Review

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A Review of the Relationship between Wnt Signal Transduction Pathway and Endometrial Cancer

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The incidence of endometrial cancer (EC) has been on the rise in recent years. Advanced EC is associated with poor prognosis in patients. Traditional classification methods for EC do not provide satisfactory diagnosis and treatment. With the rapid advancements in molecular biology, studies have associated multi-omics with signaling pathways in the pathogenesis of EC, which is critical for the diagnosis and treatment of patients. Cell signal transduction pathways may lead to the occurrence, development and metastasis of tumors through multiple effectors. The Wnt (Wingless and Int-1) signaling pathway is a highly conserved signaling route that is widely present in multicellular eukaryotes. It is involved in determining cell fate, as well as cell proliferation, differentiation, motility and apoptosis during embryonic development, and its target genes are factors involved in cell development, cell proliferation and cell migration. Abnormal signal transduction may lead to abnormalities in cell growth, differentiation, metabolism and biology, resulting in various diseases. The Wnt pathway may be involved in uterine development and endometrial maintenance, and it is associated with estrogen-induced endometrial proliferation. This paper reviews progress in research on the relationship between Wnt signaling pathway and EC.

Keywords: Wnt signaling pathway; endometrial cancer; signal transduction; estrogen and progesterone; miRNA; lncRNA; m6A

Introduction

Endometrial cancer (EC) is a cluster of epithelial malignant tumors originating from the endometrium. It is one of the three major malignant tumors of the female reproductive tract. In recent years, with increase in metabolic diseases due to changes in people's living habits and dietary composition, as well as heightened mental stress, the incidence of EC has been on a rise [1]. In China, the incidence of EC is second only to that of cervical cancer, and in the United States, EC incidence is second only to those of breast, lung, and colorectal cancers [2,3]. Due to the typical early symptoms of the disease such as postmenopausal vaginal bleeding, irregular vaginal bleeding and abnormal discharge, most patients with EC are diagnosed in time, resulting in low mortality rate [4].

The pathogenesis of EC is complex. The Wnt (Wingless and Int-1) genes are a wide family of highly conserved developmental genes that play critical cell signaling roles in embryonic development: they influence cell fate, cell proliferation, differentiation, motility, and apoptosis, and maintain tissue homeostasis in adult tissues. Aberrant regulation of the Wnt signaling pathway may play a significant role in the onset and progression of cancer. Many researchers are concerned about the functions that control the differentiation and/or proliferation of diverse stem cells and progenitor cells. Abnormal signal transduction leads to abnormalities in cell growth, differentiation, and metabolism, resulting in various diseases [5,6].

The Wnt pathway may be involved in the development of the uterus and maintenance of the endometrium, and it is related to estrogen-induced endometrial proliferation. The Wnt signaling pathway is highly conserved, and it is ubiquitous in multicellular eukaryotes. It is comprised of 3 main pathways: (a) the canonical Wnt pathway which activates the transcriptional activity of target genes through the nuclear translocation of β-catenin; (b) the planar cell polarity pathway which involves the cytoskeleton rearrangement and Ras homolog family member A (RhoA) and Jun kinase (JNK), and (c) Wnt/Ca^{2+} pathway which antagonizes the canonical Wnt/β-catenin signaling pathway [7].

With the development of bioinformatics and the accumulation of data from basic biology experiments, studies have demonstrated the association between EC and multiple genetic forms, among which miRNA, mRNA and methylation have been the most frequently investigated. Endogenous intracellular and extracellular small non-coding RNAs are known as microRNAs (miRNAs). They control cell proliferation, division, apoptosis, and metabolism as regulators of numerous biological processes by promoting the degradation of mRNAs and inhibiting their translation [8]. Zhang *et al.* [9] reported that fat mass

