more effectively compared with the transfection of either miRNA alone (13). This study suggested that a single RNA may lack efficacy, but a synergistic combination of multiple RNAs can form a regulatory network with notable effects.

miRNAs can also serve a role in intercellular communication. Grange *et al* (100) reported that microvesicles (MVs) derived from $CD105^+$ RCC cells stimulate angiogenesis and the formation of a lung premetastatic niche *in vitro* and *in vivo*. These MVs contain miRNAs involved in tumor progression and metastasis, including miR-19b, miR-29c and miR-151. These miRNAs were reported to be upregulated in renal carcinomas compared with normal renal tissue, although the specific roles of these miRNAs were not further investigated (100). Nevertheless, miRNAs can regulate the metastasis of RCC via extracellular vesicles, as these MVs are released from mesenchymal stem cells, where EMT may serve a role. This was exemplified in the work of Wang *et al* (14), which demonstrated that exosomes derived from ccRCC cancer stem cells (CSCs) had higher expression levels of miR-19b-3p compared with that in normal tissues. This miRNA can promote the EMT process by targeting PTEN, thus facilitating

Table I. EMT-associated miRNAs in RCC.

First author, year	miRNA	Expression	Function: Proliferation	Function: Metastasis	Target	Verified *in vivo*	(Refs.)
Gregory *et al*, 2008	miR-200 family	Down	↓	↓	ZEB1/2	No	(64)
Lu *et al*, 2015	miR-200a	Down	↓	↓	TGFB2	No	(65)
Wang *et al*, 2013	miR-200c	Down	NA	↓	ZEB1 and AKT	No	(66)
Machackova *et al*, 2016; Qiu *et al*, 2015	miR-429	Down	↓	↓	BMI1/E2F3	No	(69,68)
Gregory *et al*, 2008; Xu *et al*, 2018	miR-205	Down	↓	↓	ZEB1/2	No	(64,67)
Yamasaki *et al*, 2012	miR-138	Down	↓	↓	VIM	No	(73)
Berkers *et al*, 2013; Dasgupta *et al*, 2020	miR-141	Down	↓	↓	ZEB, CDKN2B-AS1, cyclin-D1 and cyclin-D2	No	(6,74)
Huang *et al*, 2013	miR-30c	Down	NA	↓	SLUG	No	(97)
Chen *et al*, 2017	miR-30a-5p	Down	↓	↓	ZEB2	Yes	(70)
Liu *et al*, 2017	miR-30b-5p	Down	↓	↓	GNA13	No	(71)
Lu *et al*, 2014	miR-145	Down	↓	↓	ANGPT2 and NEDD9	No	(75)
Lichner *et al*, 2015	miR-17	Down	↓	↓	TGFBR2	Yes	(76)
Liu *et al*, 2015	miR-134	Down	↓	↓	KRAS	No	(77)
Liu *et al*, 2016	miR-144-3p	Down	↓	↓	MAP3K8	No	(78)
Chen *et al*, 2020; Dasgupta *et al*, 2018; Han *et al*, 2020	miR-203	Down	↓	↓	HOTAIR and CAV1	Yes	(13,79,72)
Dong *et al*, 2019	miR-588	Down	↓	↓	EIF5A2	No	(80)
Chen *et al*, 2020	miR-124 and miR-203	Down	↓	↓	ZEB2	No	(13)
Pan *et al*, 2019	miR-4429	Down	↓	↓	CDK6	No	(81)
Guo *et al*, 2020	miR-206	Down	↓	↓	CDK6	Yes	(82)
Guo *et al*, 2020; Wang *et al*, 2021	miR-186	Down	↓	↓	CDK6	Yes	(83,88)
Xu *et al*, 2020	miR-143	Down	↓	↓	ABL2	No	(84)

Table I. Continued.

