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Potential signaling pathways as therapeutic targets for overcoming chemoresistance in mucinous ovarian cancer (Review)

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Abstract. Cases of mucinous ovarian cancer are predominantly resistant to chemotherapies. The present review summarizes current knowledge of the therapeutic potential of targeting the Wingless (WNT) pathway, with particular emphasis on preclinical and clinical studies, for improving the chemoresistance and treatment of mucinous ovarian cancer. A review was conducted of English language literature published between January 2000 and October 2017 that concerned potential signaling pathways associated with the chemoresistance of mucinous ovarian cancer. The literature indicated that aberrant activation of growth factor and WNT signaling pathways is specifically observed in mucinous ovarian cancer. An evolutionarily conserved signaling cascade system including epidermal growth factor/RAS/RAF/mitogen-activated protein kinase kinase/extracellular signal-regulated protein kinase, phosphoinositide 3-kinase/Akt and WNT signaling regulates a variety of cellular functions; their crosstalk mutually enhances signaling activity and induces chemoresistance. Novel antagonists, modulators and inhibitors have been developed for targeting the components of the WNT signaling pathway, namely Frizzled, low-density lipoprotein receptor-related protein 5/6, Dishevelled, casein kinase 1, AXIN, glycogen synthase kinase 3β and β-catenin. Targeted inhibition of WNT signaling represents a rational and promising novel approach to overcome chemoresistance, and several WNT inhibitors are being evaluated in preclinical studies. In conclusion, the WNT receptors and their downstream components may serve as novel therapeutic targets for overcoming chemoresistance in mucinous ovarian cancer.

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Key words: mucinous ovarian cancer, WNT signaling, chemoresistance, therapeutic targets

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1. Introduction

Epithelial ovarian cancer comprises a heterogeneous group of tumors that have distinct clinicopathological and molecular features as well as multiple underlying causative genetic mutations (1). High-grade serous ovarian cancer originates *de novo* from the fallopian tube fimbriae, while clear cell endometrioid tumors arise from endometriosis (1). Mucinous ovarian cancer accounts for approximately 10% of epithelial ovarian cancer, but its tissue origin remains controversial (2). Primary mucinous cancer frequently presents as a large (>10 cm) clinically unilateral tumor similar to benign cystadenoma and borderline tumors (3). Occasional presentation as <10-cm tumor or clinically bilateral tumor may be features that contribute to metastases from other sites including the appendix, colon, stomach, pancreas and biliary tract (3). At baseline, primary mucinous ovarian tumors progress from benign to borderline to invasive cancer in a stepwise manner, all of which generally have a good prognosis (3). Mucinous tumors are more frequently detected in early-stage disease with lower tumor grading compared with high-grade serous cancer; however, patients with advanced disease have poor clinical outcome, possibly due to resistance to taxane and platinum-based conventional chemotherapy (4). An evolutionarily conserved signaling cascade system, including growth factor pathways [epidermal growth factor receptor (EGFR), ERBB and fibroblast growth factor receptor (FGFR)] and Wingless (WNT) signaling pathways, regulates a variety of cellular functions, including chemoresistance (5). The crosstalk between EGFR/KRAS

proto-oncogene/B-Raf proto-oncogene (BRAF)/mitogen-activated protein kinase (MAPK), phosphatidylinositol-3 kinase (PI3K)/Akt (also known as protein kinase B) and WNT signaling pathways sustains PI3K/glycogen synthase kinase-3β (GSK3β)/β-catenin signal activation, which is associated with chemoresistance in cancer (6). The WNT receptors and their downstream components are being investigated as potential targets in the development of novel anticancer therapies (5,6).

The present article aimed to summarize the underlying molecular mechanisms of chemoresistance in mucinous ovarian cancer, focusing on the WNT signaling pathway. Novel therapeutics that may target chemoresistant processes from bench to bedside were also discussed. In this regard, a systematic review of the literature using an electronic search of the PubMed database (http://www.ncbi.nlm.nih.gov/pubmed) was conducted. Relevant literature published between January 2000 and October 2017 was searched. The search strategy screened for full-text original research or reviews in peer-reviewed journals with at least one of the key words 'mucinous ovarian cancer', 'chemoresistance', 'WNT/Wingless', 'EGFR/epidermal growth factor receptor', 'FGFR/fibroblast growth factor receptor', 'signaling pathway', 'inhibitor' or 'antagonist' in their titles or abstracts. English-language publication search results from PubMed and references within the relevant articles were analyzed. To minimize selection bias, screening of the studies was independently performed by two reviewers following agreement on the selection criteria.

