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Review Article

Decoding Wnt Signaling in Cancer Therapy Resistance: Current Perspectives

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Abstract

Background: Drug resistance remains a primary obstacle to effective cancer therapy, compromising both clinical response and long-term prognosis. The evolutionarily conserved Wnt signaling pathway is frequently implicated in tumor survival, proliferation, and therapeutic escape. This review aims to provide an updated synthesis of the role of Wnt signaling in cancer drug resistance and evaluate its potential as a therapeutic target.

Methods: We conducted a narrative review of the current literature by searching electronic databases (e.g., PubMed, Scopus, and Web of Science) for studies focusing on the interplay between Wnt signaling and mechanisms of chemo- and targeted-therapy resistance. Eligible studies were analyzed to synthesize current insights into Wnt-mediated resistance patterns and emerging therapeutic strategies.

Results: Wnt signaling acts as a central nexus in driving resistance through diverse, often overlapping, mechanisms, including the promotion of cancer stem cell plasticity, enhanced DNA damage repair, evasion of apoptosis, and the regulation of oncogenic ncRNAs. While Wnt pathway inhibition represents a promising therapeutic avenue, its clinical translation has been challenged by issues regarding toxicity, limited specificity, and tumor heterogeneity. Current efforts to overcome these barriers focus on direct Wnt blockade, combination regimens with standard chemotherapies, and integration into immunotherapy or other targeted therapies. Furthermore, genomic and transcriptomic profiling shows promise in predicting resistance patterns, thereby facilitating more personalized, tailored interventions.

Conclusion: Although Wnt signaling is a critical driver of therapeutic resistance, successful clinical targeting requires overcoming intrinsic biological complexities. Future strategies should prioritize precision medicine approaches, integrating multi-omics data to refine patient selection and optimize combinatorial therapeutic regimens to improve patient outcomes.

Keywords: Wnt/β-Catenin, Drug resistance, Apoptosis, DNA damage, Autophagy

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Introduction

Cancer is one of the leading causes of non-communicable mortality worldwide. Due to its complex nature, cancer cannot be attributed to a single causative factor. Multiple predisposing elements, including genetic mutations, lifestyle factors, exposure to radiation, and chemical agents, have been identified for this disease, and the intricate interplay among these factors further highlights the multifactorial etiology of cancer.[1,2]

Although surgery, chemotherapy, radiotherapy, and targeted therapies constitute the standard treatment options for cancer, they demonstrate certain limitations in terms of efficacy. Such limitations become particularly significant in the context of challenges associated with early diagnosis, ultimately contributing to persistently high mortality rates. To overcome these obstacles, research efforts have increasingly focused on the development of innovative diagnostic and therapeutic strategies aimed at improving patient outcomes and expanding the range of therapeutic options.[3] With the growing understanding of cancer biology, obstacles in its treatment have become more apparent. One key factor that diminishes therapeutic efficacy is the ability of cancer cells to adapt to their environment and develop molecular mechanisms to withstand the stressful conditions imposed by treatment. It has been estimated that up to 90% of cancer-related deaths are attributable to drug resistance.[4]

The Wnt/β-catenin signaling pathway represents an evolutionarily conserved component of the cellular signaling network. At a glance, the interaction of Wnt

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with its receptor leads to increased stability and the cytoplasmic accumulation of β-catenin.[5] Upon nuclear translocation, β-catenin orchestrates the transcriptional activation of genes that are pivotal for fundamental cellular functions, such as proliferation, growth, and differentiation.[6] Dysregulation of this signaling cascade is intricately associated with numerous physiological and oncologic cellular processes.

Research on cancer cells with treatment-resistant phenotypes has revealed a wide range of intrinsic and acquired molecular mechanisms that contribute to therapeutic failure. Key among these are alterations in drug targets, increased deoxyribonucleic acid (DNA) repair capacity, overexpression of efflux transporters, activation of detoxification pathways such as autophagy, and inhibition of apoptosis.[7,8] The current narrative review is based on literature retrieved from major biomedical databases, including PubMed, Scopus, and Web of Science. A narrative approach was adopted to enable integrative analysis of mechanistically diverse studies addressing Wnt signaling and cancer drug resistance across different tumor types and therapeutic contexts (Figure 1). The necessity of this review arises from the fragmented nature of the current literature, in which Wnt signaling is frequently discussed in relation to isolated resistance mechanisms or specific cancers. Notably, the role of non-canonical Wnt pathways and their interplay with canonical Wnt/β-catenin signaling in therapy resistance remain insufficiently integrated. The novelty of this review lies in its mechanism-oriented and translational framework, systematically linking both canonical and non-canonical Wnt signaling to interconnected resistance processes, including cancer stem cell (CSC) maintenance, DNA damage tolerance, epithelial–mesenchymal transition, and immune modulation. By providing an integrated conceptual model, this review addresses a critical gap in current knowledge and offers insights relevant to biomarker development and rational therapeutic strategies aimed at overcoming cancer drug resistance.

Molecular Mechanisms of Drug Resistance

The triggering of drug resistance in cancer cells is governed by a complex interplay of molecular mechanisms. The key components of this network include enhanced DNA repair capacity, apoptosis inhibition, and autophagy pathway activation. Among them, CSC subpopulations, characterized by distinct regulatory patterns of these mechanisms, and non-coding ribonucleic acids (ncRNAs), which exert broad regulatory effects on gene expression, play a pivotal role in amplifying resistance. Collectively, these adaptive mechanisms, both individually and cooperatively, enable cancer cells to maintain survival under the therapeutic stress that is imposed by anticancer treatments.

Deoxyribonucleic Acid Damage Response in Drug Resistance

Maintaining genomic stability is essential for cell survival, and cells deploy multiple, specialized DNA-repair pathways to counter diverse insults. Single-base lesions from oxidative stress are corrected by base excision repair (BER). Likewise, bulky photoproducts such as thymine dimers are corrected by nucleotide excision repair (NER), and replication errors are corrected by mismatch repair (MMR).[9-11] In addition, double-strand breaks (DSBs) are resolved either by error-free homologous recombination (HR) or the more error-prone non-homologous end joining; the latter is mediated by factors such as Ku70/Ku80 and DNA-PKcs and frequently co-opted by radio-resistant and chemo-resistant tumors.[12,13] When HR or p53 function is lost, tumors increasingly rely on alternative end-joining pathways (alternative non-homologous end joining/microhomology-mediated end joining), driven by DNA polymerase θ (POLQ), which can compensate for the inhibition of DNA-PK or poly (adenosine diphosphate-ribose) polymerase (PARP) and thereby promote therapeutic resistance.[14,15] The Fanconi anemia network governs the repair of interstrand crosslinks. Moreover, its hyperactivation, frequently intersecting pro-survival signaling such as mammalian target of rapamycin (mTOR), contributes to resistance to crosslinking agents, such as cisplatin.[16,17] Overall, these pathway shifts enable cancer cells to tolerate genotoxic stress and undermine DNA-damage-based therapies.

