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Wnt/ β -catenin signaling pathway in the tumor progression of adrenocortical carcinoma

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Adrenocortical carcinoma (ACC) is an uncommon, aggressive endocrine malignancy with a high rate of recurrence, a poor prognosis, and a propensity for metastasis. Currently, only mitotane has received certification from both the US Food and Drug Administration (FDA) and the European Medicines Agency for the therapy of advanced ACC. However, treatment in the advanced periods of the disorders is ineffective and has serious adverse consequences. Completely surgical excision is the only cure but has failed to effectively improve the survival of advanced patients. The aberrantly activated Wnt/ β -catenin pathway is one of the catalysts for adrenocortical carcinogenesis. Research has concentrated on identifying methods that can prevent the stimulation of the Wnt/ β -catenin pathway and are safe and advantageous for patients in view of the absence of effective treatments and the frequent alteration of the Wnt/ β -catenin pathway in ACC. Comprehending the complex connection between the development of ACC and Wnt/ β -catenin signaling is essential for accurate pharmacological targets. In this review, we summarize the potential targets between adrenocortical carcinoma and the Wnt/ β -catenin signaling pathway. We analyze the relevant targets of drugs or inhibitors that act on the Wnt pathway. Finally, we provide new insights into how drugs or inhibitors may improve the treatment of ACC.

KEYWORDS

adrenocortical carcinoma, Wnt/beta-catenin, therapeutic targets, tumor progression, cross talk

1 Introduction

Adrenocortical carcinoma (ACC) is an uncommon, aggressive endocrine malignancy originating from the adrenal gland, influencing 0.5 to 2 persons/million individuals annually worldwide (1, 2). A 5-year survival rate of about 35% following diagnosis, dropping to only 13-16% for stage IV patients, and a significant risk of recurrence and metastasis are all indicators of its typically dismal prognosis (3-5). Currently, only

Mitotane received certification from both the US Food and Drug Administration (FDA) and the European Medicines Agency for the medication of advanced ACC. However, it has minimal therapeutic efficiency and hazardous side effects in the advanced stages of the disease (6, 7). Despite advances in other treatment options, the survival rate of patients with ACC has not altered over the past 40 years (8). Various Wnt signaling inhibitors, acting on different targets, have been discovered. Many of them have shown effective and potential roles in anti-cancer. However, up to now, there are no Wnt inhibitors approved for the treatment of ACC. Previous literature reviews only described the major findings about the relationship between ACC and the Wnt/ β -catenin signaling pathway. There is still a gap in the comprehensive description of drugs with relevant potential target effects.

Based on the relationship between ACC and Wnt signaling, our study summarizes the main findings of biological mechanisms. At the same time, we first describe the new drugs that act on the Wnt signaling and its relative inhibitors, providing new insights into how drugs or inhibitors may improve the treatment of ACC.

2 Overview of the WNT signaling pathway

The Wnt signaling pathway is one of the evolutionarily conserved signaling pathways that control a variety of physiological processes, including cellular apoptosis, proliferation, cellular polarity fate, determination, stem cell maintenance, and migration during development (31, 32). The key factor in the emergence and development of several tumors is the dysregulation of Wnt signaling (33–35). The signaling cascade consists of different branches: the Wnt/ β -catenin or canonical Wnt signaling pathway, the Wnt/ Ca^{2+} signaling pathway, and the planar cell polarization (Wnt-PCP) pathway. Recently conducted studies have concentrated on the Wnt/ β -catenin signaling pathway, which is involved in the emergence of several diseases (36). Table 1 showed the Overview of the WNT signaling pathway. Figure 1 showed the Wnt/ β -catenin signaling pathway and crosstalk involved in this review.

2.1 Canonical Wnt/ β -catenin signaling pathway

For Wnt/ β -catenin signaling to occur, the Wnt ligand must attach to its coreceptor complex, which is composed of the Frizzled (FZD) protein family and low-density lipoprotein receptor-related protein 5 (LRP5) or LRP6 (37). Casein kinase I (CKI), glycogen synthase kinase 3 (GSK3 β), Adenomatous polyposis coli (APC), and Axin form a complex that phosphorylates β -catenin located in the cytoplasm in the absence of Wnt ligands. In this instance, Axin supports the formation of a complex with GSK3 β and APC (38–41). Once the complex is formed, GSK3 β promotes the phosphorylation of cytoplasm β -catenin, and APC facilitates the combination of the ubiquitin-mediated protein hydrolysis pathway to phosphorylated β -catenin in the cytoplasm. When Wnt ligands are present, they attach to their coreceptor complex and then trigger the Wnt signaling by

enlisting Dvl proteins in the cytoplasm and preventing or interrupting the fabrication of the Axin/GSK3/APC complex. This prevents β -catenin from being degraded and causes it to build up in the cytoplasm. The Accumulated proteins translocate into the nucleus, combining with T-cell Factor/Lymphoid Enhancing Factor 1 (TCF/LEF1) thereby regulating the specified genes' transcription (42–44). In addition, the Wnt/ β -catenin signaling pathway interacts with multiple other pathways. In gastrointestinal and breast cancers, it synergizes with TGF β to enhance fibrosis and EMT (epithelial-mesenchymal transition) at the transcriptional level (45, 46). Other research demonstrated that the Hippo and Notch signaling networks can interact with the Wnt/ β -catenin pathway. Several malignancies, such as endometrial carcinoma, hepatocellular carcinoma, and adrenocortical carcinoma, involve CTNNB1 genetic mutations that encode β -catenin (47–49). Phosphorylation sites necessary for the degradation of β -catenin function as mutational hotspots, leading to β -catenin translocation and accumulation to the nucleus, which in turn regulates genetic transcription (50).