2. Potential candidate gene alterations in mucinous ovarian cancer

Previous studies have identified potential gene alterations implicated in the carcinogenesis and progression of mucinous ovarian cancer (2,7-10). Mucinous tumors are likely driven by constitutive signaling activation resulting from mutagenic processes (BRAF and KRAS mutations) and growth factor amplifications (EGFR and MYC proto-oncogene amplifications) (2,8-10). The BRAF and KRAS mutations frequently identified in mucinous ovarian cancer have also been observed in low-grade serous ovarian cancer and serous and mucinous borderline tumors (7). One such activating driver mutation is $BRAF^{V600E}$, a substitution of glutamic acid for valine in codon 600 in exon 15 (7). BRAF mutations have diagnostic and prognostic value in many tumors including not only mucinous ovarian cancer, but also melanoma (11), colorectal cancer (12), thyroid cancer (13), brain tumors and various other cancers (14). Furthermore, the mutation rate in KRAS for proven pathogenic mutations is 60-70% (7). EGFR triggers cell proliferation through the RAS/RAF/MAPK signaling pathway. Erb-b2 receptor tyrosine kinase 2 (ERBB2; also known as human epidermal growth factor receptor 2, HER2) amplification is relatively common (~20%) in mucinous ovarian cancer and borderline mucinous tumor (2,7-10). Concurrent aberrant ERBB2 and KRAS signaling has been observed in a marked number of cases (~11%), suggesting that acquired ERBB2 amplification is secondary to the emergence of KRAS activating mutation (10). Although oncogenic KRAS driver mutations and ERBB2 amplification are not mutually exclusive (15), KRAS mutations may be mutually exclusive with c-MYC amplification (9).

In addition, some cases of mucinous ovarian tumors may harbor clinically targetable tumor protein p53 (TP53) mutations; indeed TP53 is the most commonly altered gene in high grade-serous ovarian cancer (2,8). TP53 mutations have been observed to be more frequent in mucinous cancer when compared with borderline tumors (57 vs. 12%, respectively) (10). Mucinous ovarian cancer has been associated with homozygous loss of the cyclin dependent kinase inhibitor 2A (CDKN2A) locus (2,8). Infrequent cases of mucinous ovarian cancer also harbored additional mutations, including in ring finger protein 43 (RNF43), WNT and WNT family members, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha, phosphatase and tensin homolog, cadherin 1, E74 like ETS transcription factor 3 (ELF3), AT-rich interaction domain 1A, GNAS complex locus (GNAS), G protein subunit alpha 11 (GNA11), forkhead box L2, FGFR2, serine/threonine kinase 11 (STK11), β-catenin (also known as catenin beta-1, CTNNB1) and SMAD family member 4 (SMAD4) (2,7,10,16). Mutations of these genes are considered to serve roles in the tumorigenesis, progression, aggressive features and clinical outcome of a subset of mucinous ovarian tumors (16). These mutated genes have been identified in a variety of tumor types, including tumors of the gastrointestinal tract, pancreas and endometrium (16). For example, mutations in RNF43, an E3 ubiquitin-protein ligase, have been observed in pancreatic, colorectal and mucinous ovarian cancers (17). Gene mutation data indicated that mucinous-type tumors from different sites have marked similarities to mucinous ovarian cancer (2). Notably, the majority of these mutated genes, including RNF43, ELF3, GNAS, GNA11, STK11, CTNNB1 and SMAD4, may serve a crucial role in regulating WNT signaling (2,7,10). Mutations in key genes and aberrations in the WNT pathway are typically requisites for mucinous-type cancers and often result in increased nuclear β-catenin (2).

The genetic landscape of a variety of benign, borderline and malignant lesions has been gradually characterized. Genetic alterations of the RAS/RAF/MAPK, PI3K/Akt and WNT/β-catenin signaling pathway members have been reported to increase in a stepwise manner from mucinous borderline tumors to mucinous ovarian cancer (18). The crosstalk between the growth factor and WNT signaling pathways may sustain PI3K/GSK3β/β-catenin signal activation, which is associated with chemoresistance in cancer (18).

3. Growth factor and WNT pathways

Growth factor pathways. Somatic mutations or amplifications of the EGFR (also known as ERBB1 or HER1), ERBB2 and FGFR family members have been reported in numerous cancers, including non-small-cell lung cancer (19), metastatic colorectal cancer, glioblastoma (20), head and neck cancer, pancreatic cancer, breast cancer and ovarian cancer (21). EGFR activates the RAS/RAF/MAPK pathway and the PI3K/Akt pathway, which leads to activation of c-Myc and cyclin D1. Members of the ERBB family of receptors serve key roles in chemoresistance (5,22). FGF stimulates SRC proto-oncogene/focal adhesion kinase, SRC/PI3K/Akt, Hedgehog, Notch, transforming growth factor-β and noncanonical WNT signaling cascades and regulates a variety of cellular functions (5,21,22). The nonreceptor tyrosine kinase Src, the downstream target

of FGFR, has been reported to serve an important role in chemoresistance in mucinous ovarian cancer (23). Thus, an association between the expression of growth factor pathways and increased resistance to chemotherapy in mucinous ovarian cancer has been implicated.