First author, year	miRNA	Expression	Function: Proliferation	Function: Metastasis	Target	Verified *in vivo*	(Refs.)
Sekino *et al*, 2018	miR-153	Down	↓	↓	Snail	No	(85)
Chen *et al*, 2021	miR-296-5p	Down	↓	↓	HMGA1	No	(87)
Niu *et al*, 2025	miR-9-5p	Down	↓	↓	HMMR	Yes	(12)
Xue *et al*, 2019	miR-296-3p	Up	→	↑	E-cadherin	Yes	(86)
Cao *et al*, 2016; Wu *et al*, 2019	miR-21	Up	↑	↑	HIF-1α	No	(102,103)
Wang *et al*, 2019	miR-19b-3p	Up	↑	↑	PTEN	Yes	(14)
Lyu *et al*, 2020	miR-222-3p	Up	↑	↑	TIMP2 and ERK1/2	No	(104)
Gorka *et al*, 2021	miR-519a-3p, miR-519b-3p and miR-520c-3p	Up	↑	↑	Wnt pathway inhibitors (SFRP4, KREMEN1, CXXC4, CSNK1A1 and ZNFR3)	No	(105)
Lei *et al*, 2021	miR-155-5p	Up	↑	↑	AIF	Yes	(106)
Kulkarni *et al*, 2021	miR-155	Up	↑	↑	lncTCL6	Yes	(15)
Li *et al*, 2021	miR-15a	Up	↑	↑	BTG2, PI3K and AKT	No	(101)
Meng *et al*, 2021	miR-765, miR-21 and miR-144	Up	↑	↑	LHPP	No	(107)
Yoshino *et al*, 2017	miR-210-3p	Up	↓	↓	TWIST1	Yes	(109)
Landolt *et al*, 2017	miR-34a	Up	NA	NA	MMP14 and AXL	No	(108)

NA, not available; ↑, promotion; →, no change; ↓, inhibition; miRNA, microRNA; RCC, renal cell carcinoma; AXL, Axl receptor tyrosine kinase; TWIST1, Twist-related protein 1; LHPP, phospholysine phosphohistidine inorganic pyrophosphate phosphatase; BTG2, B-cell translocation gene 2; AIF, apoptosis-inducing factor; TIMP2, tissue inhibitor of metalloproteinase 2; HIF-1α, hypoxia inducible factor-1α; HMMR, hyaluronan-mediated motility receptor; HMGA1, high mobility group A1; EIF5A2, eukaryotic initiation factor 5A2; SLUG, Snail family transcriptional repressor 2; ZEB, zinc finger E-box binding homeobox; HOTAIR, HOX transcript antisense intergenic RNA; NEAT1, nuclear enriched abundant transcript 1; BMI1, B-cell-specific Moloney murine leukemia virus integration region 1; E2F3, E2F transcription factor 3; GNA13, guanine nucleotide-binding protein α 13; CAV-1, caveolin-1; SFRP4, secreted frizzled-related protein 4; KREMEN1, Kremen protein 1; CXXC4, CXXC finger protein 4; CSNK1A1, casein kinase 1 α1; ZNFR3, zinc and ring finger 3; TGFB2, transforming growth factor beta 2; ANGPT2, angiopoietin-2; NEDD9, neural precursor cell expressed, developmentally down-regulated 9.

distant tumor metastasis. Experiments *in vivo* and *in vitro* have demonstrated that this miRNA markedly enhances the malignancy of ccRCC (14). Furthermore, exosomal miR-15a from adenocarcinoma human nasal (ACHN) cells has been reported to enhance EMT activity and aggravate ccRCC via the B-cell translocation gene 2/PI3K/AKT axis (101).

Several miRNAs have been identified as promoters of EMT in kidney cancer. For instance, miR-138 is downregulated in renal cancer cells and under normal physiological conditions, this miRNA inhibits the synthesis of VIM, a key component of the mesenchymal cytoskeleton. The downregulation of miR-138 facilitates the EMT process in cancer cells (73). Similarly, miR-134 directly targets KRAS, thereby suppressing the ERK signaling pathway, which enhances cell proliferation and inhibits EMT in RCC (77). Furthermore, miR-4429 exerts its effects by inhibiting CDK6 and its downregulation in RCC leads to relative upregulation of CDK6, which promotes tumor cell proliferation, invasion and metastasis, thereby predicting a worse prognosis in patients (81). The mechanisms underlying the EMT-inhibitory roles of certain miRNAs, such as miR-145 and miR-17, remain to be elucidated. The latter may regulate the EMT process through modulation of TGF-β signaling (75,76).