Research on drug-resistant cancer cells has revealed a highly efficient DNA repair capacity. According to evidence, these cells enhance their DDR pathways in response to anticancer agents, chemotherapy, and radiotherapy. In addition, such upregulation enables tumor cells to endure therapeutic stress, maintain survival, and evade treatment-induced cell death.[18] To enhance the sensitivity of cancer cells to therapy, their DNA repair mechanisms can be targeted to improve treatment responsiveness. This approach can be achieved using agents such as PARP inhibitors, cisplatin, and temozolomide, which exploit defects or dependencies in DNA repair pathways in order to promote tumor cell death.[19,20] Additionally, biological processes that indirectly bolster the DNA-repair capacity of cancer cells include hyperactivation of pro-survival signaling pathways (PI3K/AKT/mTOR and RAS/RAF/MAPK) and upregulated checkpoint signaling (ATM–CHK2 and ATR–CHK1), which collectively extend the time available for lesion resolution.[21-23] The G2/M checkpoint kinase WEE1 is a notable mediator: its overexpression in glioma and ovarian carcinoma cancers enforces G2 arrest, thereby permitting additional DNA repair and promoting resistance to genotoxic therapies. Pharmacologic inhibition of WEE1 (e.g., AZD1775) can disrupt this arrest and restore sensitivity to DNA-damaging treatments.[24]

Replication-fork protection is a key resistance mechanism; in BRCA-deficient cells, the stabilization of stalled forks, through prevention of nucleolytic degradation by factors such as MRE11 and MUS81, can confer resistance to PARP inhibitors without the restoration of HR.[25,26] PARP trapping and mutation-driven

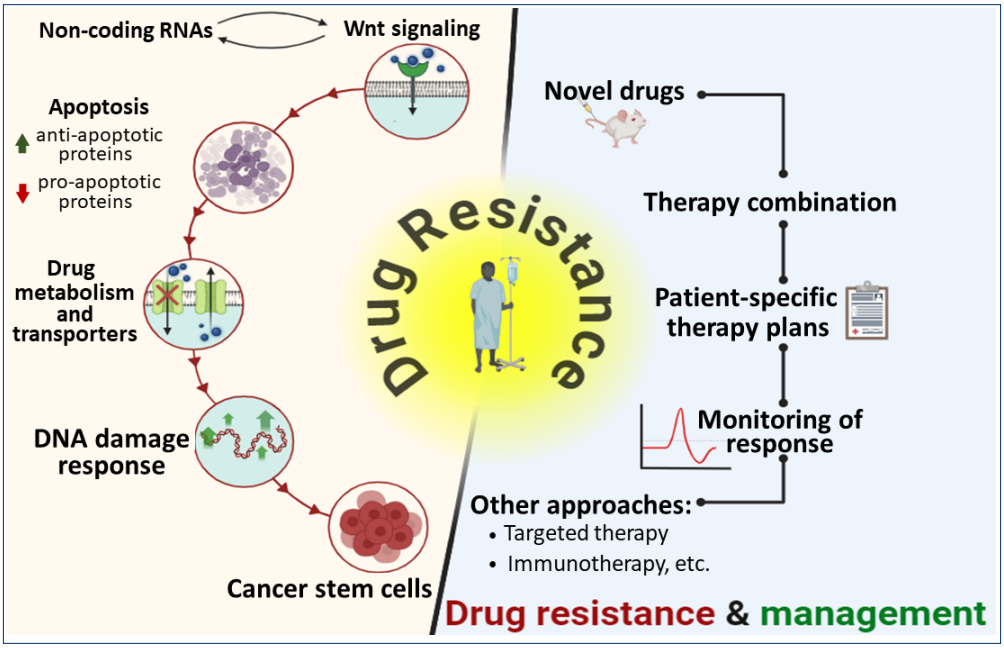

Figure 1. This schematic model illustrates Wnt signaling as a central integrative regulator of drug resistance-related mechanisms

escape are also important; PARP1 alterations that reduce stable DNA binding (often acting in concert with XRCC1-mediated single-strand repair) diminish cytotoxic PARP–DNA complexes and blunt PARPi efficacy. Finally, the upregulation of drug-efflux transporters, such as ABCB1 (P-glycoprotein), lowers intracellular drug levels (e.g., PARPi and paclitaxel), thereby promoting multidrug resistance.[27,28]

Furthermore, epigenetic modulation and ncRNAs shape the DNA-damage response; the promoter hypermethylation of genes such as *MLH1* or *BRCA1* impairs repair activity, whereas demethylation can restore expression and function. MicroRNAs (e.g., miR-182 and miR-218) directly target DDR transcripts, including BRCA1, and their dysregulation has been linked to reduced drug sensitivity (e.g., to PARP inhibitors or cisplatin).[29,30] Likewise, mitochondrial DNA repair is involved in tumor biology; defects in mitochondrial base-excision repair components (e.g., apurinic/apyrimidinic endonuclease 2 or Nei endonucleases VIII-like family glycosylases) correlate with cancer progression, and co-targeting mitochondrial BER together with nuclear DDR pathways can potentiate radiosensitization and chemosensitivity.[31]

Tumor heterogeneity, clonal selection, and secondary alterations, most notably BRCA1/2 reversion mutations that restore HR, are major drivers of treatment resistance.[32] Additionally, clonal hematopoiesis with TP53 mutations increases the risk of therapy-related neoplasms.[33] Biomarkers such as O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation and genomic homologous recombination deficiency scores are clinically useful. MGMT methylation is associated with greater sensitivity to temozolomide, while high homologous recombination deficiency scores predict responsiveness to PARP inhibitors.[34,35] Mutations in p53 further rewire the DNA-damage response and cell-death programs, altering repair fidelity and apoptotic signaling in order to promote resistance to temozolomide and radiotherapy.[36]