WNT pathways. The WNT signaling pathways have been classified into canonical [WNT/β-catenin/T-cell factor (TCF)] and two non-canonical [WNT/planar cell polarity (PCP)] and WNT/Ca^{2+} pathways (24). WNT signaling regulates a variety of cellular functions, including carcinogenesis, proliferation, adhesion, migration, invasion, angiogenesis, progression, survival, epithelial-to-mesenchymal transition (EMT) and chemoresistance (24). Aberrant activation of the WNT signaling pathway has been implicated to serve a key role in the regulation of chemoresistance in mucinous ovarian cancer (25,26).

In the canonical pathway (WNT/β-catenin/TCF), a WNT ligand forms a ternary complex with the seven-pass transmembrane receptor, Frizzled (Fzd) and low-density lipoprotein receptor-related protein 5/6 (LRP5/6), which activates Dvl homolog 1 (Dvl1) (26,27). Activation of Dvl1 dismantles the β-catenin 'destruction' complex to which it is associated, composed of Axin1 (AXIN1), adenomatous polyposis coli (APC), GSK3β and casein kinase 1 (CK1), which promotes the recruitment of β-catenin and TCF to the WNT target-gene promoters in the nucleus, to subsequently induce the transcription of target genes, including c-Myc and cyclin D1 (28). Ovarian cancer relapse, metastasis and chemoresistance may occur when the canonical WNT/β-catenin signaling induces the EMT program (29).

Alternatively, WNT ligands of the non-canonical WNT/PCP signaling pathway bind to the co-receptors Fzd and receptor tyrosine kinase like orphan receptor 2 (ROR2) to activate Dvl, which in turn promotes Rac family small GTPase 1/Ras homolog family member A signaling, leading to activation of c-Jun N-terminal kinase (JNK; also known as MAPK8) and Rho-associated coiled-coil containing protein kinase 2 (ROCK2) (30). JNK and ROCK2 are involved in cytoskeletal remodeling, cell motility and metastasis (31). In the non-canonical WNT/Ca^{2+} pathway, WNT proteins interact within a ternary complex composed of Fzd and ROR2 receptors, with the resultant activation of Dvl leading to increased intracellular Ca^{2+} levels, which in turn activate calcium/calmodulin dependent protein kinase II gamma and protein kinase C (PKC) (30). Overexpression of PKC has been associated with increased expression of multidrug resistant (MDR) proteins and chemoresistance (30). Collectively, these data suggest that the canonical and non-canonical WNT signaling pathways are important molecular determinants of chemoresistance in mucinous ovarian cancer.

Overall, the growth factor and WNT signaling pathways are an evolutionarily conserved signaling cascade system, and their mutual crosstalk may enhance the processes of carcinogenesis, progression and chemoresistance in mucinous ovarian cancer.

4. Molecular mechanism of WNT signaling implicated in chemoresistance

Overcoming intrinsic and acquired drug resistance is a challenge in the clinical treatment of patients with ovarian cancer (32). A previous review summarized numerous molecular aspects of chemoresistance, including oncogenes (EGFR/PI3K/Akt and WNT), ATP binding cassette (ABC) transporter pumps, EMT and cancer cell stemness (32). Ovarian cancer subtypes are distinct entities, having different responses to chemotherapy (23). Epithelial ovarian cancer is originally classified into two groups based on chemosensitivity. Serous and endometrioid ovarian cancers exhibit a hallmark of chemosensitivity, with higher response rates for taxane/platinum-based regimens. By contrast, mucinous and clear cell cancers are primarily resistant to chemotherapies (23). Patients with advanced-stage mucinous ovarian cancer exhibit higher rates of chemoresistance and have poorer survival outcomes compared with those with advanced-stage high-grade serous ovarian cancer (33).

