Role of non-coding RNA intertwined with the Wnt/β-catenin signaling pathway in endometrial cancer (Review)

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Abstract. Endometrial cancer (EC) ranks as the sixth most common malignancy in women around the world. Although low-grade and early-stage EC commonly have an excellent prognosis, ~20% of EC patients experience an unfavorable prognosis. Identifying the pathogenesis and novel therapeutic targets may help address this group of patients. Non-coding (nc)RNAs, such as long non-coding RNAs (lncRNAs), microRNAs and circular RNAs (circRNAs), have been associated with EC occurrence and development. In addition, the aberrant activation of the Wnt/β-catenin signaling pathway can promote the proliferation, invasion, migration and epithelial-to-mesenchymal transition (EMT) of EC cells. The network of ncRNAs has also been demonstrated to inhibit or activate the Wnt/β-catenin signaling pathway. In the present review, ncRNAs, the Wnt/β-catenin signaling pathway, and their crosstalk in EC were summarized and highlighted. This information is expected to provide novel insights into improving the management of EC using RNA as therapeutics.

Contents

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1. Introduction

Endometrial cancer (EC) originates from the endometrium and is one of the most common cancers in females worldwide, accounting for 7% of all new cancer diagnoses and leading to 4% of all estimated cancer deaths in 2022 (1). The incidence and death rates of EC appear to have been leveling off in recent years after two decades of increase since 1997 (1). Given that EC mainly affects peri- and postmenopausal women, the cancer burden of EC is likely to remain incremental due to an increase in the adult and aging populations (2). Surgery is the primary treatment of EC, which is accompanied by adjuvant therapies, such as chemotherapy, followed by external beam pelvic radiotherapy and vaginal brachytherapy. The majority of EC patients who had undergone surgery and adjuvant therapies based on clinicopathological characteristics, had a favorable prognosis with a 76-95% 5-year survival rate (3). However, since the pathogenesis of EC has not been fully elucidated, effective treatment is deficient for advanced and recurrent EC creating a need to explore new targets and develop new screening methods.

The Wnt signaling pathway is a highly conserved axis participating in various physiological and pathological processes (4). Wnt1 was first discovered in 1982 by Dr Roel Nusse (5), after which several other Wnt family proteins were identified, and their functions were studied in further detail. The Wnt signaling pathway is divided into two categories, the canonical pathway (β-catenin-dependent) and the non-canonical pathway (β-catenin-independent). The non-canonical pathways mediate cell polarity and regulate intracellular levels of calcium, while the canonical Wnt pathway is closely related to the tumorigenesis, progression, and prognosis of certain solid tumors, including EC (6,7).

Previous studies have confirmed that β-catenin is the main positive mediator that activates selected genes and plays essential roles in embryonic development, tissue homeostasis and regeneration (4,8,9). Previous studies that focused on the Wnt/β-catenin pathway in EC, evaluated the role of Catenin beta 1 (CTNNB1) gene mutation, which encodes for the β-catenin and also excessively activates the Wnt/β-catenin pathway. CTNNB1 mutation frequently occurs in endometrioid types of ECs (EECs) and is the most common mutation

in all early-stage and low-grade EC patients. Although these subsets of EC patients tend to have low-risk characteristics, the presence of CTNNB1 mutation is associated wuth worse outcomes with decreased recurrence-free survival and overall survival (10-12). Furthermore, other components of the Wnt/β-catenin pathway, and their crosstalk with other signaling pathways have been determined to occur in EC (13-17).

Non-coding RNAs (ncRNAs) are a class of functional RNAs that play critical roles in normal cellular processes, as well as in the pathogenesis of human diseases, including long non-coding RNA (lncRNA), microRNA (miRNA), and circular RNA (circRNA) (18-20). RNA-RNA interaction plays a fundamental role at multiple levels of gene expression and regulation (20,21). RNA transcripts containing miRNA binding sites (also known as seed sequence) can act as a competing endogenous RNA (ceRNA) specifically for shared miRNAs, co-regulating with each other, and integrating ncRNAs with the protein-coding RNA (21).