2.2 Non-canonical pathways

The homeostasis of both adult and embryonic tissues is connected to the non-canonical planar cell polarity (PCP) pathway, uninvolved by the co-receptor LRP5 or β -catenin. The pathway is initiated through the interaction of Wnt with co-receptors such as ROR2 (receptor tyrosine kinase-like orphan receptor 2), Ryk (RYK receptor-like tyrosine kinase), and FZD and then subsequently triggers the recruitment of protein Dvl to activate c-Jun-N-terminal kinase (JNK) and/or Rho family GTPases (51, 52). The Wnt/ Ca^{2+} pathway is an extra non-canonical pathway that also disregards β -catenin.

The interaction of Wnt ligands with FZD leads to the transient escalation of Ca^{2+} concentration and then increases the production of inositol 1,4,5-trisphosphate under the condition of activated PLC (phospholipase C). The interaction between IP3 and calcium channels located on the surface of the endoplasmic reticulum causes the elevation of Ca^{2+} concentration and the activated CaMKII (Calcium-CaM-dependent protein kinase II). Several regulatory proteins, such as NF- κ B, CREB, and NFAT, are activated by the Ca^{2+} -PLC pathway (53). Further research is required to confirm the reports that FYN-STAT and YAP-TAZ are connected to the non-canonical Wnt pathway (54–56). In addition, sFRP (secreted Fzd-related proteins), Dickkopf family (Dkks), and WIFs (Wnt inhibitory factors) can antagonistically affect tumorigenesis and development mediated by the Wnt pathway (33).

3 Alterations in Wnt

3.1 Wnt ligands

WNT proteins are a class of cysteine-rich secreted glycoprotein signaling molecules. They are involved in tumor development through biological processes such as cell proliferation, apoptosis, migration, and differentiation. According to different biological functions, they are classified into two categories, non-canonical

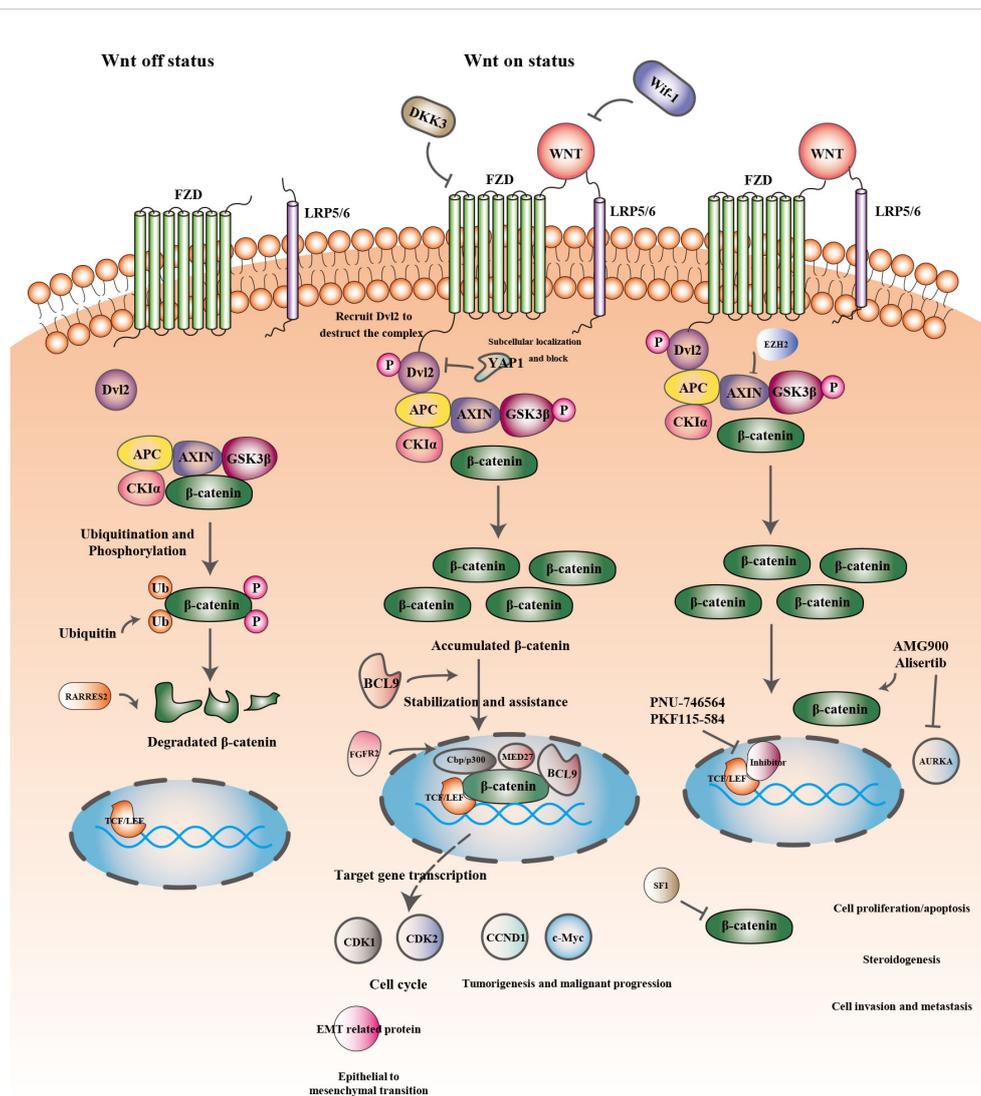


FIGURE 1 Wnt/ β -catenin signaling pathway and crosstalk involved in this review.

signaling substances and canonical WNT/ β -catenin signaling ones (57, 58). High expression of Wnt4 was detected in primary adrenocortical carcinoma cells and tissues (9). Bioinformatic analysis revealed that in ACC tumor tissues, overexpressed Wnt5A was associated with poorer prognostic survival, including progression-free interval (PFI), disease-specific survival (DSS), and overall survival (OS). In ACC, Wnt5A overexpression was positively correlated with microsatellite instability and tumor mutational load, suggesting that it may be a prognostic marker for immunosuppressive checkpoints (10).

