Role of the Wnt signaling pathway in the complex microenvironment of breast cancer and prospects for therapeutic potential (Review)

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Abstract. The focus on breast cancer treatment has shifted from the cytotoxic effects of single drugs on tumor cells to multidimensional multi-pathway synergistic intervention strategies targeting the tumor microenvironment (TME). The activation of the Wnt signaling pathway in the TME of breast cancer cells serves a key regulatory role in tissue homeostasis and is a key driver of the carcinogenic process. Modulating the crosstalk between the Wnt pathway and TME of breast cancer is key for understanding the biological behavior of breast cancer and advancing the development of novel antitumor drugs. The present review aimed to summarize the complex mechanisms of the Wnt signaling pathway in the breast cancer TME, interactions between the Wnt signaling pathway and components of the breast cancer TME and breast cancer-associated genes, as well as the interactions between the Wnt signaling pathway and other signaling cascades at the molecular level. Furthermore, the present review aimed to highlight the unique advantages of the Wnt signaling pathway in the macro-regulation of the TME and the current therapeutic strategies targeting the Wnt signaling pathway, their potential clinical value and future research directions in breast cancer treatment.

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Abbreviations: TME, tumor microenvironment; BC, breast cancer; VEGFA, vascular endothelial growth factor A; TGF-β, transforming growth factor β; MMP-9, matrix metallopeptidase-9; IL-10, interleukin-10; EMT, epithelial-mesenchymal transition; PCP, planar cell polarity; RAC, ras-related C3 botulinum toxin substrate; LRP5/6, lipoprotein receptor-related protein 5 and 6; DVL, dishevelled; Axin, axis inhibition protein; GSK-3β, glycogen synthase kinase-3β; TCF/LEF, T cell factor/lymphoid enhancer-binding factor; TAM, tumor-associated macrophage; NRP-1, neuropilin-1; TNBC, triple-negative breast cancer; CTLA-4, cytotoxic T lymphocyte-associated protein 4; TEFF, effector T cell; Treg, regulatory T cell; FoxP3, forkhead box P3; PCBP1, poly(C)-binding protein 1; DKK3, dickkopf-related protein 3; CAF, cancer-associated fibroblast; MSC, mesenchymal stem cell; BCSC, breast cancer stem cell; CiDA, compression-induced dedifferentiated adipocyte; HIF, hypoxia-inducible factor; CA, carbonic anhydrase; TP53, tumor protein P53; Ror2, receptor tyrosine kinase-like orphan receptor 2; PI3K, phosphatidylinositol-3 kinase; FGF, fibroblast growth factor; MMTV, mouse mammary tumor virus; sFRP-1, secreted frizzled-related protein 1; Shh, sonic hedgehog; PORCN, porcupine; G3BP1, Ras GTPase-activating protein-binding protein 1

Key words: Wnt signaling pathway, breast cancer, tumor microenvironment, pathway crosstalk, targeted therapy

Contents

1. Introduction

Breast cancer (BC) had 2.3 million new cases and 670,000 deaths recorded in 2022 (1). Moreover, projections indicate that by 2050, new cases will increase by 38%, and deaths will

increase by 68% (1). It is characterized by high heterogeneity, strong tendency for metastasis and resistance to treatment (2,3). The numerous types of cell that constitute the tumor microenvironment (TME) are not static bystanders within the tumor but are key drivers of disease progression. These cells secrete and express key regulatory factors, such as vascular endothelial growth factor A (VEGFA), transforming growth factor β (TGF-β), matrix metallopeptidase-9 (MMP-9), C-C motif chemokine ligand-22 and interleukin-10 (IL-10), which modulate the TME composition, thereby promoting the invasive progression of tumors, malignancy and metastasis (4). As the TME contains specific immune and stromal cell populations with notable prognostic value, its key role in tumor development is gradually gaining widespread recognition, making it an emerging field of research with therapeutic potential (5-7).

As a highly conserved signaling pathway, the Wnt signaling network serves a key role in core physiological processes, such as cell proliferation, differentiation, apoptosis, migration, invasion and maintenance of cellular homeostasis (8-10). Increasing evidence has revealed that the abnormal regulation of the Wnt signaling pathway is related to the occurrence and progression of BC (11,12). In more than half of BC cases, the tumor cell nucleus has abnormally high β-catenin expression (13). β-catenin, as a crucial activation 'hub' in the Wnt signaling pathway and a key transcriptional driving force in the epithelial-mesenchymal transition (EMT) process, is associated with the histological grade, clinical staging and lymph node metastasis and Ki-67 proliferation status of patients with BC, providing a novel perspective for understanding the pathogenesis and prognostic mechanisms of BC (14,15). Wnt signaling and the BC TME exhibit a complex and multifactorial interactive dynamic bidirectional association. Components of the TME affect the Wnt signaling pathway within tumor cells, and abnormalities in Wnt signaling in these cells drive changes in TME components (16-18). For example, abnormal activation of Wnt signaling can help tumor cells in the TME evade immune system surveillance, effectively hindering the infiltration process of T cells, thereby mediating immune tolerance. Furthermore, in the BC TME, the Wnt signaling pathway is not isolated but exhibits crosstalk with other key signaling pathways (19). These signaling pathways are coordinated, jointly regulating the dissemination and metastasis of tumors, as well as resistance to traditional treatment methods, revealing the complexity and diversity of BC pathogenesis (20-22).