Autophagy and Apoptosis in Drug Resistance

Autophagy is an evolutionarily conserved cellular process that functions as a vital quality control and recycling system. It operates through several mechanisms, including macroautophagy, microautophagy, and chaperone-mediated autophagy, that generally sustain cellular homeostasis by removing damaged components and maintaining internal equilibrium. Interestingly, this process exhibits a dual role in cancer biology. In normal physiological states, autophagy prevents malignant transformation by eliminating toxic molecules, such as reactive oxygen species (ROS), and protecting cells from metabolic stress. Conversely, in cancerous cells, the same mechanism can be co-opted to promote survival, allowing tumor cells to withstand therapeutic challenges like chemotherapy and radiation by adapting to stressful microenvironmental conditions.[37] When cancer cells encounter stress caused by chemotherapy or radiation, they frequently intensify autophagic activity to improve their chances of survival. By increasing the breakdown and removal of defective proteins and organelles, this process reduces the accumulation of cellular damage. Moreover, the recycling function of autophagy provides an internal source of nutrients; by converting degraded components into usable molecules, such as amino acids, autophagy enables tumor cells to sustain essential metabolic pathways even under nutrient-deprived or hostile conditions.[38,39] The involvement of autophagy in therapeutic resistance arises from multiple pathways, including the suppression of cell death signals, facilitation of tumor spread, and shielding of stem-like cancer cells. Key regulators, including ATG5, ATG7, and Beclin-1, are often overexpressed in resistant

tumors, thereby driving increased autophagic flow that counters anti-cancer drugs.[40] The mTOR pathway, which normally restrains autophagy via ULK1 inhibition in abundant environments, becomes suppressed under treatment-induced stress, further promoting cell endurance.[41] In addition, autophagy intersects with DNA repair responses by eliminating impaired structures, such as through mitophagy involving PINK1/Parkin, which reduces oxidative burden and averts programmed death in hypoxic tumor settings. In CSCs, this process is expected to support dormancy and regeneration.[42,43]

The interplay between autophagy and apoptosis is complex. For example, the dissociation of Beclin-1 from Bcl-2 complexes can trigger both processes, but autophagy often predominates under cellular resistance conditions, sequestering pro-death factors.[44] Interestingly, excessive autophagy can deplete cellular resources, resulting in autophagic cell death (type II). This phenomenon is exploited in therapeutic strategies that combine autophagy activators with inhibitors.[45]

Apoptosis, or type I programmed cell death, is crucial for evolutionary adaptations and tissue hemostasis. Activating this pathway, primarily orchestrated by cytochrome c release and caspase enzymes, offers a viable strategy to reduce tumor burdens. It branches into intrinsic (mitochondrial, involving Bax/Bak pores) and extrinsic (receptor-based, via Fas/TNF and caspase-8) pathways. Resistance to apoptosis frequently arises from defects in one or both of these pathways.[46] In resistant tumors, anti-apoptotic factors, such as Bcl-2 or Bcl-xL, are amplified, while pro-apoptotic factors, such as Bax or Bad, are diminished.[47] Therapeutic interventions, including BH3-mimicking drugs like venetoclax, aim to disrupt these imbalances, restoring sensitivity in conditions like leukemia.[48] Similarly, inhibitors of apoptosis protein antagonists (e.g., SMAC mimetics such as birinapant) counteract caspase blockers by mimicking mitochondrial signals.[49] The tumor suppressor p53 modulates both pathways, inducing apoptosis through targets like p53-upregulated modulator of apoptosis, or Noxa, and autophagy via damage-regulated autophagy modulator; mutations in p53 tilt the scale toward survival-oriented autophagy.[50] Epigenetic modifications, such as histone deacetylase activity or gene methylation, can mute pro-apoptotic signals, but agents like vorinostat counteract this to reinstate cell death.[51] Additionally, caspase activation follows a hierarchical pattern; initiators like caspase-9 trigger effectors (caspase-3/7), culminating in nuclear breakdown and cellular disassembly. Upregulated inhibitors such as X-linked inhibitor of apoptosis protein or survivin in resistant cells highlight targets for intervention.[52]

Drug Metabolism and Drug Transporters in Drug Resistance

Comprehending the pharmacokinetics of a medication is fundamental for attaining the best treatment outcomes. Drug metabolism predominantly takes place in the liver and comprises two distinct phases. During the first phase, drugs can undergo oxidation, reduction, and hydrolysis reactions, primarily leading to drug inactivation and efficacy alteration. However, in specific instances (e.g., prodrugs), this phase can induce activation.[53] Subsequently, in the second phase, the objective is to enhance the excretion potential of the metabolite. This process involves attaching hydrophilic compounds (e.g., amino acids, sulfates, and glucuronic acid) to the metabolites obtained from the first phase.[54,55] Glutathione S-transferases (GSTs), sulfotransferases, N-acetyltransferases, and uridine 5'-diphospho-glucuronosyltransferases are among the most important second-phase enzymes.[56]

The genetic variants of metabolizing enzymes (e.g., cytochrome P450), along with environmental influences (e.g., temperature/ultraviolet light and interactions between drugs), represent crucial determinants contributing to the varied range of patient responses to medications.[57,58]

The flow of drugs into and out of cells is mediated by transporters known as efflux and influx pumps. The elimination of drugs from cancer cells is directly linked to drug resistance. Therefore, inhibiting the efflux pumps that reduce the cytoplasmic concentration of therapeutic agents demonstrates a viable strategy to enhance treatment efficacy. The adenosine triphosphate (ATP)-binding cassette (ABC) transporter family actively expels target compounds from the cell, exploiting the energy resulting from ATP hydrolysis. This family encompasses a wide variety of substrates and is categorized into seven distinct subclasses, ranging from ABCA to ABCG.[59] In several studies, P-glycoprotein, breast cancer resistance protein (BCRP), and multidrug resistance-associated protein 1 (MRP1) have been identified as pivotal members of the ABC transporter family, significantly contributing to drug resistance and acting as notable biological supervisors.[60-62]

P-glycoprotein, encoded by the *ABCB1* gene, is crucial for drug absorption and excretion processes. Its contribution to mediating drug resistance, particularly against vinblastine, doxorubicin, and paclitaxel, is notably significant. Consequently, suppressing this efflux transporter can enhance the cytotoxic effects of these chemotherapeutic agents in cancer cells, making their toxicity more pronounced.[63,64] BCRP, a peptide consisting of 655 amino acids, exhibits varied tissue distribution, remarkably in the brain, testis, and blood-brain barrier.[65,66] Among the anticancer agents documented as substrates for BCRP are anthracyclines, mitoxantrone, and camptothecin.[67] MRP1, encoded by the *ABCC1* gene, is the most validated efflux pump in the context of drug resistance. It plays a prominent role in resistance to doxorubicin, taxane, and platinum.[68]

On the other hand, peptide transporters (PEPTs), organic anion transporters (OATs), and organic cation transporters (OCTs) are the most prominent members of the influx transporter family. Peptide-like substances (i.e., dipeptides and tripeptides) are transported by PEPTs.[69,70] Recently, there has been growing interest in the involvement of

this transporter in the context of photodynamic therapy, particularly concerning the intestinal absorption of 5-aminolevulinic acid.[71] OATs and OCTs are among the influx transporters that specialize in transporting negatively and positively charged molecules, respectively.[72] Studies have shed light on the potential of organic anion transporters in triggering resistance to methotrexate, etoposide, and teniposide.[73] Additionally, the uptake of platinum-based anticancer drugs is linked to OCTs.[74]

Overall, both metabolic enzymes and membrane transporters determine the intracellular fate of anticancer agents; their genetic and functional alterations shape therapeutic efficacy and drug resistance, thereby representing essential targets for improving cancer treatment.