3.2 Wif1

In kidney and bladder tumors, dysregulation of Wnt antagonist has been identified as an alternate mechanism for the abnormally activated Wnt signaling pathway (59, 60). Promoter CpG methylation leads to the downregulation of Wif-1 in

adrenocortical tumors. The epigenetic dysregulation might activate the Wnt/ β -catenin pathway, which would then stimulate downstream target gene CCND1 expression to participate in tumorigenesis (11). However, concrete proof is scarce for the mechanism of Wif-1 regulation in adrenocortical carcinoma.

3.3 DKK3/FOXO1

A 38 kDa secreted glycoprotein called dickkopf-associated protein 3 (DKK3), with a signaling peptide at its N-terminal, is dependent on co-expressed ligands and cell surface receptors to exert inhibitory effects in Wnt signaling (61, 62). The level of DKK3 expression is low in the majority of solid tumors and mediates cell apoptosis and/or cycle arrest in over-expression research of various cancer cell types (63–66), exerting a tumor-suppressive role of Wnt signaling regulators. Additionally, ectopic expression of DKK3 suppresses malignant invasion and migration and reverses EMT

TABLE 1 The overview of this review.

No.	Categorizations	Expression	Functions	References
1	Overview of the WNT signaling pathway			
1.1	Canonical Wnt/ β -catenin signaling pathway			
1.2	Non-canonical pathways			
2	Alterations in Wnt			
2.1	Wnt ligands	Overexpressed	Activation of Wnt/ β -catenin pathway	(9, 10)
2.2	Wif1	Downregulated	Activation of Wnt/ β -catenin pathway	(11)
2.3	DKK3/FOXO1	Downregulated	Cell motility and clonal development	(12–14)
2.4	β -catenin	Transcriptionally active	Cell proliferation and apoptosis	(15–17)
3	Transcription factor regulation			
3.1	BCL9	Overexpressed	Tumor progression	(18)
3.2	YAP1	Overexpressed	Cell migration and cell viability	(19)
3.3	AURKA	Overexpressed	Cell proliferation, viability, invasion, and cortisol release	(20, 21)
3.4	MED27	Overexpressed	Cell proliferation, invasion, apoptosis, and cycle	(22)
4	Growth factor signaling			
4.1	FGFR2	Overexpressed	β -catenin phosphorylation and response to WNT protein	(23, 24)
4.2	IGF2	Overexpressed	Cell proliferation and viability	(25)
4.3	SF-1	Overexpressed	Inhibition of Wnt/ β -catenin pathway	(26)
5	Epigenetic regulation			
5.1	EZH2	Overexpressed	Cell viability, clonal expansion, and apoptosis	(27, 28)
5.2	AFF3	Overexpressed	Inhibition of Wnt/ β -catenin pathway	(29)
5.3	RARRES2	Downregulated	Cell proliferation and cell invasion	(30)
6	Drugs and inhibitors			
7	Conclusion and prospect			

effects in multiple cancer cell types, indicating that DKK3 also has a dedifferentiation-blocking function (67, 68). DKK3 is weakly expressed in most adrenocortical carcinoma tumor tissues (12), suggesting a possible oncogenic role in ACC. However, no correlation between clinicopathological features such as age, sex, ENSAT stage, size and weight of the tumor, hormone-secreting phenotype, and expression levels has been observed to correlate significantly (12, 69). Epigenetic modifications, such as chromatin condensation and promoter methylation, are both the mechanisms of DKK3 silencing in the majority of other cancers (66). According to Joyce Y Cheng et al, promoter hypermethylation may contribute to the suppression of DKK3 expression in adrenocortical carcinoma (12). Gene copy number variations have reportedly been linked to adrenocortical carcinogenesis (70, 71). Gene copy loss downregulates DKK3 expression in most ACC samples. However, only a small percentage of these samples concurrently had promoter methylation. This implies that gene copy loss can downregulate DKK3 expression independently from promoter methylation. Furthermore, in ACC tumorigenesis, copy number alterations might manifest more precious than gene-specific methylation (12). Due to the mutations of CTNGB1 and AXIN2, constitutively active Wnt/ β -catenin

signaling is generated in the NCI-H295R cell line. This cell type is unaffected by DKK3 partial silencing or exogenous recombination in terms of viability, clonal growth, or migration, possibly due to the resistance generated by constitutively activated Wnt signaling. The endogenous DKK3 is expressed by the SW13 cell line. Silencing DKK3 expression promotes cell motility and inhibits tumor clonal development, but has little effect on cell viability (13, 14). Exogenous DKK3, in contrast, promotes migration, proposing that endogenous and secreted DKK3 represent distinct functions and may have cellular signaling targets distinct from the traditional Wnt/ β -catenin transmission (61). Additionally, constitutive overexpression of DKK3 prevents the clonal expansion and invasive activity of ACC cells, maybe because of the morphologically differentiated lobular pseudopods' increased attachment to the stroma (72–74). The function of DKK3 in promoting the ACC cell redifferentiation phenotype and/or anti-invasive signaling is partially mediated through FOXO1 (12). FOXO1 is discovered as a potential downstream target of the TGF- β signaling pathway, which also contributes to the pathophysiology of ACC. FOXO1 is weakly expressed in adrenocortical carcinomas. *In vitro*, silencing of FOXO1 resulted in apoptosis-mediated suppression of viability in

SW13 cells along with enhanced cell migration behavior. These findings point to a specific function for FOXO1 in controlling the vitality and motility of adrenocortical cells (12, 75). The tumor-suppressive effect of viability inhibition due to gene downregulation contradicts the enhanced migratory behavior, which may be related to the complex signaling crosstalk in SW13 cells. The enhanced migratory behavior may be due to the involvement of FOXO1 in Wnt signaling-mediated motility restriction, which needs to be verified by separate downstream signaling experiments. Summarily, the research of DKK3/FOXO1 signaling in the adrenal cortex may contribute to the generation of novel medications with a focus on re-differentiation.