Dysregulation of a variety of ncRNAs expression and the associated ceRNA network have been reported to engage in the genesis and progress of various malignancies, including EC. For example, lncRNA NEAT1 was reported to be abnormally expressed in several cancers, and to promote cell proliferation, migration and invasion of EC cells by sponging miR-214-3p via the HMGA1/Wnt/β-catenin pathway (22-24). LncRNA BMPR1B-AS1 was overexpressed in EC tissues, and exerted an oncogenic role by competitively binding to miR-7-2-3p to modulate the DCLK1-induced PI3K/Akt/NF-κB pathway activation (25). Also, the aberrant expression of a series of cirRNAs has been identified as oncogenic drivers or tumour suppressors in EC. For example, circ_0039569, circ_0007534, circ_0005797, circ_0001610 and more were found to affect cell proliferation, metastasis, invasion, drug-resistance and the radiosensitivity of EC cells (26-29).

In the present review, a brief overview of the non-canonical pathway is provided with a focus on the role of the canonical pathway in EC. Next, the Wnt/β-catenin signaling pathway was associated with the RNA network to further elucidate the mechanisms of initiation and progression of EC, aiming to provide new insights into EC prevention and intervention by utilizing potential targets.

2. Wnt/β-catenin signaling pathway in EC

The Wnt signaling pathway is divided into two categories, the canonical pathway (β-catenin-dependent) and the non-canonical pathway (β-catenin-independent) (6,7) (Fig. 1). The non-canonical pathway regulates intracellular calcium levels and modulates cell polarity. However, the canonical Wnt pathway has more association with tumorigenesis, progression, and prognosis of certain solid tumors, including EC.

Planar cell polarity (PCP)/Wnt signaling pathway in EC. The non-canonical Wnt signaling pathway includes the PCP pathway and calcium-dependent Wnt pathways. There are six core components involved in this pathway: i) Frizzled (FZD), ii) Flamingo (Fmi, also known as Stan, Celsr in vertebrates), iii) Vang-like (Vangl), iv) Dishevelled (Dsh; Dishevelled-like (DVL) in vertebrates), v) Prickle (Pk) and vi) Diego (Dgo; also known as Inversin and Diversin in vertebrates) (30-34). FZD, Celsr and Vangl are transmembrane proteins, while DVL, Pk and Diversin are cytoplasmic proteins. Upon interacting with these proteins, the small Rho GTPase effector molecules, c-Jun N-terminal kinase (JNK), and Nemo-like kinase (NLK) are activated (34-37). These processed lead to the asymmetric distribution of the PCP/Wnt signaling pathway proteins that consequently influence the cell polarity (34) (Fig. 1).

Several studies have confirmed that the aberrant regulations of the PCP/Wnt signaling pathway are correlated with developmental abnormalities and diseases including Kartagener's syndrome, open neural tube defects, deafness, heart defects and polycystic kidneys (38-42). Previous studies have also indicated that the upregulation of the PCP/Wnt signaling pathway is associated with poor prognosis in multiple cancers (43,44). Luga *et al* (45) reported that exosomes derived from breast cancer fibroblasts could activate the Wnt11/PCP signaling, consequently promoting an invasive behavior. As a result of this process, asymmetric distribution of the PCP/Wnt signaling pathway proteins were observed in cancer cells.

In addition, disruption of the Prickle1-Rictor complex may have the ability to inhibit breast cancer migration, while the upregulation of this complex was associated with poor prognosis (46,47). Notably, the PCP/Wnt signaling pathway is also highly associated with the epithelial-mesenchymal transition (EMT), which plays a vital role in endometrial carcinogenesis (34,48,49). Studies have also indicated that Wnt5A and Wnt11 could initiate the PCP/Wnt signaling pathway, while Wnt5A was reported as a tumor suppressor in multiple cancers. Wasniewski *et al* (50) reported that the expression of Wnt5A was decreased in patients with EC, thus, could be a potential marker in EC. However, the precise role of interaction between the PCP/Wnt signaling pathway and EMT-promoting endometrial carcinogenesis still requires further investigation.