Studies have been performed to identify the genes that contribute to chemoresistance in mucinous cancer (34,35). Previous genetic pathway enrichment analyses identified that upregulated transcripts in high-grade serous cancer were enriched for cell cycle signaling pathways, such as the TP53/breast cancer gene (BRCA) driver signaling pathway, while mucinous tumors were associated with upregulation of the WNT signaling pathway (2,35). Furthermore, a number of somatic mutations in proto-oncogenes, including in KRAS (36) and BRAF (2), have been identified in mucinous tumors. Overall, the available data indicate that crosstalk between the EGFR/PI3K/Akt and WNT signal pathways is implicated in the chemoresistance of mucinous ovarian cancer (32,36). Therefore, the WNT receptors and their downstream components may serve as novel therapeutic targets for treatment.

5. WNT-related potential candidates for overcoming chemoresistance

In particular, novel therapeutics that target chemoresistant processes may be useful from bench to bedside in mucinous ovarian cancer. Key components identified in the WNT signaling pathways are potential candidates of chemoresistance. Table I lists the WNT-related candidates and corresponding targeting agents for overcoming chemoresistance. Fig. 1 depicts the WNT pathway antagonists, inhibitors and modulators of particular interest in preclinical/clinical studies and their different mechanisms of action.

WNT ligand interacts with its cognate co-receptors LRP5/6 and Fzd. A number of approaches have been tested to target this interaction, including the use of natural compounds (37), small molecule inhibitors (38) and antibody-based inhibitors (8), with promising results (37). Natural compounds, including curcumin, 3,3-diindolylmethane, and phytoestrogen, have been tested for their capacity to reduce the activity of WNT signaling in cancer cells. Synthetic/small WNT inhibitors, including rofecoxib (cyclooxygenase-2 inhibitor), PRI-724 (β-catenin antagonist) and CWP232291 (synthetic/small WNT inhibitor), and the monoclonal antibody against Fzd receptors, vanituctumab, have been described (37). According to previous literature, several families of secreted antagonists consist of secreted frizzled-related proteins (sFRPs), the Dickkopf (Dkk) protein family, sclerostin (a soluble WNT antagonist), cerberus and WNT inhibitory factor-1 (39,40). However, the majority of these have not been incorporated into clinical

Table I. WNT-related potential candidates for overcoming chemoresistance in mucinous ovarian cancer.

Target	Therapeutic agent	Summary	Refs.
Fzd	sFzd7	Soluble Fzd7 peptide inhibitor	39
	FJ9	Small molecule inhibitor	39
	RHPDs	Small interfering peptides	39
	Salinomycin	Ionophore antibiotic	36
	Fzd7 antibody	Anti-FZD	39
	Vantictumab	Anti-FZD	41
	Ipafricept	Inhibitory FZD8-Fc fusion protein, also known as OMP-54F28	41
LRP5/6	Dickkopf1	Secreted inhibitor of the Wnt/β-catenin pathway	48
	Prodigiosin	Natural red pigment produced by bacterial species	51
Dvl	FJ9	Small molecule inhibitor	39
	RHPDs	Small interfering peptides	39
	Prodigiosin	Natural red pigment produced by bacterial species	51
	3289-8625	Synthetic compound that binds to and blocks the PDZ domain of Dvl	38,52
	HUWE1	E3 ubiquitin protein ligase	55
	WWOX	Member of the SDR protein family	56
	NSC668036	Organic molecule that binds to and blocks the PDZ domain of Dvl	54
	DACT1	Induces Dvl degradation	25,54,57
	Transmembrane protein 88	Interacts with Dvl	53
CK1	SR-3029	ATP-competitive CK1 inhibitor	58
	CX-4945	Selective ATP-competitive CK2 inhibitor	59
	Hematein (3,4,10,6a-tetrahydroxy-7, 6 adihydroindeno [2,1-c] chroman-9-one)	CK2 inhibitor	60
AXIN	XAV939	Small molecule tankyrase 1 inhibitor	62
GSK3β	Prodigiosin	Natural red pigment produced by bacterial species	51
	TDZD8	Small chemical inhibitor	65
	TWS119	Small chemical	65
	L803-mts	Peptide inhibitor	65
	Tideglusib	Selective and irreversible GSK-3 inhibitor	64
	Niclosamide	Salicyclamide-derivative anthelmintic drug	66
	DIF (1-[3-chloro-2,6-dihydroxy-4-methoxyphenyl]hexan-1-one)	Differentiation-inducing factor	67
	Salusin-β	Parasympathomimetic proatherosclerotic peptide	68
β-catenin	Caudal type homeobox 2	Suppresses the transcriptional activity of the β-catenin-TCF complex and β-catenin nuclear localization	69
	Huaier (TCM *Trametes robiniophila* Murr)	Reported to inhibit nuclear translocation of β-catenin and transcriptionally downregulate WNT/β-catenin target genes	72
	Mebendazole	Anthelmintic agent and selective inhibitor of TNIK	73
	NCB-0846	Small-molecule TNIK inhibitor	73
	HI-B1	Small molecule that directly interacts with β-catenin	74
	Polyphyllin I (component in the TCM herb *Paris polyphylla* Smith)	Reported to inhibit nuclear translocation of β-catenin and transcriptionally downregulate WNT/β-catenin target genes	72
	Pyrvinium	Anthelmintic drug	75
Others	TFF1	Trefoil factor 1	76
	CXCR4	CXC chemokine receptor 4	77
	FN1	Fibronectin 1	78
	SERPINA1	Serpin family A member 1	79
	Klotho	Co-receptor for FGF23	80
	Vemurafenib	Monoclonal antibody against $BRAF^{V600E}$	8,10