Wnt Signaling Pathway: An Overview

Investigating the Wnt signaling pathway is of great importance due to its critical involvement in essential foundational processes, including embryonic development, neurodevelopment, proliferation, differentiation, tissue homeostasis, and the regulation of stem cells.[75-78] In general, 19 Wnt proteins are encoded in humans, among which Wnt1, Wnt3a, Wnt5a, Wnt7a, and Wnt10b are particularly well-characterized. These proteins typically encompass between 350 and 400 amino acids, incorporating 23 preserved cysteine residues.[79,80] The most critical post-translational alterations essential for the biological functionality of Wnt proteins contain glycosylation at asparagine residues and lipidation, specifically palmitoylation mediated by porcupine, at serine residues.[81-83]

A destructive complex is located at the center of this pathway, which constantly counteracts the increasing concentration of the effector of the Wnt pathway, namely, β-catenin. Axin, adenomatous polyposis coli (APC), glycogen synthase kinase 3 (GSK-3), and casein kinase 1 (CK1) are members of the destructive complex. Molecular studies have determined the functional nature of the members of this complex.[84]

Axin and APC are complex scaffolds that are essential for creating the β-catenin phosphorylation platform. In addition, CK1 acts as the priming kinase, and GSK-3 performs subsequent phosphorylations.[85] Further, β-catenin undergoes a precisely arranged phosphorylation sequence at four key residues, serine 45, threonine 41, serine 37, and serine 33, to prepare it for proteasomal degradation. Furthermore, CK1 is accountable for the phosphorylation in serine 45, and phosphorylation in the other three residues occurs by GSK-3.[86,87]

The activation of the Wnt signaling pathway is triggered by Wnt binding to the primary receptor known as Frizzled and is subsequently followed by the association of a co-receptor with the receptor-ligand complex. Typically, the involved co-receptor belongs to the low-density lipoprotein receptor-related protein (LRP) family, specifically LRP-5/6.[88,89]

This complex activates the phosphoprotein called Disheveled, which suppresses the destruction complex.[90] Accumulated β-catenin translocates to the nucleus, where it interacts with the T-cell factor/lymphoid enhancer-binding transcription factor (TCF/LEF), thereby inducing the expression of the target genes of the Wnt pathway (Figure 2).[91]

The Role of Wnt Signaling in Cancer Pathogenesis

As a crucial component of the cellular communication network, the Wnt signaling pathway can impact a significant variety of biological processes. This signaling pathway not only plays an undeniable role in determining cell fate throughout embryonic development but is also involved in homeostasis and tissue regeneration due to its interaction with fundamental processes such as proliferation, differentiation, and programmed death.[92,93] Abnormalities in the Wnt signaling pathway are related to the development of oncogenic features. This dysregulation frequently results in enhanced β-catenin stability due to mutations in the *CTNNB1* gene or in key components of the β-catenin destruction complex (i.e., APC and Axin).[94-96] Elevated interaction between β-catenin and LEF/TCF leads to degradation-resistant β-catenin, thereby promoting proliferation by upregulating C-myc and cyclin D1.[97]

The epithelial-mesenchymal transition (EMT) process, a transformation significantly influenced by the Wnt signaling pathway, also referred to as the fading of epithelial features and the acquisition of mesenchymal traits, significantly increases the metastatic and invasive potential of cancer cells.[98]

Moreover, the Wnt signaling pathway has a key role in cellular survival mechanisms, particularly apoptosis.[99] Survivin, which belongs to the class of apoptosis-inhibiting proteins, is commonly overexpressed in cancer cases.[100] Wnt suppresses apoptosis by increasing the expression of survivin to take advantage of the negative relationship between survivin and caspases 3, 7, and 9.[101] Furthermore, the overexpression of antiapoptotic proteins (e.g., Bcl-2 and paraoxonase-2) is thought to be a component of the Wnt signaling pathway's survival role.[102,103] Another facet of the connection of this pathway to apoptosis is demonstrated by P53. This protein can upregulate and downregulate the pro-apoptotic and anti-apoptotic proteins in response to DNA damage.[104] Additionally, the Wnt pathway essentially suppresses the start of apoptosis by inhibiting P53.[105]

The immune system has evolved multiple defense mechanisms against cancer cells, highlighting the necessity for cancer cells to evade the immune system in order to progress. The wide-ranging interaction of the Wnt signaling pathway with the immune system is also involved in impairing the efficiency of antitumor mechanisms.[106-108]

The progression of cancer is facilitated by the induction of an immunosuppressive state in the TME through several mechanisms. Further, β-catenin plays a pivotal role in this process by upregulating regulatory T cells and modulating