Oncogenic miRNAs. In comparison with cancer-inhibiting miRNAs, the number of identified oncogenic miRNAs is relatively limited in current reports (14,15,86,101-107). miR-21 is known to exhibit oncogenic properties and can promote the formation of ccRCC tumor spheres (102). Other oncogenic miRNAs include miR-34a, although its exact mechanism is not fully understood. miR-34a may exert its effects by regulating MMP14 (108).

However, oncogenic miRNAs that are highly expressed in RCC tissues do not always promote the EMT process. For example, miR-210-3p is highly expressed in RCC cell lines and clinical ccRCC tissues; however, its expression is lower in high-grade and advanced ccRCC with metastasis compared with low-grade and early-stage ccRCC. Knockdown or overexpression of miR-210-3p promoted or suppressed tumor invasiveness, respectively. Furthermore, it was reported that miR-210-3p inhibited the EMT process, as evidenced by changes in cell morphology. Knockdown of miR-210-3p enhanced Twist-related protein 1 expression, promoting tumor metastasis. This study suggested that miR-210-3p is necessary for tumorigenesis and its inhibitory effect on EMT should be relieved in advanced metastatic stages (109).

6. lncRNAs in EMT of RCC

lncRNAs are predominantly oncogenic in RCC (74,79,110-118). For example, lncRNA HEIRCC acts as a positive regulator of EMT by suppressing the production of E-cadherin through the inhibition of ZEB1. This lncRNA is upregulated in RCC and its silencing leads to decreased tumor cell proliferation and increased apoptosis (113).

Several lncRNAs interact with miRNAs. A well-known example is HOTAIR, which has been implicated in various types of cancer like breast carcinoma (119) and prostate cancer (120). In RCC, miR-203 exerts an oncostatic effect by interacting with HOTAIR, inhibiting EMT as well as tumor cell proliferation, invasion and metastasis, as demonstrated in both *in vivo* and *in vitro* experiments (79). Similarly, CDK inhibitor 2B antisense RNA 1 (AS1) is markedly overexpressed in RCC, with its expression increasing from early to advanced stages of the disease. This lncRNA can bind to miR-141 and influence its regulation of cyclin D, subsequently regulating the EMT process (74).

By contrast, certain lncRNAs function through independent mechanisms. For instance, SNHG15 is highly expressed in RCC tissues and cell lines compared with that in adjacent non-tumor tissues and a proximal tubule epithelial cell line. Knockdown of SNHG15 markedly inhibits tumor cell proliferation. SNHG15 promotes the expression of Snail family transcriptional repressor 1, SLUG and ZEB1 through the NF-κB pathway, thereby facilitating the EMT process and promoting invasion and metastasis in RCC (114). Similarly, nuclear enriched abundant transcript 1 (NEAT1) is highly expressed in ccRCC samples and cell lines and is associated with poor patient prognosis (112). Knockdown or overexpression of NEAT1 in ccRCC cell lines markedly inhibits or promotes tumor cell proliferation, invasion and metastasis. Mechanistically, NEAT1 may act by promoting ZEB1, NEAT1 knockdown repressed ZEB1 expression in 786-O and Caki-1 cells, thereby impairing the subsequent epithelial-mesenchymal transition (112). lncRNA Z38 is highly expressed in patients with RCC, with its transcriptional level being higher in late-stage RCC. Z38 promotes tumor invasion and metastasis through the EMT process *in vitro*; however, the upstream and downstream mechanisms remain to be elucidated in further research (111).

However, certain lncRNAs exert antitumor effects (15,121-123). lncRNA NONHSAT113026 is markedly downregulated in RCC and its low expression is associated with poor prognosis. Upregulation of this RNA inhibits tumor cell proliferation *in vivo* and *in vitro* and suppresses the EMT process, reducing invasiveness and metastatic potential. Mechanistically, NONHSAT113026 functions by binding to the 3'-UTR of NF-κB/p50 and SLUG in RCC cells, inhibiting their expression (121). Similarly, lncRNA-ovarian tumor domain deubiquitinase 6B-AS1 exerts its effects by inhibiting the aberrantly activated Wnt/β-catenin pathway in tumors (122).