Calcium-dependent Wnt signaling pathway in EC. Unlike the PCP/Wnt signaling pathway, the calcium-dependent Wnt signaling pathway regulates the expression of selected gene targets by modulating intracellular calcium ion homeostasis. It has been confirmed that the binding of Wnt5A to Frizzled and activation of receptor tyrosine kinase orphan-like receptor 2 (ROR2) tyrosine kinase suppresses the canonical Wnt/β-catenin signaling pathway (51). In response to DVL and G proteins, phospholipase C is activated, resulting in an increase in diacylglycerol (DAG), inositol 1,4,5-triphosphate (IP3), and intracellular calcium (34). Calcium is a universal second messenger responsible for the activation of calcium calmodulin-dependent protein kinase II (CaMKII) and protein kinase C (PKC). CaMKII and PKC subsequently activate downstream signaling molecules such as NFκB and CREB (34). In addition, CaMKII and PKC may play suppressive roles in regulating β-catenin (52).

Previous studies have also demonstrated that Wnt5A initiates the calcium-dependent Wnt signaling pathway (34). Moreover, although Wnt5A may act as a tumor suppressor in multiple cancers, Wnt5A functions as either a proto-oncogene or a tumor suppressor depending on the cell type and receptor availability (53-56). Zmarzly *et al* (57) reported that Wnt2, Wnt4 and Wnt5A were involved in the EMT process and were significantly decreased in EC. In addition, Wnt5A may also be regulated by miR-370, miR-432 and miR-200b-5p. However,