Fzd/FZD, Frizzled; LRP5/6, lipoprotein receptor-related protein 5/6; Dvl, disheveled; SDR, short-chain dehydrogenases/reductases; HUWE1, HECT, UBA and WWE domain-containing 1; WWOX, WW domain-containing oxidoreductase; DACT1, dishevelled-binding antagonist of β-catenin; CK1, casein kinase 1; GSK3β, glycogen synthase kinase 3β; TCM, traditional Chinese medicine; TNIK, Traf2 and Nck-interacting protein kinase; TCF, T-cell factor.

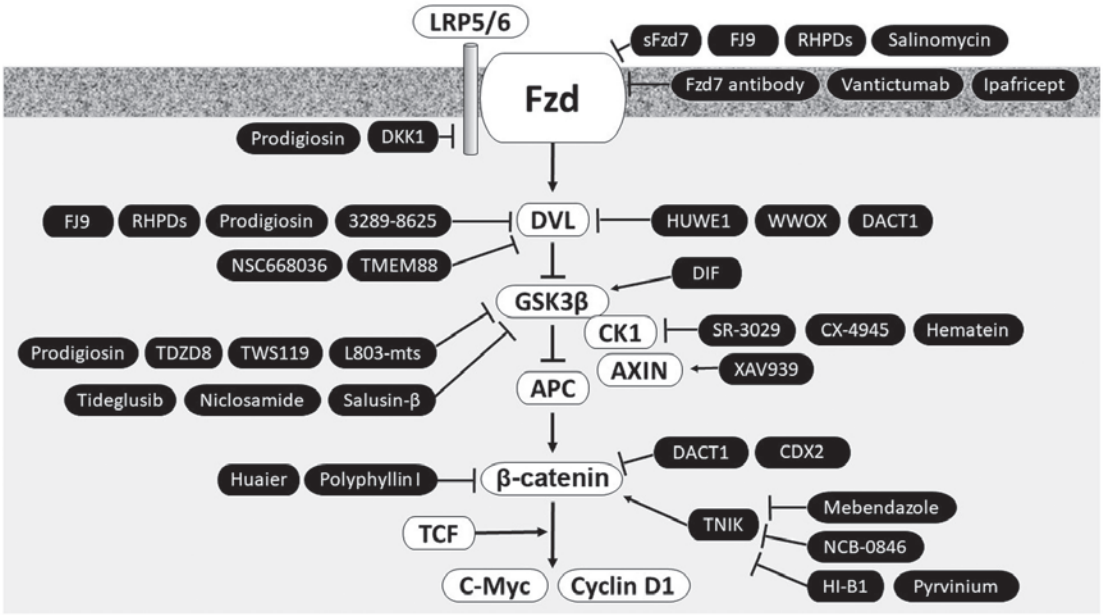

Figure 1. Schematic diagram depicting the proposed WNT pathway antagonists, inhibitors and modulators. The WNT receptor and its downstream targets are considered as promising therapeutic targets for the treatment of mucinous ovarian cancer. Arrows indicate modulators. LRP5/6, lipoprotein receptor-related protein 5/6; Fzd, Frizzled; sFzd7, soluble Fzd7 peptide; RNF43, ring finger protein 43; DKK, Dickkopf1; DVL, Dishevelled; TMEM88, transmembrane protein 88; HUWE1, HECT, UBA and WWE domain-containing 1; WWOX, WW domain-containing oxidoreductase; DACT1, dishevelled-binding antagonist of β-catenin; GSK3β, glycogen synthase kinase 3β; DIF, differentiation-inducing factor; CK1, casein kinase 1; APC, adenomatous polyposis coli; CDX2, caudal type homeobox 2; TCF, T-cell factor; TNIK, Traf2 and Nck-interacting protein kinase.

practice for the treatment of patients with mucinous ovarian cancer. These WNT inhibitors have been previously reviewed in detail (35,37,41,42).