3.4 β -catenin

Adrenocortical carcinogenesis is fueled by the abnormally active Wnt/ β -catenin signaling pathway (76), whose vital component is β -catenin and researchers have demonstrated a substantial association between the extent of β -catenin nucleus staining and higher Weiss scores, greater ENSAT tumor stage (stage III and IV), CTNNB1/APC mutations, more frequent mitosis and necrosis, and as well as with poorer OS and PFI in patients (49). In adrenocortical carcinoma, aberrant β -catenin status correlates with upregulation of its target genes LEF1, AXIN2, and ISM1, which are not increased in ACA, indicating that transcriptionally active β -catenin influences proliferative phenotype and the transcriptional level of TCF/LEF target genes (15, 16). Silencing CTNNB1 inhibits H295R cell proliferation and stimulates apoptosis by reducing Wnt/ β -catenin-LEF/TCF-dependent transcription (15). Additionally, as a Wnt/ β -catenin pathway antagonist, PNU-74654 (PNU) functions through competitively binding TCF to interfere with protein-protein interactions. It has been demonstrated that PNU promotes apoptosis and prevents proliferation by blocking the TCF/ β -catenin complex (15). Another study revealed that PKF115-584 dose-dependently promotes NCI-H295R cell apoptosis and also suppresses cell proliferation and β -catenin-dependent transcription (17). The primary cause of dysregulated cell proliferation is abnormal cell cycle progression. Different cell cycle inhibitors and proteins work together to regulate the cell cycle. CCND1, CDK1, and CDK2 are significant proteins that regulate the G1/S transition of the cellular cycle and are also repressed as downstream targets of Wnt signaling according to the aforementioned mechanism study (77). The same regulatory phenotype was observed for silencing CTNNB1 in a xenograft mouse model (16). The abnormally activated Wnt/ β -catenin pathway in the adrenal cortex of the mouse models alone results in tissue hyperplasia. A malignant phenotype occurs in the adrenal cortex when p53 is simultaneously deleted (78).

4 Transcription factor regulation

4.1 BCL9

As a transcriptional co-activator of Wnt/ β -catenin signaling, the oncogenic gene B-cell lymphoma 9 (BCL9) is essential for the formation and progression of a variety of malignancies (79).

Targeted disruption of the BCL9/ β -catenin complex inhibits oncogenic Wnt signaling (80, 81). Current studies have observed the association between the overexpression of BCL9 and tumor formation, including breast cancer, renal cell carcinoma, hepatocellular carcinoma, and colorectal cancer (82–85). BCL9 is elevated in adrenal malignancies, and its upregulation level is significantly associated with tumor aggressiveness. Immunohistochemical techniques revealed higher expression status in ACC tumor tissues with the distinct cytoplasm and nucleus diffuse expression pattern (18). Prior research has shown that BCL9 enhances tumor cell proliferation *in vitro* (83). Silencing BCL9 expression significantly inhibited the clonal growth of SW13 cells. But in H295R cells which have the CTNNB1 mutation, silencing BCL9 did not interfere with the potential for clonal growth. This phenomenon indicates that high expression of BCL9 may accelerate ACC tumor progression by triggering the Wnt tumorigenic pathway (18). Earlier research has revealed the potential functions of BCL9 in tumor metastasis and invasion in colorectal cancer (85, 86) and significant upregulation was observed in ACC. Only 5.8% of the ACA cohort revealed more than a double increase of BCL9 expression levels, while 40 percents of the ACA tissues displayed a double expression upregulation, indicating that upregulation of BCL9 expression in adrenocortical carcinoma is correlated to the malignant characters. Taylor C Brown et al. attempted to identify the relationship between the different clinical characteristics and BCL9 expression patterns. However, no significant correlation was found, but there was a propensity towards elevated expression status for elderly individuals, although not reaching significance (18), which may be due to the limited cohort sample. The activity and/or stability of both molecules may be enhanced by the capacity of BCL9 to connect with the β -catenin, while the overexpression of β -catenin may have this same benefit (87). Regarded as the co-activator of β -catenin located in the nucleus, BCL9 can translocate β -catenin to the TCF and promotes the activation of Wnt-responsive transcription genes (cyclinD1, c-Myc), several of which are strongly associated with carcinogenesis and the progression of malignancy (88). Currently, a growing quantity of research initiatives have concentrated on medications that are protein-protein interaction inhibitors that disrupt interactions between β -catenin and Bcl9 in the tumor Wnt/ β -catenin pathway in an attempt to uncover promising candidates for enhancing immunity and inhibiting tumor growth (89).

4.2 YAP1

As the Hippo pathway-associated transcription factor-like protein, Yes-associated protein1 (YAP1) is an oncogenic gene and it is involved in tissue regeneration, cell embryogenesis, and proliferation (90–92). In cancer cell lines, overexpressed YAP1 is correlated with the formation and growth of tumors. Furthermore, YAP1 can engage with multiple signaling pathways including Wnt/ β -catenin, Notch, and Sonic Hedgehog (SHH), in addition to the Hippo pathway (91, 93, 94). For instance, YAP1 synergizes with β -catenin to activate genes necessary for epithelial repair and stem cell proliferation (90). Previous research has demonstrated that YAP1 can participate in inhibiting Wnt/ β -catenin signaling by regulating