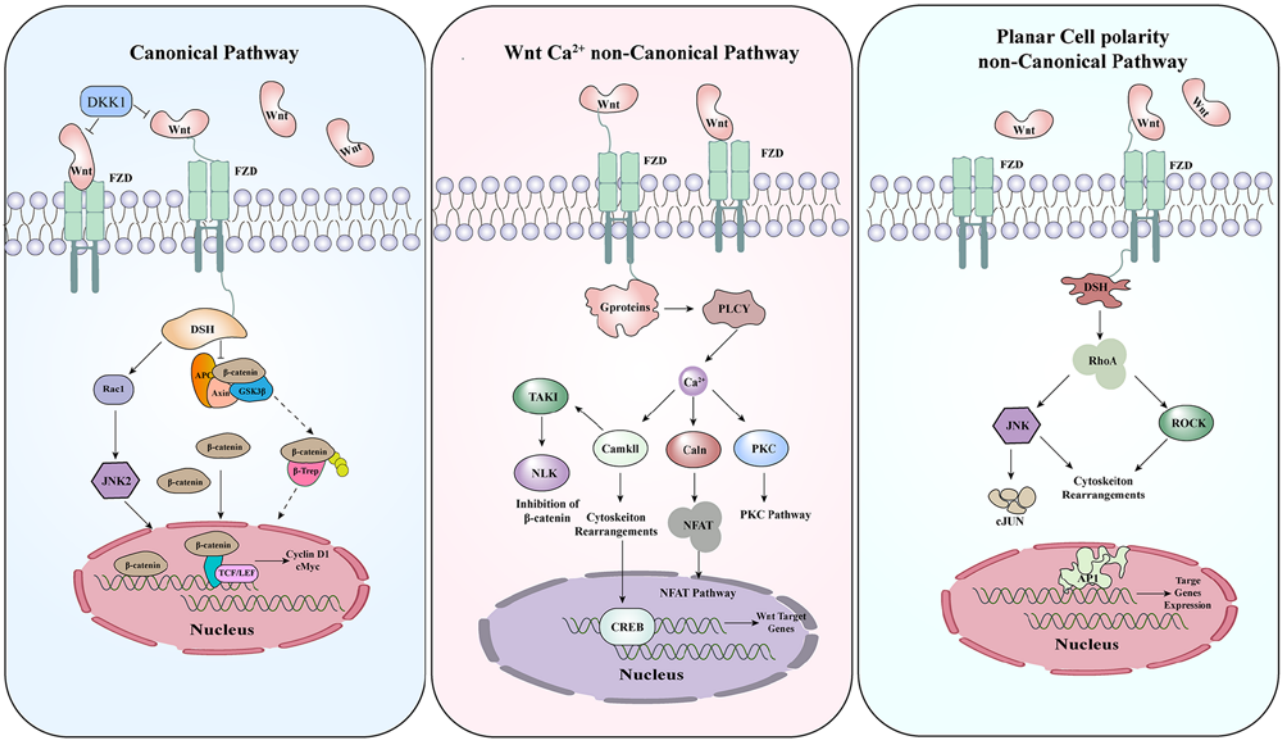

Figure 1. Pathway of the planar cell polarity/Wnt signaling, the calcium-dependent Wnt signaling and the canonical Wnt/β-catenin signaling pathways in endometrial cancer.

the role of calcium remains unclear and needs further investigation (Fig. 1).

Canonical Wnt/β-catenin signaling pathway in EC. The activation of the β-catenin-dependent Wnt signaling pathway depends on the sequential action of its components. In brief, firstly, extracellular Wnt proteins, like Wnt1 and Wnt3a, bind to the transmembrane coreceptors, which are mainly comprised of FZD and low-density lipoprotein receptor-related protein 5 or 6 (LPR5/6). With the ligation of both segments, the DVL scaffolding protein is recruited to the plasma membrane. Next, DVL phosphorylates LPR6 and dissociates the 'destruction complex', which consists of adenomatous polyposis coli (APC), AXIN, casein kinase 1 (CK1), and glycogen synthase kinase 3 protein (GSK3), to stabilize β-catenin. Then, the cytoplasm accumulated-β-catenin translocates to the nucleus and eventually cooperates with the T cell-specific factor (TCF)/lymphoid enhancer-binding factor (LEF) transcription factors to induce the transcription of targeted genes, including CCND1, c-MYC and MMPs. Conversely, β-catenin is sequestrated by the 'destruction complex' in the absence of Wnt. Subsequently, β-catenin is phosphorylated by GSK3β and CK1α, promoting its ubiquitination and subsequent proteasomal degradation (4,6,7,58) (Fig. 1).

As the hyperactivation of the Wnt/β-catenin pathway is closely associated with the tumorigenesis of EC, mutations of CTNNB1 are linked to the carcinogenesis and progression of EC. Therefore, mutations to CTNNB1 translate to clinicopathological and molecular characteristics of EC (10,12,14). In grade 1-2, stage I-II EECs, patients with a mutation to the tumor harboring CTNNB1 had lower-grade tumours, lesser myometrial invasion, a lower incidence of lymphatic/vascular space invasion, and a lower frequency of co-TP53 mutation. While these mutations are associated with more positive outcomes, they also increased the risk of recurrence (59).

Another study that included 218 low-grade, early-stage EECs confirmed that tumors with the CTNNB1 mutation are associated with reduced disease-free survival, without impacting overall survival (60). Nevertheless, Kasoha *et al* (16) reported that patients with CTNNB1 mutations make up an aggressive subset of low-risk EECs with both poorer progression-free survival and overall survival. Therefore, mutations to CTNNB1 have the potential to stratify EC into a prognostic group that requires additional therapeutic interventions.