Journal of
BIOLOGICAL REGULATORS
and Homeostatic Agents

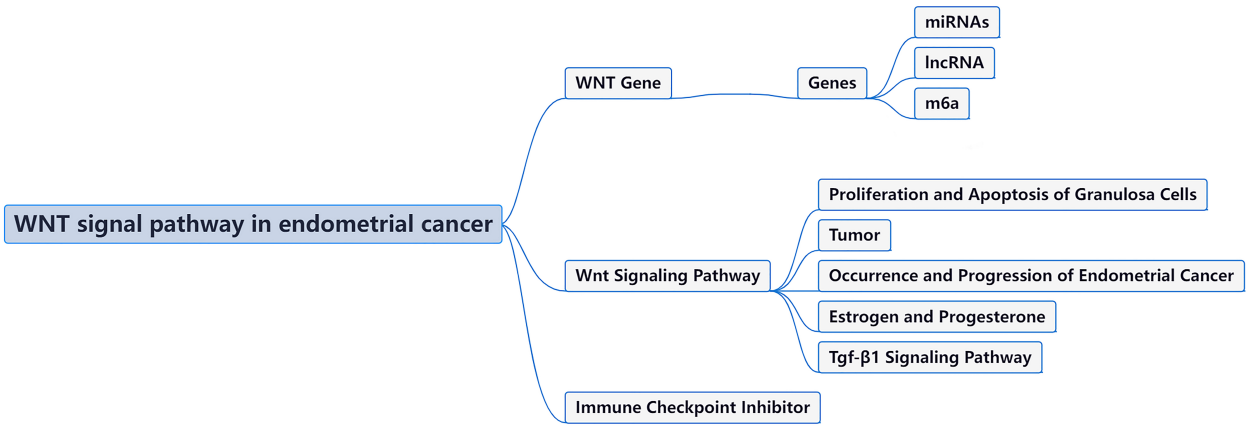

Fig. 1. The flow chart of the study. Wnt, Wingless and Int-1; miRNAs, microRNAs; m6A, N6-methyladenosine; lncRNA, long non-coding RNA; TGF-β1, transforming growth factor-beta1.

and obesity-associated protein (FTO) demethylates N6-methyladenosine (m6A) modifications in HOXB13 mRNA and promotes endometrial cancer metastasis by activating the Wnt signaling pathway [9].

Despite the moderate efficiency of early treatments for EC, the prognosis is dismal once tumor tissue invades and metastasizes, resulting in a high mortality rate. Tumor invasion and metastasis are important signs and essential manifestations of malignant tumors, and they are amongst the major causes of tumor-related deaths [8]. Epithelial-mesenchymal transition (EMT) of tumor cells plays a crucial role in tumor invasion and metastasis. It has been reported that abnormal activation of Wnt signaling pathway is closely related to EMT [9]. Therefore, the present study reviewed the progress in research on the relationship between Wnt signaling pathway and endometrial cancer. The flowchart of the study is shown in Fig. 1.

Wnt Genes

The Wnt genes are a large family of highly-conserved developmental genes. The first Wnt gene (*Wnt-1*) was discovered in a study on mouse breast cancer by Zmarzły *et al*. [10]. They induced breast cancer using mouse papillomavirus (MMTV), which was named int-1 due to the MMTV activation site in this gene [11]. Subsequent studies showed that *int-1* was a homologous gene with the *Drosophila* somite polarity gene Wingless. Therefore, the two were together called the *Wnt* gene. Currently, 19 members of the *Wnt* gene family have been cloned. They encode conserved glycoproteins with 22 or 24 cysteine residues which are essential cell signaling molecules. During embryonic development, the Wnt genes are important for determining cell fate, cell proliferation, differentiation, motility, and apoptosis, as well as maintenance of tissue homeostasis in adult tissues. Recently, several studies have focused on the involvement of the Wnt genes in controlling the differentiation and/or proliferation of diverse stem and progenitor cells [12–14].

Wnt Signaling Pathway

The name of Wnt comes from the first two Wnt proteins discovered, namely the protein encoded by the *Drosophila* Wingless (*Wg*) gene and the protein encoded by the mouse *int-1* gene. Studies have suggested that these two proteins transmit growth and developmental information between cells, and also control the normal axial development of embryos. Therefore, the combination of Wg with int-1 is called the *Wnt* gene. The human *Wnt* gene is located on chromosome 12q13 [15,16].