The present review delves into the complex and intricate mechanisms of the interaction between the Wnt signaling pathway and TME in BC, including the functional roles of key components and their secreted factors in the TME, unique properties of physical influencing factors, associations with BC-related genes and intrinsic mechanisms of interactions between cell signaling pathways. The present review further explores the therapeutic potential of modulating the Wnt signaling pathway within the BC TME and its clinical implications, thereby providing new insight for BC treatment strategies.

2. Regulation of the Wnt signaling pathway in cancer

Under physiological conditions, the Wnt signaling system acts as a core regulator of cellular functions through the canonical Wnt/β-catenin signaling, non-canonical Wnt/planar cell polarity (PCP) and Wnt-Ca^{2+} signaling pathways to ensure the balance of organismal growth, development and homeostasis. However, when key components of this network undergo mutation, epigenetic modification or crosstalk with other signaling networks, they trigger abnormal activation of the Wnt signaling cascade and its downstream genes (23). Abnormal activation of Wnt signaling is associated with accelerated tumor proliferation, extended survival time, enhanced invasiveness and the maintenance of cancer stem cell (SC) characteristics (24,25). The canonical Wnt pathway promotes proliferation by upregulating cyclin D1, enhances anti-apoptotic capacity through B cell lymphoma-extra large and maintains cancer SC properties. The non-canonical pathway regulates disruption of cell polarity and metastasis via ras-related C3 botulinum toxin substrate guanosine triphosphatases and c-Jun N-terminal kinase (JNK) signaling (26). Simultaneously, Wnt signaling combats ferroptosis by activating glutathione peroxidase 4, while mediating tissue pyroptosis and EMT via the NOD-like receptor protein 3 inflammasome (27-29). Numerous studies have explored the diverse mechanisms of Wnt signaling activation in the occurrence and development of cancer (23,30-32) (Fig. 1).

Canonical Wnt/β-catenin pathway. The canonical Wnt/β-catenin pathway is activated by a cascade of tightly controlled steps. Initially, the Wnt ligand forms a complex with the frizzled receptor and low-density lipoprotein receptor-related protein 5 and 6 (LRP5/6) co-receptors, triggering signaling. This interaction activates dishevelled (DVL), a membrane-associated protein, which subsequently obstructs the β-catenin degradation complex, composed of axis inhibition protein (Axin), glycogen synthase kinase-3β (GSK-3β) and adenomatous polyposis coli, preventing the breakdown of β-catenin. Consequently, β-catenin accumulates in the cytoplasm before being translocated to the nucleus. Upon binding to T cell factor/lymphoid enhancer-binding factor (TCF/LEF) transcription factors, it induces the activation of downstream genes. Through the activation of downstream genes, the Wnt/β-catenin signaling pathway serves a critical role in regulating cellular functions, such as proliferation, differentiation, migration and apoptosis (33). Within this pathway, a negative feedback mechanism maintains signaling equilibrium, preventing both excessive and insufficient activation, thus decreasing the risk of pathological conditions, such as cancer (Fig. 2) (34).

Non-canonical pathways. The main components of the non-canonical Wnt signaling network are the Wnt/Ca^{2+} and Wnt/PCP pathways. These signaling networks act independently of β-catenin to activate separate cellular signaling processes. Wnt proteins, including Wnt1, Wnt5a and Wnt11, activate the Wnt/Ca^{2+} signaling pathway via engagement with frizzled receptors on the cell surface. Upon binding, the G proteins are activated. These molecules activate phospholipase C, resulting in an increase in intracellular Ca^{2+} concentration. It also causes a decrease in cyclic guanosine monophosphate and subsequent activation of kinases, such as calcium/calmodulin-dependent protein kinase II, calcineurin and protein kinase C. Following these events, transcription