the subcellular localization of DVL2 or blocking DVL2 (94–96). Immunofluorescence reveals overexpressed YAP1 both in the adrenocortical tumors (ACTs) of children, as well as in the cytoplasm and nucleus of fetal adrenal cells, while diminished expression of YAP1 is observed in the postnatal adrenal cortex, pointing to the potential involvement of YAP1 in promoting tissue dedifferentiation and proliferation (19). Treatment of the NCI-H295R cell lines with a TCF/ β -catenin complex inhibitor (PNU-74654) observed a lessened protein expression but an increased mRNA expression. This phenomenon can be attributed to post-transcriptional regulation. The decrease in protein expression may result in negative feedback triggering an increase in mRNA expression. *In vitro* experiments involving the silencing of YAP1 demonstrated an increase in CTNNB1 nucleus and protein expression, without any noticeable alteration in Dishveld2 (DVL2) mRNA expression. This observation can be attributed to the ability of YAP1 to either sequester DVL2 in the cytoplasm or facilitate its translocation to the nucleus, depending on the β -catenin phosphorylation status (15, 19). In response to alterations in the different extracellular matrix (ECM), YAP1 participates in cellular mechanotransduction by interacting with cell adhesion molecule-bound α -catenin. In the hard ECM, activated YAP1 accumulates in the nucleus. Conversely, in softened ECM, YAP1 is accumulated and degraded in the cytoplasm (97–99). Additionally, increased ECM stiffness causes a deficiency of intercellular connections, which promotes metastasis and epithelial-mesenchymal transition (EMT) (100). Loss of intercellular junctions during EMT can block Hippo signaling and thus activate YAP1 (97). In the NCI-H295 cell line, the knockdown of YAP1 inhibited cell migration and cell viability, implying that YAP1 contributes to adrenocortical cell growth and metastasis. Furthermore, the mRNA expression of YAP1 was upregulated in patients with recurrence and/or metastasis (R/M) and death. The overexpression was correlated with worse OS of patients (19). These results highlight the correlation of YAP1 in relapsed and/or metastatic disease.

4.3 AURKA

The protein Aurora kinase (AURK) regulates the cell cycle and controls cell growth through involvement in DNA damage and kinase overexpression, with three subunits involved in cell division in the G1-M phase (101). In comparison to normal adrenal tissues, AURKA and AURKB expression was upregulated in adrenocortical carcinoma and three cell lines (CU-ACC1, CU-AAC2, and NCI-H295R), while no discernible differences were observed for AURKC. In both pediatric and adult patients, the overexpression of AURKA and AURKB was correlated with a worse prognosis, implying that kinases may be implicated in the tumorigenic effects of ACC (20). AMG900 is a highly selective and orally bioavailable pan-aurora kinase inhibitor that effectively reduces cell proliferation and is effective against multi-drug resistant cell lines. Treatment of the NCI-H295R cell line with AMG900 alone reduced cell viability, promoted apoptosis, and suppressed cell invasion and metastatic capacity and also inhibited

cell proliferation, increased the chemosensitivity of the NCI-H295R cell lines to a variety of drugs including mitotane, doxorubicin and etoposide, among other anticancer drugs (20, 21). The considerable increase of CTNNB1, MYC, and c-MYC was observed after the application of the NCI-H295R cell lines with AMG900, suggesting that AMG900 may contribute to activating the Wnt/ β -catenin pathway (20). The combination with PNU-74654, the Wnt/ β -catenin signaling pathway inhibitor, had a greater impact on the suppression of cellular proliferation and viability, indicating that enhanced expression of c-Myc and CTNNB1 resulting in AMG900 treatment could be interdicted by PNU-74654, thus resulting in a synergistic antitumor effect. The inhibition of Aurora kinase caused by AMG900 prevented colony production and cell invasion in NCI-H295R cells, and the combination with PNU-74654 did not enhance this effect. Conversely, blocking the Wnt/ β -catenin pathway had a better impact on reducing cortisol release from NCI-H295R compared to inhibiting Aurora kinase. The AURKA inhibitor Alisertib demonstrated good efficacy in phase I/II/III clinical trials and several tumor types. Compared to the combination of PNU-74654 and AMG900, the impact on, the combination of PNU-74654 and Alisertib was observed more effective in suppressing the cell viability of NCI-H295R cells, implying that the function generated by AMG900 on cell viability of adrenocortical carcinoma may be caused by the inhibition of AURKA. According to these studies, targeting ACC malignancies may be accomplished by inhibiting aurora kinase activity and blocking the β -catenin pathway simultaneously (20, 102).

4.4 MED27

The MED complex is a family of transcriptional co-activators consisting of multiple proteins that can participate in the regulatory process of genes dependent on RNA polymerase II transcription by interacting with transcription factors to turn on the assembly of transcription initiation complexes and consequently gene transcription (103–106). Overexpressed MED27 in ACC tissues is associated with low survival rates in patients. *In vitro* cellular and *in vivo* mouse models, silencing of MED27 decreases proliferation and cell invasion and induces apoptosis and cellular cycle organization. Additionally, suppressed MED27 resulted in altered expression levels of EMT-related proteins, suggesting that MED27 may mediate ACC invasiveness by stimulating the EMT procedure. Hongchao He et al. discovered that downregulated transcription of β -catenin and its target gene was observed by the knockdown of MED27, suggesting that Wnt/ β -catenin pathways might contribute to the phenotypic regulation mediated by MED in ACC (22).