The levels of sensitivity and specificity of immunohistochemical staining of β-catenin as an effective surrogate to CTNNBI gene sequencing remains uncertain (10,13-14,61). Individual hyperactivation of the Wnt/β-catenin pathway is insufficient to stimulate the initiation of EC. The malignant transformation from endometrial hyperplasia to EC only occurs when alterations in the Wnt/β-catenin and the loss of PTEN or unopposed estrogen are simultaneously present (15,62). Moreover, β-catenin also serves as an adhesion protein by linking E-cadherin and the actin cytoskeleton (63). Although the dual function of β-catenin appears to be independent of each other, they work together to maintain the balance of β-catenin in the cytoplasm, cell membrane and nucleus.

The Wnt/β-catenin is also recognized as a key regulator of EMT, by directly or indirectly regulating numerous EMT markers, including Zeb1, Twist, Snail1 and Slug (64). In another process, the transcription factors Twist, Snail1 and Zeb1 co-suppress E-cadherin expression (65,66). Loss of E-cadherin and increased Wnt/β-catenin induce EMT in carcinomas and the development of EC, with the exact mechanism yet to be fully understood.

Table I. Crosstalk of non-coding RNA and Wnt/β-catenin signaling proteins in endometrial cancer.

Non-coding RNAs	Expression	Role	Related factors	(Refs.)
miR-15a-5p	Downregulation	Suppressor	Wnt3a, β-catenin, Cyclin D1, p21, OCT-4, SOX2	(82)
miR-370	Downregulation	Unknown	Wnt4, Wnt5a	(57)
miR-432	Downregulation	Unknown	Wnt4, Wnt5a	(57)
miR-15a-5p	Downregulation	Suppressor	β-catenin, c-Myc, Gsk-3β, VEGF	(92)
miR-202	Downregulation	Suppressor	β-catenin, E-cadherin, N-cadherin, Vimentin, FGF2	(93)
circ_0109046	Upregulation	Oncogene	miR-105, SOX9, β-catenin, c-Myc	(83)
miR-331-3p	Upregulation	Unknown	Wnt4	(57)
miR-200b-5p	Upregulation	Unknown	Wnt5a	(57)
circ_0002577	Upregulation	Oncogene	miR-197, CTNND1, β-catenin, cyclin D1, c-Myc	(85,86)
Lnc MIR210HG	Upregulation	Oncogene	miR-337-3p, miR-137, TGF-β, c-Myc, Cyclin D1, HMGA2	(49)
Lnc HOXB-AS1	Upregulation	Oncogene	miR-149-3p, Wnt10b β-catenin, cyclin D1, c-Myc	(87)
Lnc LSINCT5	Upregulation	Oncogene	Wnt10b, β-catenin, cyclin D1, c-Myc, HGMA2	(90)
Lnc SRA	Upregulation	Oncogene	β-catenin, c-Myc, Gsk-3β, EIF4E-BP1	(91)
miR-373	Upregulation	Oncogene	β-catenin, E-cadherin, N-cadherin, LATS2	(94)
miR-652	Upregulation	Oncogene	RORA, β-catenin	(95)
Lnc NEAT1	Upregulation	Oncogene	miR-214-3p, miR146b-5p, c-Myc, MMP9	(22,23,96)

lnc, long non-coding; miR, microRNA.

Based on available evidence that the aberrant Wnt/β-catenin signaling pathway is widely involved in the progression of EC, targeting the Wnt/β-catenin pathway is a prospective choice for late-stage and recurrent EC patients (67,68).

Crosstalk between ncRNA and the Wnt/β-catenin signaling pathway in EC. ncRNAs (including lncRNAs, miRNAs and circRNAs) consist of >90% of the human transcripts and exhibit limited protein-coding capacity (69,70). However, these ncRNAs mainly participate in and regulate epigenetic modifications, cell differentiation, aging, and cell cycles by regulating the expression of target genes expression at post-transcriptional level (71,72).

An increasing number of studies have indicated that aberrant expression and dysregulation of these ncRNAs are highly linked with a variety of malignant tumors in human through several mechanisms, including tumor autophagy, tumor resistance and tumor immunity (73-75). Therefore, ncRNAs have dual roles as oncogenes and tumor suppressors (76). Consequently, they have been identified as potential biomarkers for cancers including EC (77-79).