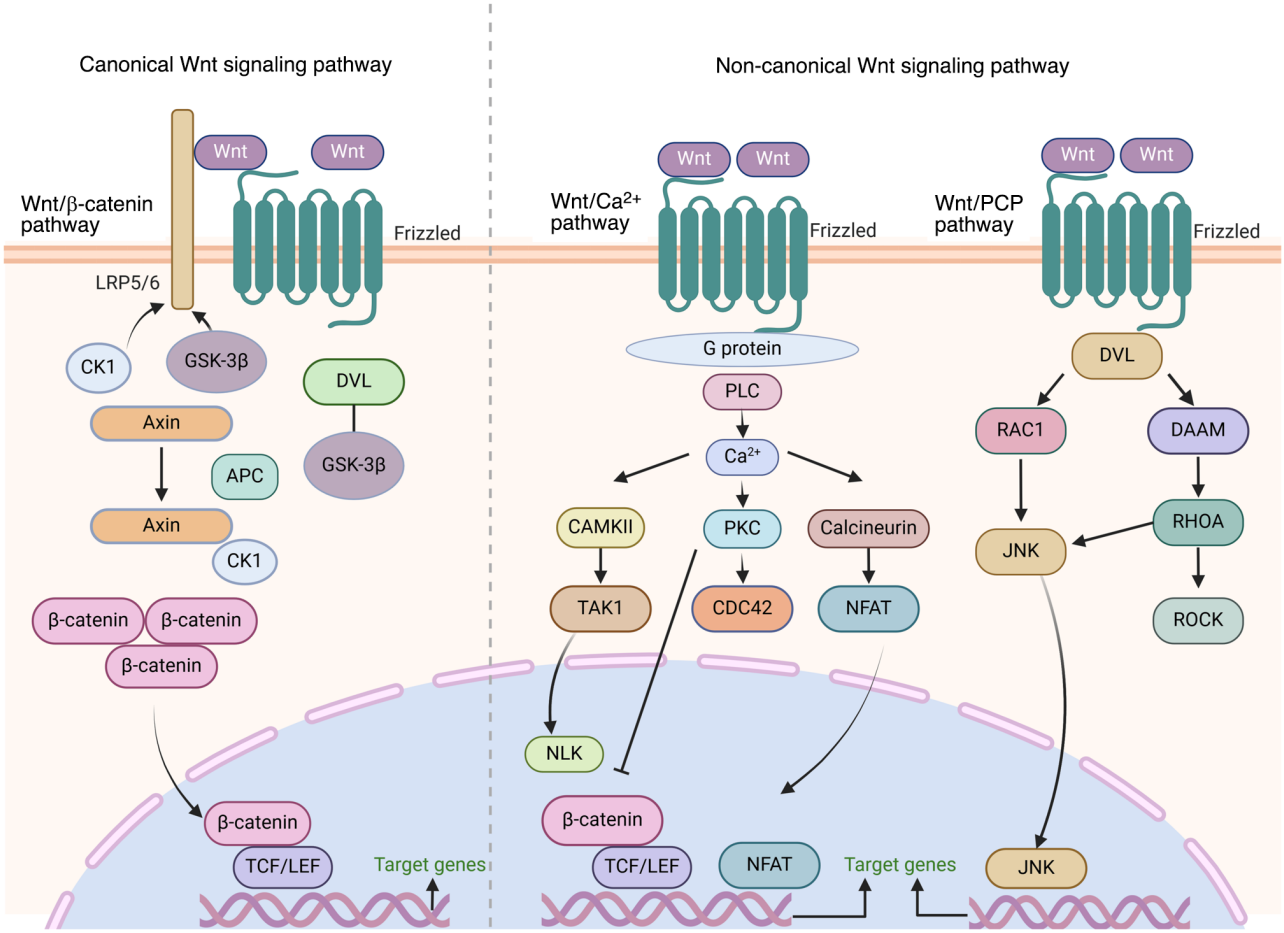

Figure 1. Schematic diagram of canonical and non-canonical signaling pathways. The primary mechanism of the canonical Wnt/β-catenin signaling pathway is to inhibit the degradation of β-catenin and promote the transcription of TCF/LEF genes. The non-canonical PCP pathway activates RHOA and RAC1 via phosphorylation and stimulates JNK; the non-canonical Ca^{2+} pathway is activated by PLC, leading to increased Ca^{2+} concentration and activation of the corresponding pathways. TCF/LEF, T cell factor/lymphoid enhancer-binding factor; PCP, planar cell polarity; PLC, phospholipase C; RHOA, ras homolog family member A; CK, casein kinase; GSK, glycogen synthase kinase; DVL, dishevelled; APC, adenomatous polyposis coli; DAAM, dishevelled associated activator of morphogenesis; LRP, lipoprotein receptor-related protein; ROCK, rho-associated coiled-coil containing protein kinase; CAMKII, calcium/calmodulin-dependent protein kinase II; PKC, protein kinase C; NFAT, nuclear factor of activated T cells; CDC42, cell division cycle 42; TAK, TGF-β-activated kinase; NLK, nemo-like kinase.

factors such as nuclear factor of activated T cells are activated (35). Alternatively, activation of the Wnt/PCP pathway begins when Wnt proteins engage with frizzled receptors, triggering DVL protein activation and subsequent activation of ras homologous/RAC guanosine triphosphatases and JNK. These signaling events lead to cytoskeletal rearrangement and regulation of gene expression. Both non-canonical pathways regulate key processes, including cell polarity, migration and signal transduction (36).