Due to the complex biological mechanisms of lncRNAs, the targets of certain lncRNAs remain to be elucidated. Certain lncRNAs exert their effects by targeting downstream miRNAs, such as SNHG12 and colorectal neoplasia differentially expressed. Others directly target factors associated with EMT, including high-expressed in RCC and LOC648987. Further research is warranted to elucidate the mechanisms through which these RNAs function. Detailed information on these lncRNAs is provided in Table II.

7. circRNAs in EMT of RCC

As presented in Table III, circRNAs primarily function as miRNA sponges during EMT in RCC. The circRNA-miRNA-gene regulatory axis is commonly observed in circRNA studies (86,124-133). When circRNAs target oncogenic miRNAs, they exert pro-oncogenic effects and are often upregulated in tumor cell lines and RCC tissues. For example, circPRRC2A, by competitively binding to miR-514a-5p and

Table II. EMT-associated lncRNAs in RCC.

			Function					
First author, year	lncRNA	Expression	Proliferation	Metastasis	Target	miRNA target genes/proteins	Verified *in vivo*	(Refs.)
Xiong *et al*, 2016	lncRNA-ATB	Up	↑	↑	NA	NA	No	(110)
Dasgupta *et al*, 2018	HOTAIR	Up	↑	↑	PTEN	-	Yes	(79)
He *et al*, 2017	Z38	Up	↑	↑	NA	NA	No	(111)
Ning *et al*, 2017	NEAT1	Up	↑	↑	ZEB1	-	No	(112)
Xiong *et al*, 2017	HEIRCC	Up	↑	↑	ZEB1	-	No	(113)
Du *et al*, 2018	SNHG15	Up	↑	↑	NF-κB	-	No	(114)
Dasgupta *et al*, 2020	CDKN2B-AS1	Up	↑	↑	miR-141	cyclin-D1 and cyclin-D2	Yes	(74)
Su *et al*, 2021	LOC648987	Up	↑	↑	Vimentin and MMP-9	-	Yes	(115)
Yu *et al*, 2021	SNHG12	Up	↑	↑	miR-30a-3p	RUNX2, IGF-1R and Wnt2	Yes	(116)
Zhang *et al*, 2021	CRNDE	Up	↑	↑	miR-136-5p	NA	No	(117)
Shao *et al*, 2023	RP11-367G18.1 V2	Up	↑	↑	H4K16Ac	-	Yes	(118)
Pu *et al*, 2019	NONHSAT-113026	Down	↓	↓	NF-κB/p50 and SLUG	-	Yes	(121)
Wang *et al*, 2019	OTUD6B-AS1	Down	↓	↓	Wnt/β-catenin	-	Yes	(122)
Zhang *et al*, 2020	SRA	Down	↓	↓	ERK	-	No	(123)
Kulkarni *et al*, 2021	lncTCL6	Down	↓	↓	Src	Src/AKT	Yes	(15)

NA, not available; ↑, promotion; ↓, Inhibition; RCC, renal cell carcinoma; lncRNA, long non-coding RNA; Src, steroid receptor coactivators; SLUG, Snail family transcriptional repressor 2; ZEB1, zinc finger E-box binding homeobox 1; H4K16Ac, histone H4 lysine 16 acetylation; HOTAIR, HOX transcript antisense intergenic RNA; NEAT1, nuclear enriched abundant transcript 1; SNHG, small nuclear RNA host gene; CDKN2B-AS1, CDK inhibitor 2B-antisense RNA 1; OTUD6B, ovarian tumor domain deubiquitinase 6B; RUNX2, Runt-related transcription factor 2; CRNDE, colorectal neoplasia differentially expressed; SRA, SET and ring finger associated protein domain; IGF-1R, insulin-like growth factor-receptor 1; HEIRCC, high-expressed in RCC; ATB, activated by TGF-β.

Table III. EMT-associated circRNAs in RCC.