The Wnt signaling pathway has been proven to function as a key pathway participating in the carcinogenesis of EC (7,80,81). A growing number of studies have revealed that ncRNAs could promote or inhibit EC tumorigenesis and progression by targeting the Wnt signaling pathway proteins (81). To elucidate the specific role of crosstalks between ncRNAs and the Wnt signaling pathway in EC, the available literature was summarized. The role of ncRNAs and their target genes are listed in Table I.

miR-15a-5p was previously reported to be significantly decreased in human EC cells and tissues (82). Overexpression of miR-15a-5p could inhibit the proliferation of EC cells and downregulate Cyclin D1and p21 by binding the octamer-binding transcription factor 4 (OCT-4), SRY-box transcription factor 2 (SOX2) and Nanog. In addition, miR-15a-5p could inhibit Wnt3a expression by directly binding with Wnt3a's 3'untranslated region. These mechanisms indicated that miR-15a-5p acts as a suppressor in ECs by inhibiting the Wnt/β-catenin signaling pathway.

Li *et al* (83) reported that circ_0109046 was highly expressed in human EC tissues and the high expression of circ_0109046 was strongly associated with poor prognosis. Knockdown of circ_0109046 could inhibit metastasis and invasion of EC cells. circ_0109046 also served as a sponge for miR-105 and regulated miR-105 expression. Overexpression of miR-105 could suppress proliferation and aggressiveness and promote apoptosis of EC cells by downregulating the expression of SOX9. SOX9 is proved to be a positive regulator of the Wnt/β-catenin pathway by increasing the protein level of β-catenin and c-Myc. This mechanism has been also confirmed in gastric cancers (84).

Zmarzly *et al* (57) found Wnt2, Wnt4 and Wnt5A were significantly decreased in EC. Subsequent experiments indicated Wnt4 might be regulated by miR-370, miR-432 and miR-331-3p (57). However, there is still lack of data about the relationship between miRNAs and Wnt, which needs further investigation. Several studies have confirmed that circ_0002577 was upregulated and highly associated with the poor prognosis of patients with EC (85,86), while circ_0002577 inhibition suppressed the proliferation and invasion of EC cells. Additionally, circ_0002577 served as a sponge for miR-197, which directly target CTNND1 and downregulated the expression of CTNND1, β-catenin, cyclin D1 and c-Myc. These results indicated that circ_0002577 acted as an oncogene in EC.

More recently, lncRNA MIR210HG was found to be upregulated in EC tissues compared with normal endometrial tissues

Table II. Drugs/agents targeting the Wnt/β-catenin signaling pathway.

Compound	Mechanism	Preclinical vs. clinical trial (phase) vs. FDA approved	Manufacturer	(Refs.)
LGK974	PORCN inhibitors	Phase I (NCT01351103) in Melanoma, breast cancer and pancreatic CA	Novartis	(99-101)
ETC-159	PORCN inhibitors	Phase I (NCTO2521844) in Refractory solid tumors, 10 patients (9 CRC, 1 Renal)	D3-Institute experimental therapeutics	(103)
OMP-18R5	Monoclonalantibody against FZD receptors	Phase 1 (NCTO1957007, NCTO2005315, NCTO1973309) in Breast cancer and Solid tumors	Bayer, OncoMed	(104-106)
OMP-54F28	FZD8 decoy receptor	Phase 1 (NCT01608867, NCT02092363, NCT02050178) in Hepatocellular cancer and Solid tumors	Bayer, OncoMed	(109-111)
PRI-724	CBP/β-catenin antagonist	Phase 1 (NCT01606579, NCT01764477) in acute and chronic myeloid leukemia, Colorectal cancers	Prism Biolab	(81,112)
DKN-01	Monoclonal antibody against DKK1	Phase I/II in Multiple Cancers (NCT01457417, NCT03395080, NCT05761951)	Leap Therapeutics	(113,114)