3. Impact of TME factors on the activity of the Wnt pathway in BC

BC progression is a multifactorial process in which the TME serves a key role. The BC TME is a diverse cellular ecosystem that includes malignant cells, immune cell populations and stromal tissue. These components and the factors they release interact with the Wnt signaling pathway, collectively driving tumor proliferation, invasion and metastasis, which are a series of malignant events (17,37). Additionally, physical factors, such as mechanical stress, hypoxia and acidification in tumor regions regulate the Wnt signaling pathway and affect the occurrence and trajectory of BC development. Analysis of the key elements within the TME that regulate Wnt signaling provides a theoretical foundation for uncovering the molecular mechanisms of BC pathogenesis and developing targeted therapeutic drugs (Fig. 3).

Immune and stromal cells in Wnt signaling transduction

Tumor-associated macrophages (TAMs). TAMs serve a central role in innate and adaptive immune responses because of their functional diversity and adaptability. In the complex pathological mechanisms of BC, a bidirectional interaction exists between Wnt signaling and TAMs, particularly M2-type TAMs. Wnt signaling drives the polarization of TAMs toward the M2 phenotype, which promotes the formation of an immunosuppressive TME, thereby supporting the growth, invasion and angiogenesis of BC and accelerating the survival and spread of tumor cells. Inhibiting the Wnt signaling pathway through the use of β-catenin inhibitors is an effective avenue to block M2 polarization, decreasing the expression levels of M2 markers and thereby reversing