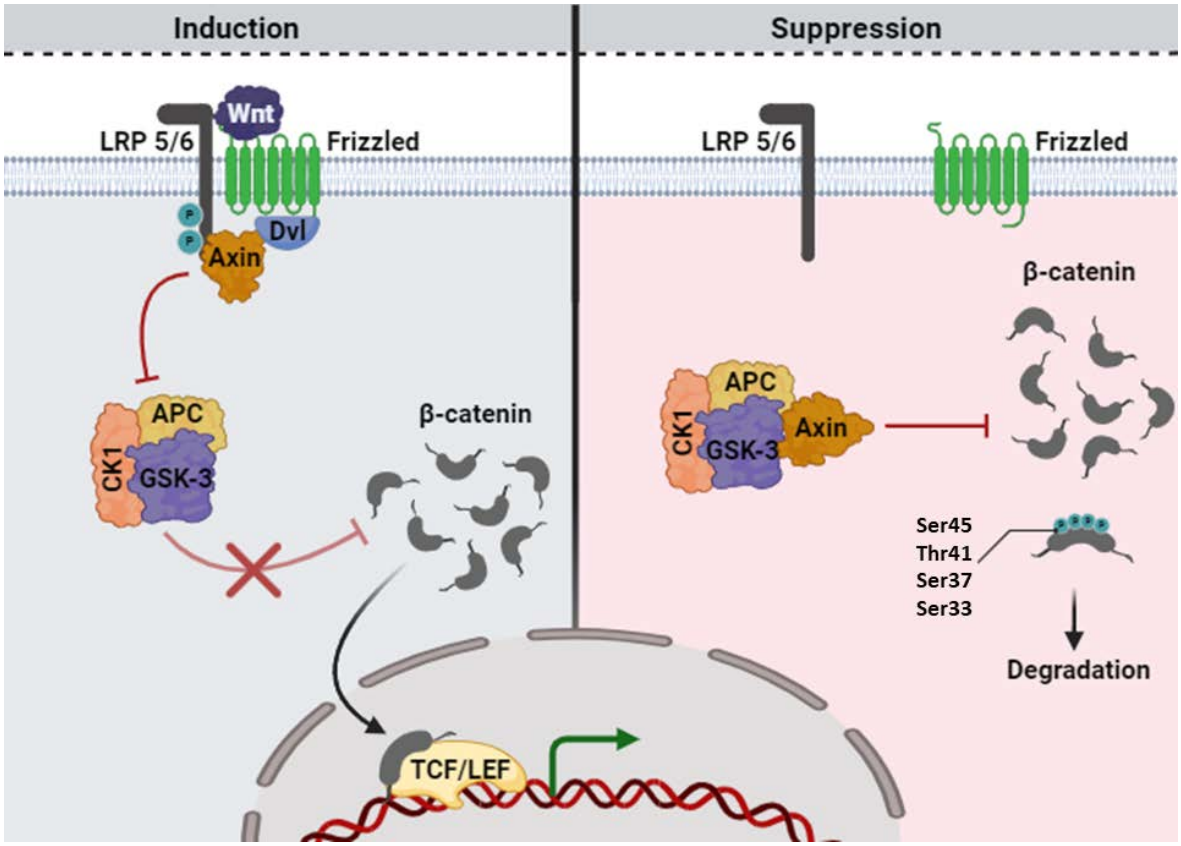

Figure 2. Schematic Illustration of the Wnt Pathway in Two Active and Inactive Forms: Degradation of β-Catenin in the Absence of Wnt by the Degradation Complex in Inactive Form and the Accumulation of β-Catenin With the Presence of Wnt, Suppressing the Destruction Complex
Note. The degradation complex includes Axin, APC, GSK-3, and CK1. LRP: Lipoprotein receptor-related protein; APC: Adenomatous polyposis coli; CK1: Casein kinase 1; GSK3: Glycogen synthase kinase 3; TCF/LEF: T-cell factor/lymphoid enhancer-binding transcription factor

immune cell infiltration. Specifically, β-catenin signaling reduces the expression of CCL4, a chemokine crucial for the recruitment of dendritic cells and T cells to the tumor site. Additionally, β-catenin interacts with other immunosuppressive pathways (e.g., TGF-beta signaling) to further enhance the immunosuppressive background.[109-112] The other consequences of the Wnt pathway include attenuating the efficacy of the antigen presentation system and upregulating innate and adaptive immune component modulators, such as PD-L1.[113,114]

In addition to β-catenin–dependent Wnt signaling, β-catenin–independent Wnt pathways have gained attention as the regulators of cancer therapy resistance. The non-canonical Wnt branches, including planar cell polarity and calcium-dependent signaling, control cellular behaviors (e.g., motility, polarity, and adaptive stress responses) rather than proliferation. Non-canonical Wnt activity is frequently associated with epithelial–mesenchymal transition, phenotypic plasticity, and metastatic competence, collectively reducing tumor responsiveness to anticancer therapies. The activation of planar cell polarity signaling enhances cytoskeletal reorganization and invasive capacity through small guanosine triphosphatase-mediated and c-Jun N-terminal kinase-mediated pathways, whereas calcium-dependent Wnt signaling supports survival under therapeutic pressure by engaging calcium-sensitive kinases and anti-apoptotic programs. In addition, non-canonical Wnt signaling has been involved in the suppression of effective antitumor immunity, thereby limiting responses to immunotherapeutic interventions.[115-117]

In contrast to canonical Wnt signaling, which predominantly sustains cancer stemness, DNA damage tolerance, and drug transporter expression, non-canonical Wnt pathways primarily facilitate invasion, dissemination, and immune escape. This functional distinction underscores the contribution of non-canonical Wnt signaling to therapy resistance and indicates the need for considering multiple Wnt signaling branches in resistance-oriented therapeutic strategies.[118]

Therapeutic Targeting of Wnt Signaling to Overcome Drug Resistance

Due to its wide-ranging involvement in the development of malignant characteristics, the Wnt signaling pathway is a key therapeutic target in cancer. In numerous studies, different chemicals have targeted key components of this signaling pathway in order to find novel medications.[119] It is a reliable approach to inhibit the porcupine enzyme, which facilitates Wnt secretion through palmitoylation, in order to impede this signaling pathway. Despite more research on porcupine inhibitors, clinically useful medications have not been licensed yet.[120] The next option is to block the Frizzled receptor, or Disheveled, to prevent the stimulation of downstream effectors.[121,122] Further investigation is necessary to more thoroughly assess

potential compounds for the design of small molecules or monoclonal antibodies like vantictumab.[123]

The main effector, β-catenin, must be under control to inhibit the expression of oncogene genes. This regulation is achieved by either management of the cytoplasmic concentration of β-catenin or its interaction with TCF/LEF or CREB-binding protein.[124,125] One unique strategy to address this carcinogenic pathway is to decrease the amount of cytoplasmic β-catenin by safeguarding the degradation complex.[126] Tankyrase targeting improves Axin stability, which is essential for degradative complex functionality (Table 1).[127,128] Even though the Wnt pathway has a significant potential for cancer, finding novel medications that effectively target it while having limited side effects is a constant challenge to improving patient outcomes.

The Role of Wnt Signaling in Cancer Drug Resistance-Related Mechanisms

The primary mediator of cellular activity is the signaling network. In turn, Wnt plays a vital role in this network and can control a variety of molecular and cellular

Table 1. Drugs Targeting the Wnt Signaling Pathway

Drug	Target	Cancer Type	FDA Approval Status	Ref.
WNT974	Porcupine	Solid tumors	Not FDA approved	129
ETC-159	Porcupine	Solid tumors	Not FDA approved	130
RXC004	Porcupine	Solid tumors, pancreatic cancer	Not FDA approved	131
CGX1321	Porcupine	Gastrointestinal cancers	Not FDA approved	132
LGK974	Porcupine	Solid tumors	Not FDA approved	133
CWP232291	Porcupine	Solid tumors	Not FDA approved	132
IWP-L6	Porcupine	Solid tumors	Not FDA approved	132
E7386	Porcupine	Solid tumors	Not FDA approved	134
ETC-1922159	Porcupine	Solid tumors	Not FDA approved	132
PRI-724	Frizzled	Colorectal cancer	Not FDA approved	135
LGK974	Frizzled	Solid tumors	Not FDA approved	136
Foxy-5	Frizzled	Metastatic breast cancer	Not FDA approved	137
OMP-18R5	Frizzled	Solid tumors	Not FDA approved	138
SM08502	Frizzled	Solid tumors	Not FDA approved	139
Vantictumab	Frizzled	Solid tumors	Not FDA approved	140
Fz5-antibody	Frizzled	Breast cancer	Not FDA approved	141
Fz7-antibody	Frizzled	Breast cancer	Not FDA approved	142
OMP-54F28	Frizzled	Solid tumors	Not FDA approved	138
Ipafricept	Frizzled	Pancreatic cancer	Not FDA approved	143
PRI-724	Dishevelled	Colorectal and pancreatic cancers	Investigational	132
E7386	Dishevelled	Breast cancer	Investigational	144
LF3	Dishevelled	Breast and lung cancers	Investigational	145
IWP-2	Dishevelled	Breast, colorectal, and pancreatic cancers	Investigational	115
CWP232291	β-catenin/TCF	Colorectal cancer	Investigational	132
C-82	β-catenin/TCF	Solid tumors	Investigational	146
PKF115-584	β-catenin/TCF	Colorectal cancer	Investigational	132
BC2059	β-catenin/TCF	Various solid tumors	Investigational	147
AZD5363	β-catenin/TCF	Solid tumors	Investigational	148
G007-LK	β-catenin/TCF	Colorectal cancer	Investigational	132
ETC-159	β-catenin	Advanced solid tumors	Investigational	149
Pyrvinium Pamoate	β-catenin	Colorectal cancer	Investigational	150
K-756	Tankyrase	Colorectal cancer	Investigational	132
XAV-939	Tankyrase	Various	Investigational	151
G007-LK	Tankyrase	Various	Investigational	152
IWR-1	Tankyrase	Various	Investigational	152
IWR-2	Tankyrase	Various	Investigational	152
JW55	Tankyrase	Various	Investigational	153
AZ1366	Tankyrase	Various	Investigational	153