5 Growth factor signaling

5.1 FGFR2

Different fibroblast growth factors can stimulate the proliferation and expansion of adrenocortical cells (107–109). As

a tyrosine kinase receptor, FGFR2 (Fibroblast growth factor receptor type 2) consisting of an intracellular tyrosine kinase structural domain and an extracellular immunoglobulin-like structural domain is encoded on human chromosome 10q26 (110, 111). The basic fibroblast growth factor-regulated transcriptional co-activator CITED2 (Cbp/p300 interaction transactivator 2) participates in adrenal development in adrenocortical cells (23). Research has revealed that FGFR2 is associated with the growth and development of adrenal glands in mice. Absence of this receptor subtype leads to impaired adrenal differentiation and growth during the development of adrenal (112). Adrenocortical progenitor cells are stimulated to proliferate and prevent apoptosis by FGFR2 signaling (113). Current studies identified abnormal FGFR2 signaling as an essential factor in carcinogenesis and a possible therapeutic approach for various tumor types (114). The activated WNT/ β -catenin pathway is one of the main mechanisms involved in the pathophysiology of adrenocortical carcinoma. Approximately 10 to 15 percent of patients have CTNNB1 activating mutations, which lead to aberrant nucleus accumulation of β -catenin (115). While FGFR signaling has been determined to trigger the canonic WNT signaling through β -catenin phosphorylation and increased cellular response to Wnt in other cell types (24). The majority of adrenocortical carcinomas had diverse degrees of FGFR2 expression in the cytoplasm and nucleus, according to Matthias Haase et al. However, due to insufficient sample size, no significant correlation was discovered between CTNNB1 mutation status and other clinical characteristics (116). Alternatively, FGFR signaling may promote adrenocortical tumors by triggering WNT signaling upstream of growth, independent of CTNNB1 activating mutations. Additionally, there are two separate isoforms of FGFR2, namely FGFR2b (epithelial variation) and FGFR2c (mesenchymal variant), which differ in their immunoglobulin-like structural domain. Variable expression and splicing of FGFR2 isoforms may promote tumor progression under the mechanism of EMT (117). Therefore, further experiments might concentrate on the differential expression and intracellular localization of FGFR2 isoforms in adrenocortical cancer cells.

5.2 IGF2

As a key growth factor for adrenocortical growth, insulin-like growth factor 2 (IGF2) (117), acts as a mitogen binding with cell surface receptor IGF-1R, auto-phosphorylates and activates downstream signaling cascades and participates in processes such as cellular proliferation, and the regulation of cell cycle (118). IGF2 expression is upregulated in ACC, and *in vitro*, high concentrations of IGF2 promote H295R cell proliferation and increase cell viability while having no effect on invasive capacity (25). The overexpression of IGF2 is normally correlated to constitutive activation of β -catenin in ACC patients, implying that variations in both signaling pathways might expedite the development of malignancy. However, in the IGF2 transgenic adrenal tissues, Coralie Drelon et al. failed to detect activated Wnt/ β -catenin signaling (119). Provided that Wnt signaling is activated, overexpressed IGF2 moderately accelerates cancer

development but is insufficient to initiate the progression of malignant tumors (120).

5.3 SF-1

Steroid growth factor 1 (SF-1) is a nuclear receptor and it is involved in the expression of cell cholesterol homeostasis genes and steroid hormone synthesis (121) and also involved in the growth and development of steroid-producing glands such as adrenal and gonadal tissues (122, 123). By interacting with particular response components in target gene promoters, SF-1 recruits repressor complexes to silence target genes or activator complexes to activate target gene transcription by regulating histone modifications to activate target gene transcription (124–126). Anna Ehrlund et al. found that SF-1 may regulate target gene expression by adversely influencing Wnt/ β -catenin pathways through the inhibition of β -catenin transcription (26), but the impact on oncological phenotypes has not been elucidated completely.

6 Epigenetic regulation

6.1 EZH2

Figure 2 showed the epigenetic regulation and Wnt/b-catenin signaling pathway in ACC. Histone methyltransferase (EZH2) is one of the primary catalysis enzymes in the polycomb repressor complex (PRC2) and catalyzes the trimethylation of histone H3 lysine 27 (H3K27me3) to mediate target genes silencing (127). In adrenocortical carcinoma, EZH2 is the most dramatically dysregulated histone modifier, and its overexpression is correlated to poor prognosis and tumor proliferation in patients (27). *In vitro*, RNA interference with EZH2 inhibits H295R cell viability and clonal expansion and induces apoptosis (28). In other tissues, EZH2 stimulates Wnt signaling by inhibiting WNT antagonists (AXIN2, NKD1, PPP2R2B, PRICKLE1, SFRP5, CXXC4) (128–130), but its role in Wnt signaling in ACC has rarely received attention.

6.2 AFF3

AFF3 is expressed in the adrenal tissue of mice throughout embryonic development and may be involved in the formation of adrenal glands. According to the immunohistochemical results, B Ragazzon et al. found that AFF3 expression was significantly higher in nuclear β -catenin-stained positive cohorts than in nuclear-stained negative and normal adrenal tissue, while high expression of AFF3 is correlated to poorer OS of patients. Additionally, suppression of either Wnt/ β -catenin/TCF or LEF1 decreases AFF3 mRNA levels (29). Regulation of downstream target genes by Wnt/ β -catenin generally involves the binding of the transcription factors LEF/TCF to the Wnt response element (WRE), as well as the accumulation of β -catenin. AFF3 has two