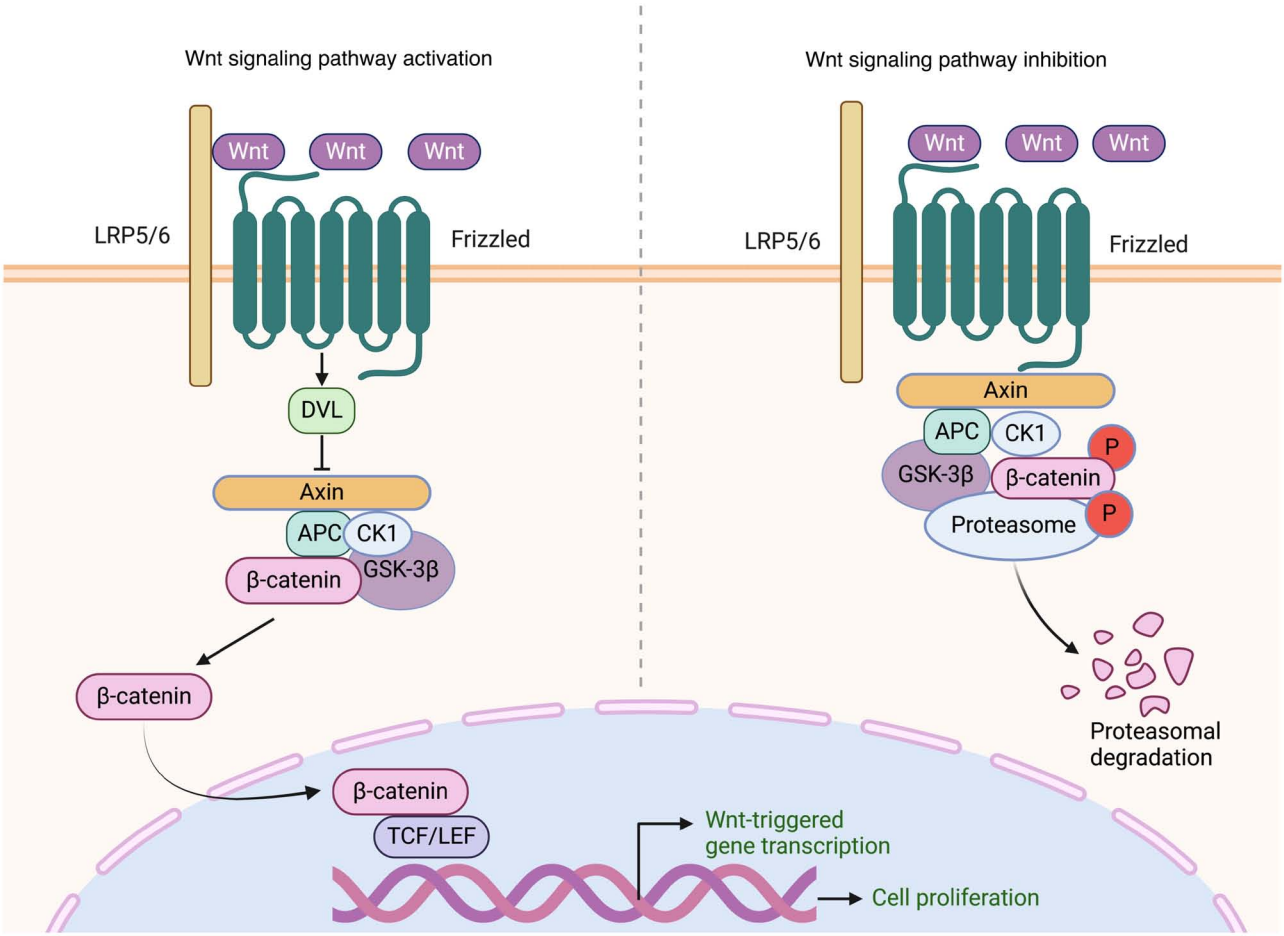

Figure 2. Wnt/β-catenin pathway activation and inhibition. Activation of the Wnt signaling pathway leads to the formation of the Wnt-FZD-LRP complex, which suppresses GSK-3β activity, preventing normal phosphorylation of β-catenin and subsequent binding with TCF/LEF transcription factors in the nucleus to activate downstream target genes. Inhibition of the Wnt signaling pathway results in normal degradation of β-catenin, precluding its entry into the nucleus for transcription. TCF/LEF, T cell factor/lymphoid enhancer-binding factor; LRP, lipoprotein receptor-related protein; GSK-3β, glycogen synthase kinase-3β; FZD, frizzled; APC, adenomatous polyposis coli; CK1, casein kinase 1; DVL, dishevelled.

the tumor-promoting effects of TAMs (38,39). Additionally, M2-type TAMs serve another key role by secreting VEGFA, which activates the neuropilin-1 (NRP-1)/GTPase-activating protein and VPS9 domain-containing protein 1/Wnt/β-catenin signaling cascade in triple-negative BC (TNBC) cells, enhancing the self-renewal ability and metastatic potential of tumor cells (17). Moreover, TAMs serve a critical role in regulating the activation state of the Wnt signaling pathway. $CD68^+$ and M2-polarized $CD163^+$ TAMs release Wnt5a, a signaling molecule that triggers Wnt signaling activity in malignant and stromal cells, forming a cycle that continuously drives tumor progression (40-43). Due to the potential of Wnt signaling to regulate the M2 polarization of TAMs and the activation of Wnt signaling pathways by factors secreted by M2-type TAMs, the Wnt-TAM axis may be a therapeutic target in BC.

T lymphocytes. T lymphocytes are key elements of adaptive immune responses, and their dysfunction is associated with tumor progression and the formation of immune escape mechanisms (44,45). Research has revealed the impact of the Wnt/β-catenin signaling pathway on T cell function, which reshapes the immune response potential of T cells by regulating the expression of immune checkpoints, cytokine synthesis and T cell differentiation status (46). Specifically, the activation of the Wnt/β-catenin signaling pathway upregulates immune checkpoint markers on the surface of $CD8^+$ T cells, such as programmed death receptor-1 and cytotoxic T lymphocyte-associated protein 4 (CTLA-4) (47-49). This upregulation pushes T cells toward exhaustion and promotes the formation of an immunosuppressive microenvironment, facilitating tumor progression (50). In the immune regulatory network of BC, DVL2 is a key hub of the Wnt signaling cascade that controls the expression pattern of Wnt target genes in $HER2^+$ BC cells by regulating the transcriptional activity of genes related to immune function and T cell survival (51). Moreover, the loss of B cell lymphoma 9, a key transcriptional coactivator of β-catenin, can effectively weaken abnormal Wnt/β-catenin signaling, thereby enhancing T cell-mediated tumor immunogenicity, offering potential for BC immunotherapy (52). In $CD8^+$ T cells, Wnt signaling inhibits the differentiation of these cells into effector T cells (TEFFs). This mechanism not only maintains the self-renewal potential of $CD8^+$ T cells, but also affects the differentiation fate of T cell progenitors, contributing to the diversity and complexity of T cell function (53). Future research should investigate the interaction network between different T cell subtypes, their secreted cytokines and