The Wnt signaling pathway is highly conserved during evolution, and it plays an important role in embryonic development, tumorigenesis and tumor progression. The Wnt proteins are ubiquitous class of secreted glycoproteins, 19 types of which are currently known. Based on the different ways of Wnt protein transduction signal, the Wnt signal transduction pathway is divided into three types: the canonical Wnt signal transduction pathway (canonical Wnt/β-catenin pathway) which activates the transcriptional activity of target genes through nuclear translocation of β-catenin, with target genes comprising factors involved in cell development, cell proliferation and cell migration, such as matrix metalloproteinases (MMPs) [17,18]. The non-classical Wnt signal transduction pathways include the cell plane polarity (PCP) pathway and the Wnt/Ca^{2+} pathway. These two pathways do not function through β-catenin, and they may inhibit the activity of β-catenin in the nucleus [19]. The PCP pathway involves RhoA protein and Jun kinase (JNK), and it controls the developmental time and space of the embryo. At the cellular level, this pathway regulates cell polarity by rearranging the cytoskeleton [20]. The Wnt/Ca^{2+} pathway induces increases in intracellular Ca^{2+} concentration and activates Ca^{2+}-sensitive signal transduction components which antagonize and inhibit the Wnt/β-catenin pathway [21].

Wnt/β-Catenin Signaling Pathway and Proliferation and Apoptosis of Granulosa Cells

The growth and development of follicles are dependent on the proliferation of granulosa cells. In primordial follicles, only a limited number of follicles are activated during a given estrous cycle, with few undergoing ovulation, but most follicles are lost through atresia [22]. During the normal development of the follicular cycle, various stages of follicular atresia are closely related to the apoptosis of granulosa cells. Specifically, granulosa cell apoptosis is the main mechanism of follicular atresia. A shift in the balance between cell survival and cell death signaling pathways in granulosa cells may determine the fate of ovarian follicles [23].

In granulosa cells of normal follicles, *Wnt2* is strongly expressed, but it is weakly expressed in granulosa cells of atretic follicles. Knockdown of *Wnt2* gene significantly inhibits the proliferation and induces apoptosis of granulosa cells [24]. Co-immunoprecipitation has revealed that *Wnt2* regulates the β-Catenin pathway of granulosa cells through its receptor FZD9, thereby promoting their proliferation and inhibiting their apoptosis. The Wnt/β-Catenin signaling promotes ovarian granulosa cell apoptosis and inhibits its apoptosis by activating Foxo3a and its downstream effectors, and the Wnt/β-Catenin pathway inhibitor IWR-1 suppresses the expression of apoptosis genes in ovarian granulosa cells and promotes their proliferation, resulting in enhanced follicular development and increased steroid production [25,26].

Wnt Signaling Pathway and Tumor

It is currently believed that the accumulation of β-catenin in cells is a marker of the activation of the canonical Wnt signaling pathway. Therefore, any gene mutation involved in the canonical pathway leading to accumulation of β-catenin will activate the canonical Wnt signaling pathway [27]. Studies have confirmed [28,29] that abnormal accumulation of β-catenin in cells is linked to the occurrence of various human tumors such as colorectal cancer, lung cancer, breast cancer, and cervical cancer. About 90% of sporadic colorectal cancers show abnormal activation of classical Wnt signaling. Non-canonical and canonical Wnt signaling pathways are involved in regulating the expression of intercellular adhesion molecules and extracellular matrix proteins, and are related to the migration, invasion and metastasis of tumor cells [30]. Therefore, both canonical and non-canonical Wnt signaling pathways are involved in tumorigenesis and tumor progression. There is also crossover amongst different Wnt signaling pathways, and between Wnt signaling pathways and other signaling pathways, which complicate the underlying molecular mechanism [31].