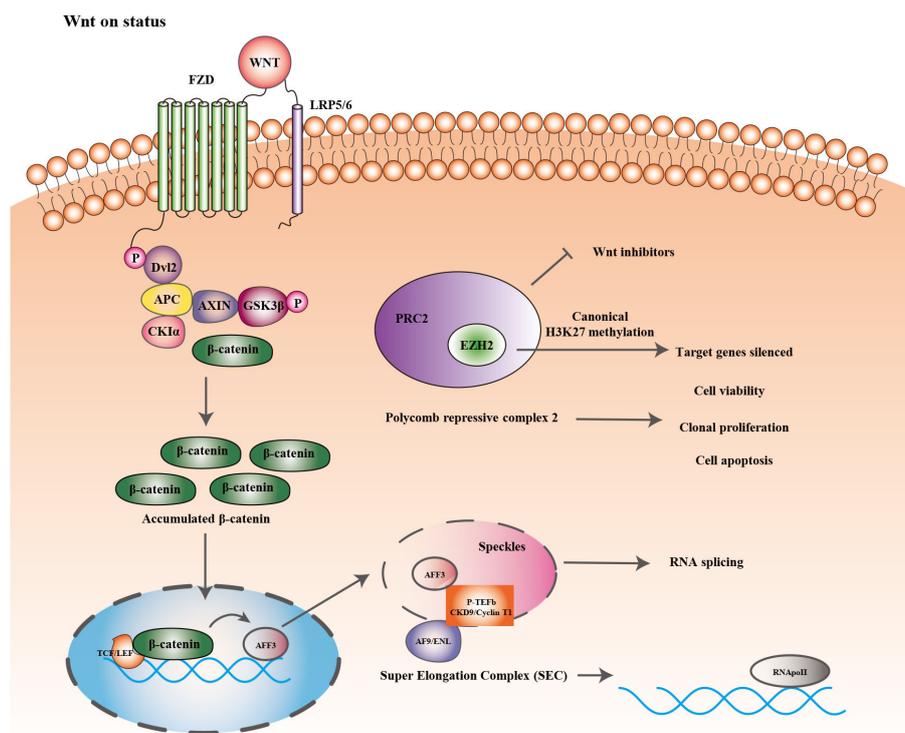


FIGURE 2 Epigenetic regulation and Wnt/ β -catenin signaling pathway.

transcriptional start sites (TSS). In H295R cells, the WRE site, located at nucleotide position -1408 of the AFF3 TSS, participates in regulating Wnt/ β -catenin signaling. Earlier studies have discovered that AFF proteins are present in nuclear patches and involved in mRNA shearing (131). The super elongation complex (SEC) composed of the protein AFF (AF4/FMR2), positive transcriptional elongation factor b (P-TEFb), and other elongation factors modulate RNA polymerase II's transcriptional elongation (132). AFF3 exists in the SEC of adrenocortical cells and its interaction with CDK9 and cell cycle protein T1 (a crucial component of P-TEFb) changes the nuclear distribution of the latter (29). The results above suggest that in adrenocortical cells AFF3 can regulate the activity of P-TEFb. Therefore, the discovery and development of potential antagonists that interfere with the stability or organization of SEC and affect the accumulation of cancer genes to chromatin would be promising anticancer medicines.

6.3 RARRES2

Regarded as a secreted ligand of the G protein-coupled receptor chemokine-like receptor 1 (CMKLR1), Retinoic acid receptor response protein 2 (RARRES2) (133, 134) participates in the immunological defense by acting as a chemokine that recruits CMKLR1-expressing immune cells to the positions of injured lymphoid tissues and organs (133). In ACC, CpG

hypermethylation silences the expression of RARRES2 with significantly decreased and correlated mRNA and protein expression levels. *In vitro*, overexpression of RARRES2 through transient transfection inhibited cell proliferation and cell invasion but had no significant effect on cell migration. In addition, stable overexpression of RARRES2 resulted in reduced colony formation in clone formation assays and wall-independent cell growth in soft agar colony formation assays. The degree of inhibition was directly proportional to the level of RARRES2 expression, indicating that RARRES2 has a dose-dependent growth inhibitory effect. Mechanistic studies revealed that overexpression promoted β -catenin phosphorylation at Ser33/Ser37/Thr41, leading to increased degradation of β -catenin, thereby reducing total β -catenin levels. Furthermore, the excessive expression of RARRES2 inhibited the activity of the transcription factor TCF/LEF, which in turn inhibited the Wnt/ β -catenin signaling pathway and downstream gene expression. Phosphorylated p38 signaling is present in most ACC tumor samples (30). Overexpression of RARRES2 inhibits p38 mitogen-activated protein kinase phosphorylation, which is considered a promising treatment target for adrenocortical tumors (135). Previously conducted studies found that RARRES2 acts as a secreted protein that recruits CMKLR1-expressing NK cells to tumor sites to exert tumor suppressive effects indirectly (133). However, endogenous receptors were not detected in adrenocortical carcinoma cell lines, suggesting that the observed tumor suppressive effects may be independent of immune mechanisms.

7 Drugs and inhibitors

From the mechanism aspect, the transmission of the Wnt/ β -catenin pathway is regulated at four levels. This also provides new directions for the development of clinical medicine treatment. Including extracellular and cell membrane (expression of WNT ligand, WIF1, DKK), cytoplasm (expression level and stability of β -catenin), cell nucleus (involvement of TCF/LEF, SF1 transcription factors), and crosstalk of other signaling pathways (FGFR, IGF2).

Curcumin, as a natural product derived from turmeric, has been used in the treatment of other cancers (145). Several preclinical studies and clinical applications have reported its therapeutic effect (146, 147). *In vitro*, it has been demonstrated that curcumin has significant antiproliferative effects on a variety of cancer cells through the inhibition of Wnt signaling. EF24, a more soluble curcumin derivative, has similar safety efficiency and higher anticancer activity (148). According to Loris Bertazza's study, EF24 exerts antiproliferative effects in ACC through multiple pathways, including the Wnt/ β -catenin signaling, NF- κ B pathway, MAPK pathway, and PI3k/Akt pathway (140).

Nutlin-3a, a classical MDM2 inhibitor, has unexpected pharmacological effects in cancer cells with mutations in CTNNB1. CTNNB1 is a subunit of the calmodulin complex, encodes β -catenin, and acts as an intracellular signaling molecule to activate the Wnt signaling pathway (149). Activating mutations or overexpression of CTNNB1 results in the activation of the Wnt/ β -catenin pathway, and is also associated with tumorigenesis in ACC (150). Wen Hui used bioinformatics analysis, and *in vitro* and *in vivo* experiments to demonstrate that Nutlin-3a inhibits several characteristics of H295R cells, including proliferation, EMT, hormone production, and tumorigenesis, making Nutlin-3a an attractive drug for the treatment of CTNNB1-mutated ACC (142).