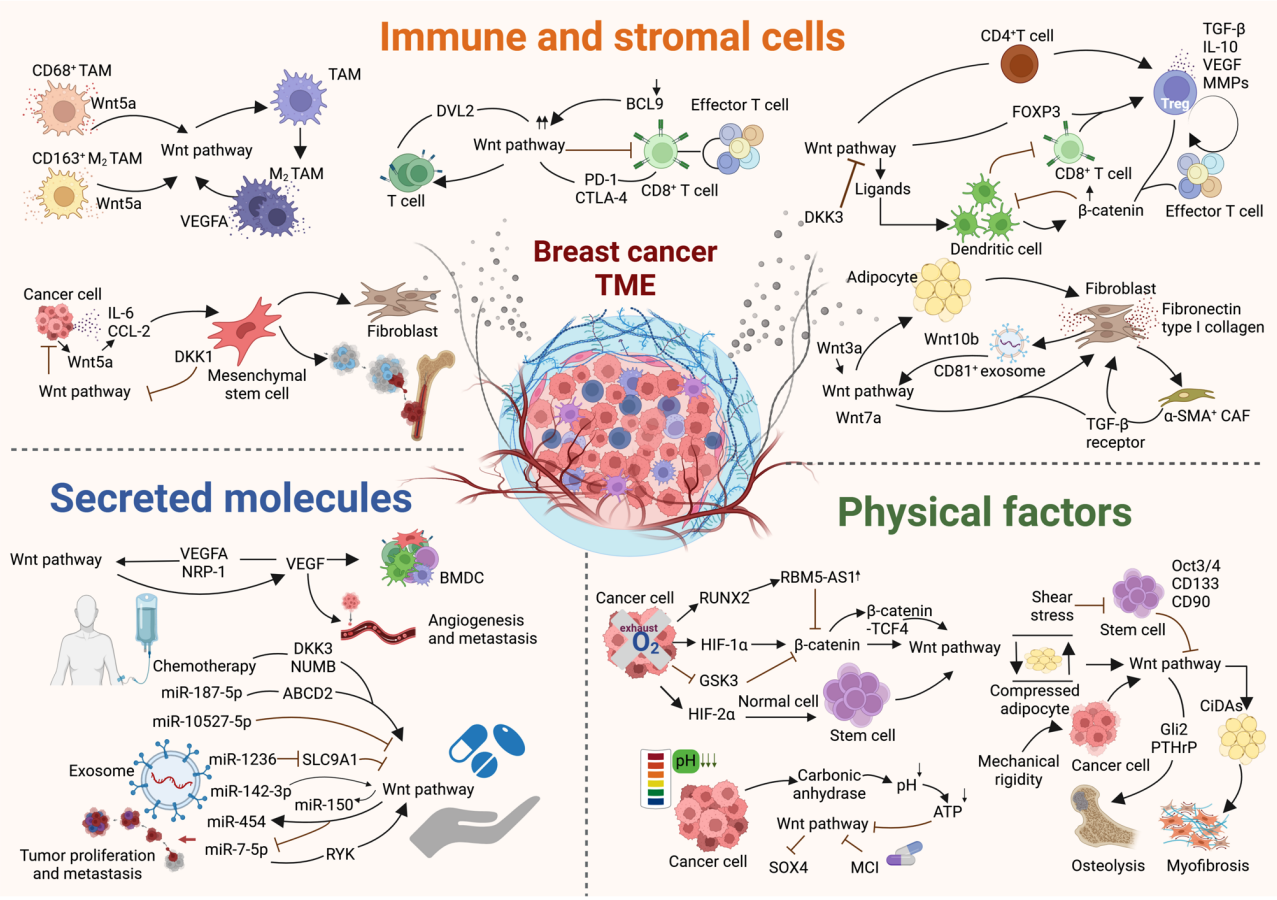

Figure 3. Wnt signaling within the breast cancer TME. Macrophages, T cells, regulatory T cells, fibroblasts, mesenchymal cells, VEGF and exosomes interact with the Wnt signaling pathway in the breast cancer TME. The hypoxic microenvironment, mechanical stress and tumor acidity also influence the Wnt signaling pathway. TME, tumor microenvironment; VEGF, vascular endothelial growth factor; TAM, tumor-associated macrophage; CCL, C-C motif chemokine ligand; DKK, dickkopf; DVL, dishevelled; SMA, smooth muscle actin; CAF, cancer-associated fibroblast; NRP, neuropilin; BMDC, bone marrow-derived dendritic cell; NUMB, protein numb homolog; ABCD, ATP-binding cassette sub-family D; miR, microRNA; RYK, receptor-like tyrosine kinase; RBM5-AS1, RNA binding motif protein 5 antisense RNA 1; HIF, hypoxia-inducible factor; GSK, glycogen synthase kinase; MCI, mitochondrial complex I; TCF, T cell factor; CiDA, compression-induced dedifferentiated adipocyte; Gli2, GLI family zinc finger 2; PTHrP, parathyroid hormone-related protein.

Wnt signaling components to provide more precise strategies for BC immunotherapy.