Fzd inhibitors (sFzd7, FJ9, RHPD, salinomycin, Fzd7 antibody, vantictumab and ipafricept). Extracellular WNT ligand proteins bind the Fzd receptor family and activate the canonical and non-canonical WNT pathways (39). The sFRP family has been proposed to have inhibitory activity through binding and sequestering WNT ligands (43,44). The expression of sFRPs is downregulated through promoter hypermethylation in cancer (45). Silencing of sFRP expression results in an increase in chemoresistance in ovarian cancer (36). Pharmacological inhibition of Fzd by the soluble extracellular peptide of Fzd (sFzd7) (39), small interfering peptides (RHPDs) (39), a small molecule inhibitor (FJ9) (39), an ionophore antibiotic (salinomycin) (36), anti-Fzd antibody (vantictumab) (41) or ipafricept (FZD8-Fc; also known as OMP-54F28) (41) blocks the signaling ability of the WNT pathway. Generally the WNT antagonists inhibit WNT-induced EMT (46) and potently sensitize cancer cells to taxane and platinum (47). Therefore, targeted inhibition of Fzd represents a rational and promising novel approach for cancer therapy (39). An ongoing clinical trial is evaluating vantictumab and ipafricept (27).

LRP5/6 inhibitors (DKK1 and prodigiosin). DKK1 and DKK3 are secreted inhibitors of the WNT/β-catenin pathway (48). DKK antagonizes WNT signaling by binding to the WNT co-receptor, LRP5/6 (48). Inactivation of DKK3 has been observed in mucinous ovarian cancer, which may exert a proliferative effect (49). Furthermore, DKK is able to inhibit EMT and ovarian cancer cell metastasis (50).

As a more generally-acting agent, prodigiosin, a natural red pigment produced by bacterial species, particularly strains of *Serratia marcescens*, has also been reported to promote anticancer activity through inhibition of the WNT signaling by targeting multiple sites of this pathway, including LRP6, Dvl and GSK3β (51).

Dvl inhibitors [3289-8625, transmembrane protein 88 (TMEM88), NSC668036, HECT, UBA and WWE domain-containing 1 (HUWE1), WW domain-containing oxidoreductase (WWOX), dishevelled-binding antagonist of β-catenin (DACT1) and FJ9]. Negative regulators of the downstream targets of WNT signaling are Dvl, APC, CK1, AXIN and GSK3β. Dvl is overexpressed in drug-resistant cancer and its inhibition by its inhibitor (the synthetic compound 3289-8625) or Dvl short hairpin RNA inhibits WNT signaling and increases sensitivity to platinum (38,52). FJ9, a soluble Fzd7 peptide inhibitor, disrupts the interaction between Fzd7 and Dvl (39). TMEM88 inhibits WNT signaling through direct interaction with Dvl (53). The organic molecule NSC668036 that binds to and blocks the PDZ domain of Dvl also inhibits WNT signaling (54). As alternative methods of inhibition, HUWE1 ubiquitylates Dvl to promote its degradation (55); while WWOX, a member of the short-chain dehydrogenases/reductases protein family, prevents nuclear import of Dvl proteins (56). Similar to HUWE1, DACT1 (also known as dapper antagonist of catenin-1) antagonizes WNT/β-catenin signaling by inducing Dvl degradation (54,57). A previous study identified mucinous ovarian cancer to have a higher level of methylation of the DACT1 promoter compared with high-grade serous cancer and normal controls (25). Furthermore, DACT1 overexpression inhibited platinum

resistance through inactivation of canonical WNT signaling and suppression of P-glycoprotein expression in mucinous ovarian cancer (25).

CK inhibitors (SR-3029, CX-4945 and hematein). Canonical WNT signaling induces the disassociation of a complex comprising of Dvl, AXIN and the protein kinases CK1 and CK2 and GSK3β. This WNT signaling may be interrupted by CK inhibitors, including SR-3029 (an ATP-competitive CK1 inhibitor) (58), CX-4945 (a selective ATP-competitive inhibitor of CK2) (59,60) and hematein (a CK2 inhibitor; 3,4,10,6a-tetrahydroxy-7, 6a dihydroindeno [2,1-c] chroman-9-one) (61).

AXIN inhibition with Tankyrase (TNKS) inhibitor (XAV939). AXIN, the rate-limiting factor for the stability of the β-catenin destruction complex, interacts with APC, β-catenin, GSK3β and protein phosphate 2. Thus, AXIN is considered as a negative regulator of the WNT signaling pathway (62). TNKS, a poly-ADP-ribosyltransferase, promotes WNT signaling by transferring ADP-ribose moieties onto AXIN (63). The TNKS inhibitor XAV939 (a small molecule TNKS1 inhibitor) stabilizes AXIN and subsequently inhibit WNT signaling (62). In this interaction, XAV939 binds the TNKS catalytic poly-ADP-ribose polymerase domain (62).