Many genes that regulate cell proliferation, differentiation, and tumorigenesis are regulated by the Wnt signaling pathway. In addition, Wnt signaling affects cell growth and proliferation by inducing the expression of growth factors (GFs) and their receptors. The expressions of fibroblast growth factors (FGF) are up-regulated in gastric cancer and colon cancer, and the promoter is activated by the T-cell factors (TCF)/β-catenin. A series of immunohistochemical staining studies in colorectal cancer revealed that Wnt signaling also regulates tumor stem cells that determine tumor metastasis [32]. It is worth noting that tumor cells with nuclear accumulation of β-catenin exhibit cell cycle arrest and epithelial-mesenchymal transition no longer express E-cadherin but express the mesenchymal cell marker fibronectin [33]. As a result, Wnt signaling may be activated directly by the overexpression of Wnt ligands, or indirectly through the transfer of mutations in Wnt signaling downstream components, ultimately leading to the occurrence of malignant events and generation of aggressive tumor cells. These findings demonstrate that the Wnt signaling pathway may accelerate the cell cycle, increase cell proliferation, and prevent apoptosis, thereby influencing tumor formation and development [34,35].

In addition, tumor invasion and metastasis are closely related to the occurrence of EMT in tumor cells, and the Wnt signaling pathway is one of the main factors that induce EMT. The activation of β-catenin signaling in the classical Wnt signaling pathway increases the expression of transcription factors Slug, Snail, and Twist; reduces the expression of E-Cadherin, causes loss of cell epithelial polarity and connection, enhances the occurrence of EMT in cells, and improves the migration and invasion of cells [36].

Wnt Signaling Pathway and the Occurrence and Progression of Endometrial Cancer

The Wnt signaling is involved in cell formation, differentiation and proliferation, and migration. Mutation in a factor, or aberrant protein expression may result in the development of illnesses, including cancers. The Wnt/β-catenin pathway plays an important role in the occurrence of EC, and about 40% of ECs show abnormal activation of the Wnt/β-catenin pathway [37]. Liu *et al*. [38] found that the expression of Wnt4 mRNA in the endometrium of EC patients was significantly down-regulated, indicating the potential involvement of Wnt4 in the pathogenesis of endometrial cancer. The study also found that the expressions of Wnt2, Wnt3, and Wnt5a were down-regulated in endometrial carcinoma. Subsequent research showed that the Wnt/β-catenin signaling pathway, including *β-catenin* gene-activating mutations and adenomatous polyposis coli (*APC*) gene-inactivating mutations, may play significant role in the early onset of endometrial cancer [9]. Compared with normal endometrium, β-catenin aggregation is significantly increased in EC, a process which is associated with a single base missense mutation in the *β-catenin* gene [39].

Journal of
BIOLOGICAL REGULATORS
and Homeostatic Agents

Studies have shown that Catenin-β1 (CTNNB1) exon 3 (Exon3) mutations that lead to β-catenin accumulation and activation of the Wnt signaling pathway, are associated with high-grade and high-stage EC in young women, and also with poor overall prognosis. Moreover, high expressions of Catenin-β1 (CTNNB1), MYC and CC-ND1 are linked to poor prognosis in low-grade EC [40]. Chen *et al* [41]. analyzed the expressions of Wnt10A and Wnt10B in EC tissues, and showed that the expression of Wnt10B was significantly increased, when compared with proliferative endometrial tissues. There are differences in Wnt10B expression levels in different tissue types, Federation of Gynecology and Obstetrics (FIGO) stages, and lymph node metastasis. Elevated Wnt10B expression indicates good prognosis in EC patients.

Dellinger *et al*. [42] found that mutations in exon 3 of *CTNNB1* gene which encodes β-catenin, may be related to the initiation of endometrioid adenocarcinoma in poorly differentiated, low-stage EC in young women. Gene mutation may be an important molecular event leading to the accumulation of β-catenin and the occurrence of EC, which may provide a new basis for the early diagnosis and prognosis of the disease. The use of β-catenin as gene or drug therapy target is expected to improve the efficacy of treatment for EC. In addition, it has been reported that the expression of Wnt7A is increased in EC tissue, and that it is related to pathological grade, FIGO stage, myometrial invasion, and lymphatic metastasis. There is great potential for Wnt7A as an independent predictor of the overall survival rate and recurrence-free survival time of EC patients [43].