Regulatory T cells (Tregs). As regulators of immune homeostasis, Tregs play key roles in regulating immune response and preventing excessive autoimmunity (54). Previous studies have analyzed the mechanisms of the Wnt signaling pathway and related molecules, including Wnt ligands, forkhead box P3 (FoxP3), poly(C)-binding protein 1 (PCBP1), and dickkopf-related protein 3 (DKK3) in the TME of Tregs (55-58). Specifically, Wnt ligands activate β-catenin signaling in dendritic cells, driving the balance between TEFF and Tregs (55). However, when β-catenin signaling is overly active, this balance is disrupted, leading to impaired dendritic cell recruitment, inhibition of $CD8^+$ T cells, and proliferation of Tregs, which suppress the antitumor immune response (16,56). By inducing FoxP3 expression, the Wnt/β-catenin signaling pathway promotes the activation and differentiation of Tregs, triggering the release of immunosuppressive factors, such as TGF-β and IL-10. This facilitates tumor growth and immune evasion (56,59,60). In BC, the role of PCBP1 in modulating Wnt signaling is key for stimulating adaptive antitumor immune responses, and its decreased expression is associated with the imbalance of immune cell populations within tumors, which promotes the expansion of Tregs and subsequently inhibits the activation of antitumor immune responses (57). Additionally, DKK3 secreted by tumors may promote the reprogramming of $CD4^+$ cells into Tregs by blocking the Wnt signaling pathway, thereby supporting the survival and spread of tumor cells (56,58). Thus, the association between Wnt/β-catenin signaling and Tregs in the BC TME may provide a theoretical foundation for developing targeted treatment strategies aimed at enhancing antitumor immune responses and improving clinical outcomes.

Cancer-associated fibroblasts (CAFs). CAFs, a highly plastic and heterogeneous stromal cell population in the BC TME, not only maintain the structural framework and mechanical stability of tissue but also regulate biochemical signal transduction processes (61,62). In response to Wnt/β-catenin signaling, CAFs undergo transformation under the induction of Wnt proteins, secreting a range of bioactive molecules and generating exosomes, which facilitate tumor growth and invasion (63,64). There is an association between the origin of CAFs in BC and Wnt proteins. For example, Wnt7a transforms quiescent fibroblasts into α-smooth muscle actin-positive CAFs by binding to TGF-β receptors, thereby activating their

potent tumor-promoting potential (62). Tumor-derived Wnt3a promotes conversion of adipocytes to CAFs by activating the Wnt/β-catenin signaling pathway (62,65). Further research has revealed that CAFs, as a key source of Wnt ligands, actively promote BC progression by releasing paracrine signals (65,66). These signals maintain tumor stemness, stimulate the growth of the primary tumor and accelerate the metastatic colonization process (63,64). For example, Wnt3a activation enhances the synthesis of key matrix proteins, such as fibronectin and type I collagen, which further induces synthesis of MMP-9 in BC cells, thereby enhancing their migration and invasion capability (65,67,68). CAF-derived exosomes carrying CD81 serve a key role in stimulating BC cell motility due to activation of the Wnt/PCP signaling pathway. Wnt10b contained within the exosomes triggers a self-reinforcing cycle by activating the Wnt/β-catenin pathway, promoting progression and widespread dissemination of tumors (66,69). Therefore, the interaction between CAFs and the Wnt signaling pathway underlies the progression of BC and may provide a basis for development of innovative treatment strategies.

Mesenchymal SCs (MSCs). MSCs have garnered attention for their potential to differentiate into various cell types, such as adipocytes, osteoblasts and chondrocytes, which affect tumor angiogenesis, immune modulation and responses to antitumor therapy (70-72). In regulating interactions with BC cells, the Wnt signaling pathway serves as a key factor in driving tumor growth and bone metastasis, while also inhibiting tumor progression through diverse mechanisms (73). Specifically, the Wnt signaling pathway connects MSCs with cancer cells, enhancing the pro-tumorigenic properties of MSCs by inducing their differentiation into CAFs (74). Wnt5a released by BC cells triggers the secretion of IL-6 and monocyte chemoattractant protein-1, which enhances the phagocytic-like activity of MSCs and accelerates tumor dissemination. In *in vitro* models of BC bone metastasis, the Wnt/β-catenin pathway regulates osteogenic activity in a bone microenvironment composed of human MSCs, promoting the progression of BC bone metastasis (75,76). The functions of MSCs are not limited solely to promoting tumorigenesis; they also have the ability to inhibit tumor growth (77-79). MSCs effectively limit tumor progression through a number of biological mechanisms, including weakening Wnt and AKT signaling, blocking angiogenesis, stimulating the recruitment of inflammatory cells and inducing cell cycle arrest and apoptosis (77-82). In Michigan Cancer Foundation-7 cells, DKK1 derived from MSCs successfully inhibits tumor cell proliferation by downregulating β-catenin signaling (65,77). Additionally, in controlled experimental settings, chondrogenic membrane-derived MSCs inhibit the proliferation of BC cells, an effect mediated by the regulation of the Wnt/β-catenin signaling cascade. These findings revealed the dual nature of MSCs in BC, emphasizing their potential in both promoting and inhibiting tumor progression through different signaling pathways. Future studies should clarify the specific functions and pathways of MSCs in BC.