GSK3β modulators [prodigiosin, TDZD8, TWS119, L803-mts, tideglusib, niclosamide, differentiation-inducing factor (DIF) and salusin-β]. GSK3β is a multifunctional serine/threonine protein kinase. Tideglusib, a potent, selective and irreversible GSK3β inhibitor, exhibits antitumor activity and improves survival in mice (64). Other specific GSK3β inhibitors include the small chemicals TDZD8 (4-benzyl-2-methyl-1,2,4-thiadiazolidine-3,5-dione) and TWS119 (4,6-disubstituted pyrrolopyrimidine) and the peptide L803-mts [N-myristol-GKEAPPAPPQS(p)P] (65). In addition, niclosamide, a U.S. Food and Drug Administration approved salicyclamide derivative anthelmintic drug used for the treatment of tapeworm infections, binds to GSK3β and inhibits WNT pathway functions (66). DIF [1-(3-chloro-2,6-dihydroxy-4-methoxyphenyl)hexan-1-one], a putative morphogen produced by *Dictyostelium discoideum*, suppresses the WNT/β-catenin signaling pathway via the activation of GSK3β and subsequently reduces the expression levels of c-Myc and cyclin D1 (67). Meanwhile, salusin-β is an endogenous parasympathomimetic proatherosclerotic peptide, which has been reported to accelerate the proliferation and EMT of ovarian cancer via activation of the WNT/β-catenin pathway through suppression of GSK3β (68); therefore it may also be a therapeutic target in mucinous ovarian cancer.

β-catenin modulators [caudal type homeobox 2 (CDX2), huaier, mebendazole, NCB-0846, HI-B1, polyphyllin I (PPI) and pyrvinium]. The CDX2 gene is a member of the caudal-related homeobox transcription factor gene family. CDX2 may regulate cancer cell proliferation by suppressing transcriptional activity of the β-catenin-TCF complex and β-catenin nuclear localization (69). CDX2 also upregulates MDR1 by binding to its element in the promoter of the MDR1 gene, which may lead to drug resistance in mucinous ovarian cancer (70,71). Huaier (*Trametes robiniophila* Murr), a traditional Chinese medicine, and PPI, a component in the traditional Chinese medicinal herb *Paris polyphylla* Smith, have been reported to inhibit the nuclear translocation of β-catenin and to transcriptionally downregulate certain WNT/β-catenin target genes (LRP6, WNT5A and cyclin D1) (72).

Traf2 and Nck-interacting protein kinase (TNIK) mediates WNT signaling through the β-catenin and T-cell factor-4 (TCF-4) complex. A number of small-molecule compounds targeting TNIK, including mebendazole, an anthelmintic agent and selective inhibitor of TNIK (73), NCB-0846, a small-molecule TNIK inhibitor (73) and HI-B1, a small molecule that directly interacts with β-catenin (74), have been demonstrated to exert anti-tumor effects against various cancers. At present, mebendazole is under clinical evaluation (73). In addition, pyrvinium, a potent WNT inhibitor used as an anthelmintic drug, may also sensitize ovarian cancer cells to chemotherapy (75).

Others. Trefoil factor 1 (TFF1). The secretory protein TFF1 has been identified to be highly expressed in mucinous ovarian cancer, but not serous or any other type of ovarian cancer (76). TFF1 promotes cell proliferation, invasion and chemoresistance through regulating the activation of WNT/β-catenin signaling and the upregulation of Twist expression (76). Notably, TFF1 is considered to serve an oncogenic role in mucinous ovarian cancer (76).

CXC chemokine receptor 4 (CXCR4). CXCR4 may activate the canonical WNT pathway and upregulate the expression of mesenchymal markers including vimentin and snail family transcriptional repressor 2 transcripts, leading to ovarian cancer cell invasion, metastasis and chemoresistance (77). Thus, CXCR4 may be a novel therapeutic target for the treatment of chemoresistant ovarian cancer.

Fibronectin 1 (FN1). FN1 is involved in cell attachment, spreading and migration processes including embryogenesis and cancer metastasis (78). FN1 activates the WNT/β-catenin signaling pathway through interaction with integrin-β1 (78). Through this mechanism, FN1 may serve a role in the development of resistance to taxane and platinum (78).