First author, year	circRNA	Expression	Function		Target	miRNA target genes/proteins	Verified *in vivo*	(Refs.)
			Proliferation	Metastasis				
Zhang *et al*, 2019	circ_000926	Up	↑	↑	miR-411	CDH2	Yes	(126)
Li *et al*, 2020	circMYLK	Up	↑	↑	miR-513a-5p	VEGFC	Yes	(127)
Li *et al*, 2020	circPRRC2A	Up	↑	↑	miR-514a-5p and miR-6776-5p	TRPM3	Yes	(128)
Liu *et al*, 2020	circPTCH1	Up	NA	↑	miR-485-5p	MMP14	Yes	(129)
Yan *et al*, 2021	hsa_circ_0065217	Up	↑	↑	miR-214-3p	ALPK2	No	(130)
Li *et al*, 2022	circCSNK1G3	Up	↑	↑	miR-181b	TIMP3	Yes	(131)
Cen *et al*, 2023	has_circ_0057105	Up	↑	↑	miR-557	COL1A1/VDAC2	Yes	(132)
Yang *et al*, 2021	hsa_circ_101705/circTXNDC11	Up	↑	↑	p-ERK/p-MEK	-	Yes	(134)
Xue *et al*, 2019	hsa_circ_0017252/circ-AKT3	Down	→	↓	miR-296-3p	E-cadherin	Yes	(86)
Xie *et al*, 2022	circPSD3	Down	↓	↓	miR-25-3p	FBXW7	Yes	(133)

↑, promotion; →, no change; ↓, inhibition; RCC, renal cell carcinoma; circRNA, circular RNA; FBXW7, F-box and WD repeat domain containing 7; COL1A1, collagen type I α 1 chain; VDAC2, voltage-dependent anion-selective channel 2; TIMP3, tissue inhibitor of metalloproteinase 3; ALPK2, α protein kinase 2; TRPM3, transient receptor potential melastatin-3; CDH2, cadherin 2.

miR-6776-5p, disrupts their inhibitory effect on the target gene transient receptor potential melastatin-3, resulting in increased expression of this oncogene and promotion of EMT, tumor cell proliferation and metastasis (128). Similarly, circRNAs that act as sponges for pro-oncogenic miRNAs can exert oncogenic effects. For instance, circ-AKT3 upregulates the expression level of its downstream target, E-cadherin, by adsorbing miR-296-3p, thereby inhibiting the EMT process and suppressing RCC cell proliferation, invasion and migration both *in vitro* and *in vivo* (86).

However, circTXNDC11 regulates EMT through direct modulation of the ERK/MEK pathway. In this study, the researchers observed changes in the expression levels of phosphorylated (p)-ERK and p-MEK proteins without involving any miRNA molecules (134). Further studies on how circRNAs exert effects on EMT through other mechanisms are warranted.

Although circRNAs have only recently gained notable research attention, they have been reported to serve key roles in regulating gene expression. Therefore, future research in this area has a lot of potential.

8. Other ncRNAs in EMT of RCC

A number of ncRNAs also contribute to the EMT process in RCC, such as transcribed-ultra conserved regions (T-UCRs) and pseudogenes, which require further investigation.

T-UCRs represent a novel class of ncRNAs, typically located at fragile sites and cancer-associated genomic regions. One such T-UCR, Uc.416+A, which has been reported to be upregulated in gastric cancer and downregulated in prostate cancer, exhibits high expression levels in RCC, particularly in metastatic RCC tissues. Knockdown of Uc.416+A in RCC cells resulted in reduced cell proliferation and migration activity, along with notable changes in EMT biomarker levels. Luciferase reporter assays confirmed that Uc.416+A is directly regulated by miR-153, a miRNA known to promote EMT through Snail. Uc.416+A promotes RCC EMT by binding to and sequestering miR-153, thus preventing its regulatory functions. To the best of our knowledge, this is the first T-UCR confirmed to modulate EMT (85).

Pseudogenes, traditionally regarded as 'junk DNA', share sequence similarity with ≥1 paralogous genes but lack functional protein-coding ability. However, a subset of pseudogenes can regulate gene expression by acting as decoys or ceRNAs (135). For instance, Chen *et al* (87) identified that the pseudogene heat shock protein family B (small) member 1 pseudogene 1 promotes RCC proliferation and metastasis by targeting the miR-296-5p/high mobility group AT-hook 1 axis. This finding has expanded the understanding of the regulatory functions of ncRNAs in RCC.

In certain cases, pseudogenes and T-UCRs have been classified as lncRNAs due to their unique characteristics. However, due to their distinct features, pseudogenes and T-UCRs were chosen to be discussed separately in the present review.