and was associated with poor prognosis (49). Knockdown of the MIR210HG inhibits Wnt/β-catenin and the TGF-β pathway via the miR-337-3p/137-HMGA2 axis. Liu *et al* (87) reported that lncRNA HOXB-AS1 expression was significantly higher in EC than that in adjacent normal tissues. In addition, the overexpression of lncRNA HOXB-AS1 promotes the proliferation, migration and invasion of EC cells and was associated with shorter survival. Through a certain mechanism, lncRNA HOXB-AS1 also decreased Wnt10b, β-catenin, cyclin D1, and c-Myc expression by targeting miR-149-3p. Wnt3a is an important member of the Wnt family, which has been confirmed to participate in the development and progression of multiple cancers including EC (88-90). A recent study has indicated that lncRNA LSINCT5 promoted the proliferation and invasion of EC cells by activating the Wnt3a/β-catenin/c-Myc signaling pathway via HGMA2 (90).

Park *et al* (91) further documented that the expression of lncRNA SRA (steroid receptor activator) was significantly higher in EC tissues. Overexpression of SRA upregulates the level of β-catenin and c-Myc mRNAs and downregulates the level of Gsk-3β mRNA. As a result of these modulations, SRA promoted proliferation, migration and invasion of EC cells by activating the Wnt/β-catenin signaling pathway. Wang *et al* (92) also reported that miR-15a-5p suppressed the viability, migration and invasion of EC cells by decreasing the expression levels of the Wnt signaling pathway-related proteins, including β-catenin, c-Myc, Cyclin D1 and p-GSK3β. miR-15a-5p also blocked EMT process by increasing expression level of E-cadherin, while decreasing vimentin and N-cadherin expression (92). Chen *et al* (93) found that miR-202 was downregulated in EC cells and tissues. In addition, miR-202 acted as a tumor suppressor by inactivating the Wnt/β-catenin signaling pathway and blocking the EMT process, through the overexpression of FGF2.

Overexpression of miR-373 also promotes the proliferation, migration and invasion of EC cells by directly targeting LATS2 and upregulating β-catenin (94). Sun *et al* (95) reported that the expression of miR-652 was increased in human EC tissues, which promoted their proliferation, migration and invasion by targeting RORA (Retinoic acid receptor-related orphan receptor A). The concurrent overexpression of miR-652 and knockdown of RORA upregulates the expression of β-catenin. These outcomes indicated that the activation of the miR-652/RORA/β-catenin axis could promote EC.

A previous study indicated that lnc NEAT1 was overexpressed in EC, which promoted the proliferation, migration and invasion of EC cells (23). Previous studies have indicated that lnc NEAT1 targets miR-214-3p and miR146b-5p which are involved in EC by regulating the Wnt/β-catenin signaling pathway (22,96). Overexpression of lnc NEAT1 leads to a decreased amount of miR-214-3p and miR-146b-5p, which in turn upregulates c-Myc and MMP9. In addition, progesterone could suppress EC progression by inhibiting c-Myc and MMP9. These results indicated that lnc NEAT1 acts as an oncogene while miR-214-3p and miR-146b-5p serve as tumor suppressors.

3. Therapies targeting the Wnt/β-catenin signaling pathway

It is thus evident that the Wnt/β-catenin signaling pathway plays a vital role in the development and progression of EC. Therapeutic agents targeting the Wnt/β-catenin signaling pathway have gradually become a research focus (4,6,81). Based on their varied mechanisms of action, drugs targeting the Wnt/β-catenin signaling pathway can be divided into several classes, including porcupine (PORCN) inhibitors, monoclonal antibodies against FZD, FZD8 decoy receptors, CBP/β-catenin antagonists and DKN-01 (81,97,98). These were illustrated in Table II.