Note. FDA: The Food and Drug Administration; TCF: T-cell factor.

processes. For instance, Wnt is accountable for setting up collaboration across multiple processes to accomplish a single objective: drug resistance. In addition, the Wnt pathway regulates various key processes responsible for drug resistance, including transporters, apoptosis, autophagy, the genome protection system, and enzymes that metabolize drugs. Consequently, this signaling pathway is likely to be targeted to overcome resistance to cancer therapy.

Wnt Signaling and Apoptosis/Autophagy in Drug Resistance

Apoptosis and autophagy exhibit dual biological activities in relation to the Wnt pathway. Depending on the cellular context, β-catenin can both boost and diminish the activity of these processes. Although promoting autophagy and preventing apoptosis assist cancer cells in becoming resistant to drugs, recent research indicates that this signaling pathway also possesses anti-tumor properties.[154,155] As previously mentioned, research has linked the Wnt pathway to elevated expression of anti-apoptotic proteins, such as survivin. Additionally, they have documented a rise in the Wnt3a molecular level correlated with an increase in Bcl-2 expression.[156] Throughout studies on the anti-apoptotic nature of the Wnt pathway, a great deal of attention has been devoted to Wnt-1. In more detail, the pro-survival activity of Wnt-1 has been reported to be associated with the up-regulation of cyclooxygenase-2 and Wnt-1-induced secreted protein 1, which block c-Myc-induced apoptosis.[157,158] Furthermore, the anti-apoptotic aspect of this signaling pathway is demonstrated by preventing the release of cytochrome c from mitochondria while activating other survival signaling pathways, such as nuclear factor kappa B.[159,160] However, findings prove that the Wnt pathway is also pro-apoptotic. The stimulation of the intrinsic mitochondrial apoptotic pathway through increasing the activity of caspases 3 and 9 and decreasing the expression of the BCL-2 family is one of the most relevant examples.[161,162]

Reducing the activity of autophagy while increasing the toxicity of anticancer drugs increases the efficiency of treatment.[163] Research on how the Wnt pathway enhances autophagy has revealed that temozolomide-induced autophagy is connected to higher expression of ATG9B by β-catenin.[164] Interestingly, the Wnt pathway's suppression of autophagy increases susceptibility to therapy while reducing autophagic cell death.[165,166]

The suppression of autophagy by the Wnt pathway has been linked to a decrease in LC3 and Beclin1 expression and repressive regulation of p62/SQSTM1.[167-169] Remarkably, autophagy contributes to the suppression of the Wnt pathway through facilitating the destruction of Dishevelled.[170]

Wnt Signaling and Deoxyribonucleic Acid Damage Response and Repair in Drug Resistance

Wnt signaling is activated as a part of the DNA repair system in response to various genotoxic factors and determines whether the cell is given time to restore the damage or cell death is triggered. For instance, the activation of the Wnt pathway allows the cell to withstand adverse circumstances (e.g., increased ROS via radiation) and avoids cell death by dropping ROS while enhancing DNA repair.[117]

Important findings have been obtained on the function of APC and Axin in the DNA repair system. In general terms, the accumulation of DNA damage is linked to the decrease or absence of APC.[171] The Base excision repair (BER) mechanism's effectiveness is enhanced by the interaction of APC with DNA polymerase beta and endonuclease-1 (Fen-1).[172] Furthermore, a decrease in APC has been demonstrated to result in a boosted ability to tolerate doxorubicin-induced apoptosis in triple-negative BC cells, indicating the anti-tumor role of the repair system, with apoptosis triggered in response to doxorubicin toxicity.[171,173]

The involvement of axin in the DNA damage response is mainly centered around the p53-dependent manner. One of the most significant tumor suppressors, promyelocytic leukemia protein (PML), sets the stage for cell cycle arrest by phosphorylating p53. The C-terminal binding of axin to PML causes PML activation.[174,175] Thus, investigating the mechanism of inducing apoptosis subsequent to radiation exposure makes the HIPK2-dependent stabilization of p53 more evident. It should be noted that axin is documented as a HIPK2 coactivator in this process.[176]

Apoptosis and DNA damage are highly possible outcomes of oxidative stress. According to some studies, secreted frizzled-related protein 3 and secreted frizzled-related protein 4 suppress oxidative stress.[177,178] Along with the decrease in ROS, there is a connection between the overexpression of SFRP5 and the inhibition of Bax expression.[179]

In addition to modulating cyclin D1 and Cdc25A, GSK-3β has a significant function in DSB repair.[180,181]

The interaction of GSK-3β with TRAX/DISC1 leads to the facilitation of ATM-dependent DNA repair.[182,183] Furthermore, research aimed at enhancing the radiation sensitivity of glioblastoma has revealed that GSK-3β phosphorylates 53BP1 to enhance DSB repair following translocation to the nucleus. Therefore, it is rational to employ targeted therapy to suppress GSK-3β.[184,185]

The expression of genes involved in DNA repair (i.e., *c-myc*, *Nkx2.2*, *MITF*, *RARγ*, *cyclin D1*, and the like) is responsible for the widespread role of β-catenin in this process.[186]

Wnt Signaling and Cancer Stem Cells in Drug Resistance

The Wnt pathway is crucial for the tumorigenic potential of stem cells. The primary biological implications of this pathway on CSCs include enhancements in their capacity to control the cell cycle, tolerate adverse conditions, enhance self-renewal capability, and proliferate.[187-189]

Studies to shed light on the relationship between markers of CSCs (e.g., CD133, CD44, CXCR4, EpCAM, ALDH1A1, NANOG, SOX2, and OCT4) are in progress.