A study by Liu *et al*. [44] showed that the tumor suppressor gene phosphatase and tensin homolog (PTEN), which plays an important role in various signaling pathways, is also related to Wnt/β-catenin. Loss of *PTEN* gene function leads to inactivation of adenomatous polyposis coli (APC) which forms a "degradation complex" that activates the Wnt/β-catenin pathway, resulting in EC. Loss of PTEN and APC functions is associated with early onset and aggressiveness of EC, resulting in poor prognosis of EC patients [45]. In addition, research has found that various factors that regulate the Wnt signaling pathway play important roles in the occurrence and progression of EC. van der Zee M *et al*. [46] have reported that protocol in PC-DH10 induced apoptosis and inhibited the growth of early-stage endometrial cancer (EEC) cells and cells in transplanted tumors, while metastasis-associated lung adenocarcinoma transcript 1 (MALAT1), a long non-coding RNA (lncRNA), regulated the inhibitory effect of protocadherin10 (PCDH10) on EC tumors.

Wnt Signaling Pathway, Estrogen and Progesterone

Estrogen homeostasis is critical for maintenance of normal physiological regulation of the endometrium. Estrogen-induced periodic endometrial hyperplasia is involved in the occurrence and progression of early-stage endometrial cancer (EEC), suggesting a certain causative relationship between estrogen exposure and type I endometrial cancer [47]. Epidemiological evidence has shown that estrogen, a suspected carcinogen, is associated with cancers of the breast, endometrium and cervix. Research has confirmed that estrogen and progesterone affect the occurrence and progression of EC by regulating the Wnt signaling pathway. During the proliferative phase of the endometrium, β-catenin is located in the nucleus, while during the secretory phase it is located in the cytoplasm and membrane [48]. Estrogen up-regulates the Wnt/β-catenin signal route during the proliferative phase, while progesterone inhibits Wnt/β-catenin signaling, thereby antagonizing the proliferative effect of estrogen on the endometrium. Therefore, under stimulation by high levels of estrogen without progesterone antagonism, the endometrial hyperproliferation may induce the occurrence of EC [49]. Progesterone may inhibit the Wnt/β-catenin pathway by upregulating negative regulators of Wnt/β-catenin signaling, i.e., Dickkopf-1 (DKK1) and Forkhead Box Protein O1 (FOXO1). It has been reported that loss of progesterone receptors may result in the aggressive phenotype of EC, which in turn affects prognosis in patients [50]. It has been reported that injection of estrogen into mice rapidly upregulated the mRNA expression levels of Wnt5 and Frizzled2, a process which was independent of the estrogen receptor [51].

Wnt Signaling Pathway and MiRNAs

Micro-RNAs (miRNAs) are a class of important gene regulators that specifically bind to the mRNA3cUTR region, resulting in mRNA degradation or blockage of its translation, thereby negatively regulating mRNA. These miRNAs are closely linked to the occurrence and development of various tumors, including EC. It has been reported that abnormally-expressed miRNAs such as *miR-139-5p*, *miR-183* and *miR-195*, may be crucial in the occurrence and development of endometrial cancer via targeting and regulating the expressions of related genes, thereby affecting tumor cell proliferation, invasion and apoptosis [52–54].

One miRNA closely related to tumorigenesis is *miR-497-5p*, and it plays an important tumor suppressor role by regulating the biological behavior of cells. It inhibits Ishikawa cell proliferation and invasion, and it induces apoptosis. This indicates the role of *miR-497-5p* as a tumor suppressor gene in the development of endometrial cancer [55]. It has been reported that *miR-497-5p* reduced the expression levels of key proteins Wnt3a, E-catenin and downstream c-myc and cyclinD1 in the Wnt3a/E-catenin signaling pathway in Ishikawa cells, while PE expression level of catenin protein was significantly increased [56]. Moreover, *miR-497-5p* inhibits the activation of Wnt3a/E-catenin pathway in Ishikawa cells. Thus, *miR-497-5p* may

inhibit the occurrence and development of endometrial cancer by targeting Wnt3a expression, thereby blocking the activation of Wnt3a/E-catenin pathway. Moreover, bioinformatics software prediction and dual luciferase reporter gene experiments were used to confirm that *miR-497-5p* has a complementary binding site in the Wnt3a3cUTR region, indicating that *Wnt3a* is a potential target gene of *miR-497-5p*.