9. Potential of EMT-associated ncRNAs in the diagnosis and treatment of RCC

RCC is an aggressive carcinoma with a rising incidence, the age-standardized incidence rate (ASIR) rose from 2.88 to

4.37 per 100,000, an increase of ~52% (136), and 25-30% of patients with RCC present with metastasis at the time of diagnosis (137,138). Therefore, identifying appropriate biomarkers and therapeutic targets is of notable importance for the clinical treatment of RCC.

Currently, it is commonly considered that the EMT process may be a key step in tumorigenesis and progression (139,140). After the EMT process in RCC, cells enhance their invasiveness and metastatic potential and increase their drug resistance (141). Therefore, the early detection of ongoing EMT via ncRNA signatures presents a key target for therapeutic intervention. Halting or reversing the EMT process at this stage could prevent the acquisition of invasive and metastatic capabilities, potentially improving patient outcomes in the future (142).

The EMT process in RCC is heavily regulated by ncRNAs. Exploring the mechanisms through which ncRNAs modulate EMT is key to identify novel therapeutic strategies and targets in RCC. As previously discussed, several EMT-associated ncRNAs are differentially expressed in tumor tissues compared with normal tissues, and the expression levels of certain ncRNAs are associated with tumor stage, malignancy and metastasis. These observations highlight the potential of using these ncRNAs as diagnostic and prognostic markers for RCC in the future (112,143). For example, Silva-Santos *et al* (144) demonstrated that miR-141 and miR-200b could effectively distinguish renal tumors from normal renal tissues and miR-21, miR-141 and miR-155 could serve as prognostic markers for patients with RCC. Furthermore, Zhang *et al* (145) constructed a risk-scoring system using EMT-associated lncRNAs, which can predict overall survival and immune microenvironment status in patients with ccRCC.

Since the EMT process is reversible to a certain extent, EMT-associated ncRNAs also offer potential as therapeutic targets for RCC in the future. Approaches such as the synthesis of mimics of oncogenic ncRNAs or antisense oligonucleotides targeting oncogenic ncRNAs may prove effective. For example, cerebellar degeneration-related protein 1 antisense (ciRS-7), an oncogenic RNA in RCC, is highly expressed in tumors and its expression is associated with poor prognosis. Researchers have developed poly(β-amino ester)/si-ci-ciRS-7 nanocomplexes, which can markedly inhibit its oncogenic effects both *in vitro* and *in vivo* (143). This approach also illustrates the potential to combine RNA-based therapies with nanomaterials in RCC treatment. Furthermore, CSCs may induce EMT by secreting exosomes containing ncRNAs, which contribute to TME formation and distant metastasis. Removing $CD103^+$ CSC exosomes may represent a novel strategy for the treatment of patients with metastatic RCC in the future (14).

A notable portion of advanced RCC treatment relies on targeted therapies, such as sunitinib. However, several patients are either insensitive to these treatments or develop resistance over time, leading to poor prognosis (146). A previous study reported that the level of EMT-associated miR-141 can influence the therapeutic response to sunitinib in patients with RCC (6). Therefore, altering drug resistance by modulating the EMT process through ncRNAs may offer a promising adjuvant therapeutic strategy in the future.

Furthermore, as miRNAs can be regulated by other ncRNAs, such as circRNAs and lncRNAs, these molecules can serve as natural inhibitors of oncogenic miRNAs. Compared with linear RNAs, circRNAs have a more stable molecular structure, making them less susceptible to degradation by RNases and prolonging their half-life (147). Furthermore, circRNAs typically contain numerous RNA-binding sites, which allow them to efficiently sponge miRNAs. Unmodified circRNAs are less immunogenic compared with linear mRNAs and N6-methyladenosine modification of exogenous circRNAs almost entirely abrogates their immunogenicity (148). Furthermore, lipid nanoparticle-delivered (LNP) circRNAs provoke minimal immune responses following injection, highlighting their safety profile (149). These properties make circRNAs promising candidates for reliable cancer biomarkers in the future and anticancer drugs with fewer side effects, however, their clinical translation necessitates further investigation. A circRNA-based vaccine platform has demonstrated notable efficacy in B16 orthotopic melanoma and B16 lung metastasis models (150). Thus, it is conceivable that circRNA-based vaccines targeting EMT could be a viable therapeutic approach for RCC.