The most frequently employed marker for CSC isolation is CD133/prominin-1, which is a pentaspan transmembrane glycoprotein whose detailed function is obscure.[190,191] A reduction in the expression of CD133 has been linked to the application of Dickkopf-1 to block the Wnt pathway, which leads to an improved prognosis.[192]

Analyzing the mechanism of CD44-mediated proliferation revealed that CD44 suppression can increase cell cycle inhibitors (e.g., p21) but decrease cyclin D1.[193] The Wnt pathway is positively regulated by CD44 in an LRP6-dependent manner to promote proliferation.[194] The positive interplay of Wnt with CSC markers is more evident in the context of EpCAM. This CSC marker, which is primarily involved in the biology of cell adhesion, is expressed less if the Wnt signal is suppressed.[195,196]

An additional unique perspective is revealed by the impact of circulating endothelial cell markers on dedifferentiation in the EMT process. An essential component of the EMT process, the expansion of cancer cells, is the reverse rotation of differentiated cells to produce more stem cell markers and stem-like characteristics.[197-199]

Research aimed at elucidating the function of circulating endothelial cell indicators in metastasis, carcinogenesis, and drug resistance has yielded important results, particularly with regard to ALDH1A1. The poor prognosis resulting from ALDH1A1 is reported mainly due to the positive effect on β-catenin.[200,201] Similarly, some studies have reported a poor prognosis due to this marker, mostly due to the positive impact of β-catenin on increasing EMT-related markers, such as Slug and Vimentin.[202,203] Additionally, frizzled class receptor 5 increases the stemness properties of ovarian cells by increasing the molecular level of ALDH1A1.[204]

It is arguably right to think of CXCR4 as a marker of metastasis because of its major involvement in raising the potential of metastasis.[205] CXCR4 employs the Wnt pathway to promote EMT and cancer cell invasion. This cooperative axis (CXCR4/β-catenin/EMT) has been confirmed through the inhibition of the Wnt pathway by Dickkopf-1.[206] Not to mention that other markers, such as Nanog, Sox2, and Oct4, are also involved in maintaining the properties of stem cells, increasing invasive potential, proliferation, resistance, and the like through the Wnt pathway.[207,208]

Wnt Signaling, Drug Metabolism, and Drug Transporters in Drug Resistance

Molecular transporters and metabolizing enzymes influence the bioavailability and applicable half-life of a drug.[209,210] The aberrant activity of the Wnt pathway entering the drug-metabolizing enzymes at a high level leads to an increase in the rate of drug inactivation, which is another description of drug resistance.[211,212] CYP3A4 is recognized for its involvement in the first metabolic phase of numerous therapeutic substances.[213,214] Pharmacokinetic studies have linked CYP3A4 to resistance to several chemotherapeutic medications, including taxanes, anthracyclines, vinca alkaloids, erlotinib, and gefitinib.[215-217] The Wnt pathway can have varied effects on these enzymes; for example, activating β-catenin can boost the expression of CYP1A1 and CYP1A2, but negatively affect CYP3A4.[218,219] The mechanism of β-catenin inhibition on CYP3A4 expression was partially elucidated by the discovery of CYP3A4 up-regulation by PPARα. Simply put, β-catenin indirectly modifies the expression of CYP3A4 by inhibiting PPARα.[220] Interestingly, CYP3A4 expression was positively impacted by the Wnt pathway in another investigation.[221] Aryl hydrocarbons stimulate the production of CYP1A1 through a signal that is mediated by the aryl hydrocarbon receptor. It has been reported that the suppression of apoptosis caused by aryl hydrocarbons in BC cells can be achieved by blocking the aryl hydrocarbon receptor.[222,223]

Reducing estrogen production is one of the targeted therapeutic strategies for BC.[224] The research demonstrated the great potential of Wnt3a for therapeutic applications by blocking the expression of aromatase, which is the primary enzyme involved in the synthesis of estrogen.[225]

Furthermore, it may be possible to make cancer cells more sensitive to radiation by blocking the Wnt pathway. This view mostly relies on β-catenin's ability to enhance aldehyde dehydrogenase.[226,227] In addition to radiation, this enzyme is involved in forming resistance to a variety of drugs, such as cyclophosphamide.[228]

The Wnt pathway positively regulates GST, which is one of the most significant detoxifying enzymes in the second phase of drug metabolism.[229,230] A basic description of the resistance mechanism that GSTs create is the addition of glutathione to many medicinal drugs to assist in the elimination process. Resistance to cisplatin, adriamycin, and chlorambucil is related to the conjugation activity of GSTs.[231,232] Additionally, studies investigating the effect of GST inhibitors (e.g., ethacrynic acid) on melphalan-resistant cells have clarified the role of GSTs in melphalan resistance.[233]

Coordination can also play an essential role in developing resistance; for instance, the combination of GSTP1 and MRP1 actions may be responsible for the resistance of melanoma cells to etoposide.[234]

To address the knowledge gap in this area, more research is required on the association between the Wnt pathway and significant enzymes that metabolize chemotherapeutic medicines, such as dihydropyrimidine dehydrogenase, which is crucial for 5-fluorouracil resistance.[235]

On the other hand, the Wnt pathway can mediate drug bioavailability and create resistance by influencing molecular transporters.[236,237] Although several transporters are involved in drug resistance, few of them are known to be related to the Wnt pathway. Table 2 is a brief overview of the most important transporters.

Interaction of Non-Coding Ribonucleic Acids With Wnt Signaling: Drug Resistance

ncRNAs constitute a diverse group of RNA molecules that do not encode proteins. Within this expansive family, pivotal members include circular RNAs, transfer RNAs, microRNAs (miRNAs), ribosomal RNAs, and long

Table 2. Summary of the Most Important Transporters Influenced by the Wnt Pathway

Transporter	Effect of Wnt/β-Catenin	Related Drug Resistance	Key Associated Cancer	Ref.
ABCB1 (P-gp)	Upregulation	Resistance to doxorubicin, paclitaxel, and etoposide	Breast, colon, lung cancer, and chronic myeloid leukemia	116,238
ABCC2 (MRP2)	Upregulation	Resistance to cisplatin, doxorubicin, methotrexate, epirubicin, etoposide, vincristine, and tamoxifen	Breast and pancreatic	238-241
ABCC1 (MRP1)	Upregulation	Resistance to cisplatin, doxorubicin, etoposide, methotrexate, vincristine, mitoxantrone, and irinotecan	Leukemia, breast, prostate, lung, ovarian, melanoblastoma, colon, and neuroblastoma	241,242
ABCC3 (MRP3)	Upregulation	Resistance to cisplatin, doxorubicin, vincristine, and methotrexate	Lung	243,244
SLC22A2 (OCT2)	Upregulation	Resistance to cisplatin	Renal cell carcinoma and pancreatic cancer	245-247
SLC22A3 (OCT3)	Downregulation	Increased sensitivity to oxaliplatin and irinotecan	Colorectal and kidney	248,249