Wnt Signaling Pathway and LncRNA

Endometrial cancer (EC) may be divided into two categories, namely, estrogen-dependent (type I) and estrogen-independent (type II), based on etiology, histology and biological characteristics. In a study, Zhao *et al*. [48] reported that MALAT1 was highly expressed in endometrial hyperplasia and type I endometrial cancer, while its expression was significantly lower in poorly-differentiated and aggressive type II endometrial cancer [57]. The MALAT1 expression was highly related to low-grade histopathological stage but not to FIGO stage. Further investigation revealed that aberrant MALAT1 expression in EC was linked to the Wnt/-catenin signaling system, and that the transcription factor T-cell factor 4 (TCF4), which is downstream of the Wnt pathway, enhanced *MALAT1* gene transcription by interacting with the MALAT1 promoter region [58]. However, Li *et al*. [59] studied 23 type I endometrial cancer tissues and their paired adjacent tissues, and found that MALAT1 was lowly expressed in most of the tissues, and the expression of MALAT1 was correlated with FIGO stage of EC and pathological grade. However, the depth of tumor invasion was not significantly correlated with FIGO stage and pathological grade. The differences in the expression level of MALAT1 among extant research results may be related to this specificity of type I endometrial cancer itself as an estrogen-related tumor [48]. Therefore, the specific mechanism and function of MALAT1 in endometrial cancer remains to be unraveled.

Endometrial Cancer and m6A

The discovery of the first m6A demethylase FTO in 2011 revealed that m6A modifications are dynamically regulated in cells. In 2012, with the development of m6A-based immunoprecipitation sequencing method, the distribution of m6A in mRNAs was fully revealed: about 1/3 of mRNA have m6A modifications with a common DRACH [D = G, A or U; R = G or A; H = A, C or U] binding sequence [60]. Modification of m6A regulates RNA stability, translation, splicing, degradation and other metabolic processes. In addition, m6A participates in the regulation of cell function and in the occurrence of various pathological processes, tumors, inflammation and other diseases. Currently, only a few studies have investigated the overall m6A modification level in ovarian cancer tissues. A study showed no difference in m6A levels between drug-resistant and parental strains of ovarian cancer [59]. Overall, m6A levels are elevated in ovarian endometrioid carcinoma. Bioinformatics analysis of data derived from MERIP-seq of EC tissue samples showed that the m6A peak in EC was significantly reduced. These genes with distinct m6A modifications were associated with insulin resistance and extracellular matrix regulation. The m6A level in endometrial carcinoma was significantly lower than that in normal tissue. Recently, we reported that total m6A levels were lower in metastatic EC. However, the role of m6A as a prognostic indicator requires further research. Wang *et al*. [51] found that the overall m6A level in cervical cancer tissue was lower than that in normal cervical tissue. This decrease is related to various factors such as increased tumor HGO stage, tumor size, decreased differentiation, lymph node metastasis, and recurrence, and it serves an independent factor that affects patient prognosis [9].