10. Study limitations and future perspectives

Despite comprehensively summarizing the regulatory role of ncRNAs in RCC EMT, the present review also highlighted several inherent limitations in the current body of literature that should be addressed in future research.

Firstly, the mechanistic insights discussed in the present review are predominantly derived from *in vitro* cell line experiments and murine xenograft models. Although these studies were valuable, these models cannot fully recapitulate the intricate TME, immune cell interactions and physiological pressures present in human patients. Potential confounding factors, such as the selective pressure of cell culture and the lack of a fully functional immune system in immunodeficient mice, may oversimplify the complex role of ncRNAs *in vivo* (151). Future studies should prioritize more physiologically relevant models, such as patient-derived organoids, orthotopic implantation models and genetically engineered mouse models of RCC, to validate these findings (152).

Secondly, there is a notable heterogeneity across published studies regarding RCC subtypes (for example, ccRCC vs. papillary), sampling techniques and methodological approaches (for example, RNA extraction, normalization methods in reverse transcription-quantitative PCR). This heterogeneity poses a challenge for direct comparison and meta-analysis. The clinical translation of ncRNA biomarkers will require rigorous standardization of protocols and validation in large-scale, multi-center, prospective patient cohorts to ensure reliability and reproducibility (153).

Thirdly, to the best of our knowledge, due to the paucity of data on EMT-associated ncRNAs in RCC, molecules other than the well-characterized miR-200 family are typically described in single reports, precluding longitudinal or cross-study comparisons. As the majority of these publications remain methodologically constrained, most notably by the absence of *in vivo* validation, the present review contended that systematic re-evaluation of previously identified ncRNAs constitutes a clinically relevant and underexplored avenue of investigation.

Lastly, while the present review outlined numerous ncRNAs with therapeutic potential, their delivery to tumor sites *in vivo* remains a notable hurdle. Future research should focus on developing efficient and targeted delivery systems, such as LNPs or exosome-based vectors, conjugated with ligands specific to RCC cells to potentially minimize off-target effects and maximize therapeutic efficacy in the future.

Addressing these limitations will be key to moving the field forward from descriptive mechanistic studies to the clinical realization of ncRNA-based diagnostics and therapies for patients with RCC.

11. Conclusions

The study of the metastatic mechanisms of RCC is of notable clinical importance, as a large proportion of patients with RCC present with metastasis at the time of their initial diagnosis. EMT serves as a pivotal driver of RCC metastasis and the present review has systematically elucidated the regulatory roles of ncRNAs, particularly miRNAs, lncRNAs and circRNAs, in this process. miRNAs are central to these ncRNA-mediated regulatory networks in RCC, with the most extensive research conducted in this area. Most circRNAs, T-UCRs, pseudogenes and certain lncRNAs regulate EMT by targeting miRNAs, primarily via the ceRNA mechanism.

Beyond summarizing current knowledge, the present review highlighted the notable clinical potential of EMT-associated ncRNAs. Their differential expression across tumor stages and metastatic states positions them as promising diagnostic and prognostic biomarkers. Furthermore, their involvement in therapeutic resistance and metastasis underscores their potential value as novel therapeutic targets. For instance, strategies such as synthetic miRNA mimics, antisense oligonucleotides or circRNA-based vaccines offer potential avenues for intervention in the future. The stability, low immunogenicity and efficient regulatory capacity of circRNAs, make them promising candidates for next-generation RNA therapeutics.

In conclusion, RCC can enhance its malignancy through the EMT process, which is tightly regulated by various ncRNAs. This highlights the notable potential of these molecules in RCC diagnosis, prognosis and treatment in the future. Through further research on these ncRNAs, novel biomarkers for RCC may be identified and novel therapeutic targets may be revealed that potentially improve patient outcomes in the future.

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Authors' contributions

ZL and HZ conceptualized the present review. ZL reviewed the data and wrote the manuscript. CZ provided supervision. CZ, ZL, JS, YQ and XG reviewed and edited the manuscript. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

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Competing interests

The authors declare that they have no competing interests.

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