RNAs (lncRNAs). Beyond their established involvement in fundamental cellular processes, such as cell cycle progression, DNA replication, transcriptional and translational control, as well as EMT and angiogenesis, the comprehensive scope of their biological function, which is based on the regulation of gene expression, remains obscure.[37,250] The components of autophagy, apoptosis, the DNA repair system, and other mechanisms involved in drug resistance can be directly/indirectly regulated by different ncRNAs; thus, the role of ncRNAs in the drug resistance of cancer cells extends far beyond other factors.[251-253] miRNAs act as guides for the RNA-induced silencing complex and regulate gene expression through mRNA inhibition. Therefore, the wide-ranging role of mRNA in the life of the cell makes miRNAs have a high penetrating power in the biological system.[254] Various miRNAs play a pivotal role in modulating drug resistance mechanisms. For instance, miR-125b, miR-24a, and miR-133 suppress apoptosis, while miR-214, miR-26b, and miR-375 promote autophagy.[255-257] Circular RNAs, which are characterized by their high stability due to eliminating free ends, exert a regulatory role by sponging miRNAs. This regulatory mechanism is exemplified by circ-0000515 and circ-0027345, which promote autophagy by targeting miR-326 and miR-345-5p, respectively.[258,259] The precise contribution of numerous lncRNAs to drug resistance remains largely elusive, yet mounting evidence underscores their involvement in this phenomenon.[260,261] Specifically, lncRNAs, such as SNHG14 and HCP5, have been involved in conferring drug resistance in BC through the modulation of the apoptosis pathway.[260,262] By blocking the Wnt pathway, anti-tumor miR-34a and miR-34b trigger apoptosis and offset drug resistance.[263,264] Studies on hepatocellular carcinoma (HCC) have identified HOX transcript antisense RNA (HOTAIR) as a cause of taxol resistance. Taxol resistance in HCC has been linked to HOTAIR. HOTAIR, through targeting miR-34a, contributes to the down-regulation of β-catenin and Akt phosphorylation.[265]

The Wnt/β-catenin pathway mediates the up-regulation of miR-552 as a biomarker for medication resistance. By blocking p53, miR-552 prevents chemotherapy-induced apoptosis.[266] The molecular activity of this Wnt pathway is elevated when β-catenin excessively relocates to the nucleus. Research has linked this translocation to an array of biochemical alterations, including a decrease in VHL. miR-21 may assist in increasing drug resistance mechanisms by blocking VHL.[267]

The prospect of utilizing ncRNAs for therapeutic purposes has been made possible by the discovery of their interaction with this pathway. For instance, it is clinically useful to inhibit the metastasis-associated lung adenocarcinoma transcript 1 (MALAT1)/Wnt signaling axis in order to limit stemness and metastasis in HCC.[268]

It is critical to employ mechanisms that guide and expedite research since the network of interactions between ncRNAs and the Wnt signaling pathway is extensive, and numerous essential elements remain unknown.[269,270] By putting the relevant datasets at artificial intelligence's disposal, it becomes feasible to utilize specific algorithms to link various components and reveal the network's hidden segments. In this domain, machine learning can shed light on significant ncRNA-related drug resistance characteristics.[271-275]

Clinical Implications

Recently, attention has been drawn to the remarkable connection that exists between drug resistance mechanisms and the Wnt pathway.[211] Therefore, it makes sense to attempt to develop a new medication that will block this pathway in order to lessen the capacity of the resistance system of cancer cells.[276]

In the treatment of many disorders, using targeted therapy to uncover clinically useful inhibitors of the components of this pathway can be a significant step forward. Considering that this system has a limited physiologic role in many adult cells, it is expected that these inhibitors have minimal adverse effects. However, there are not many Wnt pathway inhibitors that can be clinically approved (Table 1).[277,278] Research has revealed that the antitumor mechanism of obatoclax involves inhibiting the Wnt pathway to prevent the rise in survivin levels tied to colorectal cancer.[279]

On the other hand, coupling the inhibitors of this pathway with traditional anticancer medications will boost their efficacy and decrease the cancer fatality rate. Paclitaxel targets tubulin to prevent the development of mitotic spindles. When used in conjunction with LGK

974, this anti-cell cycle medication dramatically slows the proliferation of tumor cells.[280,281] Artemisinin, in combination with oxaliplatin, increases the antitumor efficacy of oxaliplatin by inhibiting the Wnt pathway.[282] Not to mention that eliminating the Wnt pathway-induced TME immunosuppressive circumstances will enhance the immune system to combat cancer cells.[283] Overall, understanding the mechanism that governs how the Wnt pathway interacts with resistance processes will help overcome the drug resistance of cancer cells. In-depth awareness of this interaction at the molecular level provides the background knowledge needed to make novel medications, expanding the available treatment options.[122,284] One way to attain the best possible care and enhance results is through the creation of an individualized treatment strategy. The most crucial prerequisite for individualized treatment is a patient's genome analysis to assess the possibility of medication resistance.[285,286]

In addition, aberrant Wnt pathway activity in cancer can be utilized as a biomarker to predict of the patient's response to treatment, thereby determining the patient's prognosis.[287] For instance, a rise in lymphoid enhancer-binding factor 1 frequently signals the need for more intense care.[288]

Despite the growing interest in targeting Wnt signaling for overcoming drug resistance, several challenges must be addressed before broad clinical implementation can be achieved. Wnt pathway activity is highly context-dependent and varies across tumor types, disease stages, and microenvironmental conditions, which may partly explain the heterogeneous responses observed in clinical studies. In addition, prolonged or systemic inhibition of Wnt signaling may affect tissue homeostasis, particularly in regenerative compartments, indicating the need for optimized dosing strategies and selective targeting approaches.[237] Future therapeutic success will likely rely on biomarker-guided patient stratification to identify tumors with Wnt-dependent resistance mechanisms, as well as on rational combination regimens that integrate Wnt inhibitors with chemotherapy, targeted agents, or immunotherapy. Addressing these challenges will be essential to translate Wnt-targeted interventions into durable clinical benefits for patients with therapy-resistant cancers.[121]

Conclusion

Even though the molecular network behind drug resistance is complicated, understanding the role of the Wnt pathway in this network will assist researchers in handling this therapeutic challenge. Weakening the resistance-related processes entails inhibiting the Wnt pathway. The insufficiency of research in the field of clinical usage of Wnt pathway inhibitors can be interpreted from limitations governing the licensed medications.

It is possible to employ ncRNAs to regulate this pathway in a variety of ways, such as by delivering ncRNAs to specific tissues via engineered exosomes. Not to mention that innovative methods must be employed to improve the outcome/prognosis of cancer patients. Furthermore, using artificial intelligence and already-existing databases, it is possible to reduce the quantity of time spent finding safe therapeutic compounds and shed light on the unexplored aspects of drug resistance that are related to the interaction of the ncRNA-Wnt pathway.

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