Endometrial Cancer and Immune Checkpoint Inhibitor (ICI)

Recent research has identified a link between several cell death mechanisms and anticancer immunity, and even in ICI-resistant tumors, activation of pyroptosis, ferroptosis, and necroptosis, in conjunction with ICIs, resulted in synergistically improved anticancer efficacy [61]. *De novo* pyroptosis in ICI-resistant cancers produces an inflammatory milieu that mediates the susceptibility of tumors to immune checkpoint inhibitors, thereby promoting enhancing pyroptosis and inhibiting growth of autochthonous tumors [62]. Nonetheless, the mechanism through which ICI mediates Wnt signal and endometrial cancer is still poorly understood. It is known that transforming growth factor-beta1 (TGF-β1) is a well-recognized fibrogenic pathway that promotes the activation of inflammatory factors in the early stages of lung fibrosis, as well as fibroblast division and proliferation [63]. Moreover, TGF-β1 enhances collagen synthesis and inhibits collagenase degradation and excessive extracellular matrix deposition in the late stages of lung fibrosis, and regulates the process of lung fibrosis through the TGF-β/Smad pathway [63]. Research has revealed that there is crosstalk between the TGF-β/Smad3 and Wnt/β-catenin signaling pathways: GSK-3β in the Wnt/β-catenin protein pathway influences TGF-β1 signaling by regulating the stability of Smad3, and Smad3-mediated regulation enhances the stability of β-catenin and promotes the activation of downstream target genes [64]. This may be the direction for future research.

Discussion

Abnormal activation of Wnt signaling in adult tissues is associated with the pathogenesis of multiple tumors such as rectal cancer, ovarian cancer, breast cancer, and lung cancer. The proposed mechanism involves acceleration of the cell cycle, cell proliferation, and inhibition of apoptosis through interaction between the Wnt pathway and its

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BIOLOGICAL REGULATORS
and Homeostatic Agents

downstream molecules. Current studies on the Wnt signaling pathway and the pathogenesis of endometrial diseases are limited to the expressions of components in this system, but this provides a reasonable basis for further investigations on the mechanism of the Wnt signaling pathway. The roles of disease-causing factors, and the associated mechanisms will offer a theoretical foundation for the potential use of pathway-specific target gene therapy in the treatment of endometrial illnesses.

The Wnt signaling pathway plays an important role in tumorigenesis and tumor progression. Therefore, inhibition of abnormal activation of the Wnt signaling pathway will be beneficial to cancer treatment. At present, anti-tumor therapeutic factors that target the Wnt signaling pathway include Wnt pathway inhibitors, nucleic acids and small molecule interfering substances that inhibit the inactivation of "degradation complexes" in this pathway. Studies on the involvement of Wnt signaling in the formation and progression of EC may reveal novel targets and therapeutic strategies that may give rise to clinically viable therapies. Furthermore, improperly expressed Wnt signaling molecules may be employed as tumor markers for early diagnosis and prediction of prognosis. A thorough understanding of tumor microenvironmental factors such as estrogen and progesterone will facilitate understanding of the complex interactions that influence tumorigenesis and progression. Moreover, these factors may be targeted to modulate Wnt signaling, with important implications for the diagnosis and treatment of EC.

This review has summarized and described the mechanism underlying the role of the Wnt signaling pathway in EC, and provided updates in related research. Furthermore, we delved into the significance and potential of the influence of Wnt signaling pathway in the treatment of EC, and the impacts of different influence modes on EC, in addition to providing effective biomarkers for future drug design. A summary of the related genes was made available, and a rationale was provided for the possible application of pathway-specific target gene therapy in the treatment of EC. It has also provided some insights into future clinical treatments and diagnosis of EC, as well as drug design.

However, this study has the following limitations: it is only a summary of the current literature, with no specific *in vitro* or *in vivo*, or animal experiments to establish the exact mechanism involved in the impact of these genes. In addition, at present, the curative effect of traditional Chinese medicine (TCM), single or combined prescription, in the treatment of endometrial cancer is definite, whether before or after surgery, and adjuvant chemotherapy modalities demonstrate good curative outcomes. Although we gave illustrations in this regard due to the lack of content about the effect of specific drugs on EC based on the Wnt signaling pathway, we did not specifically explore whether TCM treatment has any effect on the Wnt signaling pathway. This is also our future research direction.

Author Contributions

XLZ and JC designed the research study. JW performed the research. YCT and ZWX analyzed the data. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

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Conflict of Interest

The authors declare no conflict of interest.

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