Rottlerin is a natural plant polyphenol. In recent years, it has been shown anticancer activity in several cancers, such as prostate cancer and pancreatic cancer (151). Yi Zhu demonstrated Rottlerin inhibits cell proliferation, invasion, and metastasis and induces apoptosis and cell cycle arrest by inhibiting Wnt/ β -catenin signaling (143).

Abiraterone Acetate is a potent inhibitor of 17 α -hydroxylase/17,20-lyase (CYP17A1) (152). Due to its inhibition of the synthesis of adrenal androgen, it has been used in metastatic castration-resistant prostate cancer (CRPC). In Sandra Sigala's view, abiraterone exerts a cytotoxic effect through the progesterone receptor (PgR). In the H295R cell line, abiraterone inhibits nuclear translocation of β -catenin, thereby inhibiting the Wnt/ β -catenin signaling (144).

Tegavivint, a newly developed inhibitor of TBL1, is in clinical trials now. On the one hand, it disrupts the binding of β -catenin and the transactivator protein β -like protein 1 (TBL1, a key bridging protein for β -catenin binding and transcriptional activation). On the other hand, it promotes SIAH-1-mediated degradation of nuclear β -catenin (153–156). Tegavivint inhibits the Wnt/ β -catenin signaling pathway, decreases the expression of extracellular matrix components, and inhibits cell viability and tumor growth (136). PKF115-584 is a T cell factor/ β -catenin antagonist, that dose-dependently inhibits β -catenin-dependent transcription and cell proliferation (17).

Vitamin D receptor is overexpressed in H295R cells due to hypermethylation. By inhibiting Wnt/ β -catenin signaling through the activation of VDR, calcitriol inhibits tumor proliferation and growth (137). The combination role of mitotane and calcitriol, regulates the VDR and Wnt/ β -catenin signaling, exerting antiproliferative effects (139). Mechanistically, calcitriol, the activated form of vitamin D, promotes β -catenin binding to VDR and reduces binding with the transcription factor TCF/LEF. Current drugs and inhibitors that modulate Wnt/ β -catenin are shown in Table 2.

TABLE 2 The current drugs and inhibitors.

No.	Name	Target	Intervention mechanism	References
1	Tegavivint	TBL1	Inhibits tumor growth by interfering with β -catenin binding to TBL1	(136)
2	PKF115-584	TCF	Inhibits cell proliferation by interfering with β -catenin binding to TCF	(17)
3	Calcitriol/Seocalcitol	VDR	Suppresses cell proliferation and tumor growth by activating VDR signaling and inhibiting Wnt/ β -catenin signaling	(137)
4	Telomelysin	TERT	Inconclusive	(138)
5	Mitotane + 1 α ,25-dihydroxy vitamin D3	VDR+Wnt/ β -catenin	Inhibits cell growth and viability synergistically	(139)
6	EF24	Multiple pathways	Inhibits cell viability, invasion, and clone through multiple pathways	(140)
7	Progesterone	Wnt/ β -catenin	Promotes apoptosis	(141)
8	Nutlin-3a	MDM2	Inconclusive	(142)
9	Palbociclib/Ribociclib	CDK4/6	Induces apoptosis, cell cycle arrest, and senescence	(138)
10	Rottlerin	Wnt/ β -catenin	Inhibits cell proliferation and invasive metastasis. Induces apoptosis and cell-cycle arrest	(143)
11	Abiraterone	CYP17A1	Inhibits cortisol and androgen, and increases progesterone secretion. Inhibits cell viability and proliferation via PgR	(144)

Telomerase reverse transcriptase (TERT) and regulator of telomere elongation helicase 1 (RTEL1) play key roles in telomere homeostasis (157). Studies have shown that they present in ACC with an increasing number of gene copy and promoter mutations, and relate to clinicopathologic features and poor prognosis. Bioinformatics analysis indicated that high TERT and RTEL1 mRNA levels were associated with the Wnt/ β -catenin signaling pathway (158), but there is no experimental proof. Studies of combination therapy of Telomelysin and pembrolizumab for various solid tumors are currently undergoing (NCT03921021, NCT04685499, NCT02293850, NCT03190824). However, whether Telomelysin (OBP-301 and INO5401) can play a role in the treatment of ACC remains to be confirmed.

As an inhibitor of CDK6, Palbociclib has been approved by the FDA and used for the first-line treatment for advanced or metastatic breast cancer with HR⁺ or human epidermal growth factor receptor 2-negative (HER2⁻) (159). Djihad's vitro experiments demonstrated that palbociclib induced the reduction of active β -catenin, and also inhibited the induced transcription and β -catenin-dependent apoptosis (138).

8 Conclusion and prospect

In recent years, there has been significant progress in the studies of targeted drugs and molecular inhibitors as a means to inhibit tumor progression. This has provided a new perspective on the treatment of ACC and opened up exciting possibilities for more effective therapies. Given that ACC pathogenesis has been linked to prolonged stimulation of the Wnt/ β -catenin signaling pathway, it is crucial to investigate its involvement as a driving factor. From aspects of Wnt signaling pathway alteration, transcription factor regulation, growth factor signaling pathway, and epigenetic regulation, our review describes the interaction of different molecules and complexes with the Wnt signaling pathway in

ACC. At the same time, we summarize the new drugs and inhibitors that regulate the Wnt signaling pathway. In conclusion, obstructing Wnt/ β -catenin signaling could be an appropriate alternative treatment for ACC patients and it is crucial to identify methods that can safely and effectively prevent the activation of the β -catenin pathway for patients.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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