PORCN inhibitors (such as LGK974, ETC-159 or CGX1321) prevent the palmitoylation of Wnt proteins, which in turn inhibits its secretion (7). LGK974 as a drug for numerous advanced solid tumors has completed phase I clinical trials (NCT01351103, NCT02278133). However, due to bone-related toxicities, the efficacy and safety of LGK974 needs further study (99-101). ETC-159, another PORCN inhibitor, prevents the secretion and blocks function of Wnt proteins, suggesting that ETC-159 could be an effective therapeutic agent for EC (81,102). A phase I clinical trial to evaluate the safety and tolerability of ETC-159 (NCT02521844) for different solid malignancies is in progress (103).

OMP-18R5 is a monoclonal antibody against FZD and inhibits the canonical Wnt signaling pathway. Similar to LGK974, concerns are emerging around the bone-related safety of OMP-18R5 which has become a major obstacle for future clinical use (NCT02050178, NCT02278133) (104-106). OMP-54F28 is composed of the IgG1 Fc and the extracellular ligand-binding FZD8 domains and exhibits an antitumor effect in several cancers by sequestering secreted Wnts (107,108). Several phase I clinical trials have indicated OMP-54F28 might be an effective agent to target the Wnt signaling pathway in advanced solid tumors, including colorectal and pancreatic cancer (NCT01608867, NCT02092363, NCT02050178) (109-111).

PRI-724, an inhibitor of the downstream Wnt/β-catenin pathway, reduces the expression of β-catenin-TCF-responsive genes by targeting the complex formation of β-catenin and CBP (NCT01606579, NCT01764477) (81,112). Dickkopf -1(DKK-1) is a Wnt signaling modulator overexpressed in gynecologic cancers. DKN-01 is a humanized monoclonal antibody with DKK1 neutralizing activity. DKN-01 was applied in multiple myeloma (NCT01457417) (113). On September 25, 2020, the Food and Drug Administration granted accelerated approval to DKN-01 for gastric or gastroesophageal junction adenocarcinoma. Notably, a phase II basket study indicated a promising clinical activity of DKN-01 in EC patients with high DKK1 expression (NCT03395080) (114). Meanwhile, a combination therapy consisting of DKN-01 and pembrolizumab is currently being evaluated in clinical trials for advanced or recurrent EC (NCT05761951).

In addition, another study indicated that medroxyprogesterone acetate suppresses the proliferation of early endometrial carcinoma by inactivating the Wnt/β-catenin signaling pathway (115), followed by the evidence that when therapy was halted, a marked recurrence was reported (116). Preclinically, niclosamide, salinomycin and curcumin have all been proven to interfere with the Wnt/β-catenin signaling pathway in cancer cells (117-119).

Based on these promising roles of ncRNAs, numerous ncRNAs are expected to become potential therapeutic targets in the near future (120). Clinical trials of ncRNAs based therapies are currently underway and are already exhibiting prospective clinical applications (120,121).

4. Challenges and perspectives

Abnormal activation of the Wnt/β-catenin signaling pathway and β-catenin mutation contributes to the development and progression of various cancers including gynecological cancers. Numerous therapies that target the Wnt/β-catenin signaling are currently tested in clinical trials in various cancers and have demonstrated promising outcomes.

Although the molecular mechanism of the Wnt/β-catenin signaling pathway in EC remains unclear, accumulating evidence indicates that the crosstalk that occurs between ncRNAs and the Wnt/β-catenin signaling pathway play significant roles in drug resistance, metastasis and recurrence (7,81). The present review focused on the interaction between the lncRNA/circRNA-miRNA network and the Wnt/β-catenin signaling pathway related proteins associated with EC. ncRNAs may serve as potential targets for EC treatments. However, there are still a large number of uncharacterized ncRNAs. The role of ncRNAs' interaction with the Wnt/β-catenin signaling as targeting therapy still needs further investigation.

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Authors' contributions

YT and RG were responsible for the concept of the review. YT and TL were responsible for writing the manuscript. YT and ZL made all the figures in this manuscript. ZL, MM, YL and YJ revised the manuscript critically. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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