Serpin family A member 1 (SERPINA1). SERPINA1 is a serine protease inhibitor with targets including elastase, plasmin, thrombin, trypsin, chymotrypsin and plasminogen activator (79). SERPINA1 is regulated by prospero homeobox 1, which may enhance WNT/β-catenin signaling (79). In general, SERPINA1 has been implicated to serve a role in the chemoresistance of ovarian cancers (79).

Klotho. Klotho, a co-receptor for FGF23, may serve as a tumor suppressor, and also inhibit the WNT/β-catenin signaling pathway and reduce expression of c-Myc and cyclin D1 (80). Since Klotho is typically silenced in ovarian cancers (80), this gene is a potential key target for therapy.

Monoclonal antibody against $BRAF^{V600E}$ (vemurafenib). Frequently mutated genes observed in mucinous ovarian cancer are KRAS, BRAF, CDKN2A and TP53 (2). Targeting the RAS/RAF pathway to treat recurrent or advanced-stage mucinous ovarian cancer may be an effective therapeutic

strategy (8,10). Vemurafenib, as a highly selective $BRAF^{V600E}$ inhibitor, may become a model drug for targeted therapy of mucinous ovarian cancer.

6. Combination of cytotoxic agents with therapeutic antibodies or sensitizing agents

Activation of the EGFR or HER/PI3K/Akt cascade is considered to represent a major mechanism of chemoresistance in ovarian cancer (81). Therapeutic antibodies, including cetuximab (EGFR inhibitor), lapatinib (EGFR kinase inhibitor), rituximab (chimeric monoclonal anti-CD20 antibody) and trastuzumab [HER-family receptor tyrosine kinase (HER2) inhibitor] elicit an effective therapeutic response (82). Therefore, addition of EGFR/HER antibodies may improve the therapeutic effect of the conventional cytotoxic agents. Recent developments and the future potential in antibody-based targeting of the EGFR pathway have been previously reviewed in detail (83).

Chemotherapy with taxanes promotes activation of WNT signaling (47). The WNT inhibitors/antagonists, including vantictumab (anti-FZD) and ipafricept (FZD8-Fc), potentiate taxane-mediated cancer cell death. Furthermore, platinum treatment may induce activation of Src kinase (23). Combination therapy of oxaliplatin with dasatinib, a Src inhibitor, has previously exhibited antitumor effects in a mucinous cancer model (23). Additionally, the ABC inhibitors verapamil and elacridar re-sensitized chemoresistant cells to taxanes (84). Therefore, chemotherapeutics may be combined with tyrosine kinase inhibitors or P-glycoprotein inhibitors to enhance cytotoxicity (85).

7. Conclusions

Advanced mucinous ovarian cancer is established to be resistant to taxane- and platinum-based chemotherapy and is associated with poor clinical outcome, and there remains to be a requirement for effective anti-cancer therapies. The present article reviewed the underlying molecular mechanisms of chemoresistance, focusing on growth factor and WNT signaling pathways. Chemoresistance is mediated by the coordinated action of the WNT signaling axis, together with crosstalk from other growth factor receptor pathways, notably EGFR, ERBB2 and FGFR. Research has focused on molecular mechanisms for antagonizing WNT signaling by directly or indirectly targeting Wnt receptors on the cell surface and their downstream components (36). The present review described the characterization of synthetic small molecule inhibitors, small interfering peptides, antibiotics, organic molecules, proteases, protease inhibitors, and monoclonal antibodies that disrupt WNT signaling. Several WNT antagonists, inhibitors or modulators, including Fzd, LRP5/6, Dvl, CK1, AXIN, GSK3β and β-catenin (Table I and Fig. 1), are being evaluated in preclinical/clinical studies. WNT antagonists or blockades may have synergistic effects with platinum and taxane (47). From the published data it may be hypothesized that key components identified in the WNT signaling pathways are potential candidates of chemoresistance. Thus, the WNT inhibitors may provide novel therapeutic benefit in combination with current chemotherapies for mucinous ovarian cancer.

In conclusion, the present review has summarized promising WNT inhibitors for the targeting of chemoresistant processes in mucinous ovarian cancer from bench to bedside.

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Availability of data and materials

The analyzed data sets generated during the study are available from the corresponding author on reasonable request.

Authors' contributions

EN and SM collected the data for the signaling pathways and underlying mechanism of chemoresistance in mucinous ovarian cancer. KI performed the systematic review and had supervised the study. YY, KO and NK, skillful and dedicated coworkers for many years, made substantial contribution to the conception involved in the study. HK, current leader of the department, contributed to the study design and analysis on many basic research studies. The final version of the manuscript has been read and approved by all authors.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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