Secreted molecules and Wnt signaling transduction

VEGF family. VEGF is a key factor in regulating angiogenesis, tumor progression and metastatic spread and promotes the generation of a tumor immune-suppressive environment (83,84). Wnt signaling influences endothelial cells and paracrine signaling, further regulating vascular smooth muscle and vascular network structure (85,86). In BC, the canonical Wnt pathway not only drives the transcription of VEGF but also interacts with VEGF and its key receptor NRP-1, whereas the non-canonical Wnt pathway collaborates with VEGF to affect angiogenesis and cancer progression. Activation of the Wnt/β-catenin pathway can directly lead to the transcription of multiple target genes, including VEGF, by stabilizing β-catenin and promoting its transfer to the nucleus, thereby driving angiogenesis (87). In the formation of BCSCs and the induction of tubular angiogenic structures, the binding of VEGFA to its receptor NRP-1 serves a key role. In the VEGFA/NRP-1 signaling axis, the Wnt/β-catenin signaling pathway acts as a key downstream effector; its transmission is triggered by the activation of VEGFA, thereby facilitating persistence of CSCs (88,89). This cascade enhances the invasive potential of tumors and accelerates the malignant transformation of breast tissue. In addition, the non-canonical Wnt pathway often works together with VEGF, regulating key events in tumor angiogenesis, such as endothelial cell movement, increased vascular permeability and extracellular matrix remodeling (90,91). Given the key role of Wnt signaling in BC angiogenesis, precise therapeutic strategies targeting this pathway may provide novel avenues for overcoming resistance to traditional anti-angiogenic therapy, thus holding clinical translational potential.

Exosomes. Exosomes, as nanoscale vesicles for intercellular communication, play a key role in tumor progression and acquisition of therapeutic resistance within the TME (37,92-96). In BC, the Wnt signaling pathway influences the evolution of tumors, chemoresistance and the development of resistance reversal strategies by regulating the content of microRNAs (miRNAs or miRs) in different exosomes (97,98). Specifically, under the action of the Wnt signaling pathway, BC cells decrease levels of miR-7-5p in exosomes, thereby enhancing their migration and invasion capability and releasing miR-454 to maintain the self-renewal potential of CSCs (99,100). The roles of exosomal miRNAs in BC progression vary. Among them, exosomal miR-10527-5p can block the Wnt/β-catenin signaling pathway to inhibit cancer cell migration and invasion, whereas miR-7-5p from exosomes derived from less invasive BC cells inhibits metastasis by targeting the receptor-like tyrosine kinase gene and the non-canonical Wnt pathway (99,100). Conversely, upregulated miR-142-3p expression activates the Wnt pathway and induces miR-150 production, thereby promoting the over-proliferation of BC cells (101). Exosomes serve a central role in chemoresistance. Chemotherapy-induced exosomes activate the Wnt/β-catenin pathway by targeting DKK3 and Notch signaling pathway inhibitor protein numb homolog, inducing resistance; exosomes released by paclitaxel-resistant BC cells carry miR-187-5p that regulates ATP-binding cassette subfamily D member 2 and the Wnt/β-catenin pathway, affecting proliferation. Exosomes transported from adipose-derived MSCs transfer miR-1236, which decreases resistance to cisplatin by inhibiting solute carrier family 9 member A1 activity and Wnt/β-catenin signaling (101). These findings not only reveal the dual role of exosomes in BC progression, but also provide a basis for exploring resistance reversal strategies in BC.

Wnt signaling-related physical factors

Mechanical stress. Mechanical stress resulting from the integrated action of multidimensional factors, such as tissue topography, matrix stiffness, physical stretching, shear stress and compression, is closely related to the initiation, development and dissemination of cancer (102,103). Mechanical stress regulates BC progression by affecting the response of adipocytes, SCs, cancer cells and fibroblasts to the Wnt signaling pathway. For example, shear stress can downregulate the expression of SC marker molecules, thereby blocking the Wnt/β-catenin pathway, increasing cellular stiffness and inducing the differentiation of cancer cells toward a mature state (104). Adipocytes, an important component of breast tissue, undergo dedifferentiation transformation via the mechanosensitive response mechanism of the Wnt/β-catenin pathway when subjected to physical compression, forming compression-induced dedifferentiated adipocytes (CiDAs) (105). CiDAs accelerate myofibroblastosis within the TME, facilitating BC cell proliferation (105). Matrix rigidity serves a key role in regulating the invasive potential of breast tumor cells at the primary site of disease (106-108). The combination of matrix rigidity and matrix-secreted factors stimulates Gli family zinc finger protein 2 and parathyroid hormone-related protein through Wnt signaling in osteolytic breast cancer cells, driving tumor-induced osteolysis (109). Intervention strategies targeting physical factors and the Wnt signaling pathway may provide an effective therapeutic approach to delay tumor metastasis (103,109).

Hypoxic microenvironment. Hypoxia, a constant and heterogeneous characteristic of the TME, is pervasive in most types of solid tumor owing to the abnormally high expression of hypoxia-inducible factors (HIF) under low-oxygen conditions (110,111). In the hypoxic microenvironment of BC, HIF regulates the Wnt signaling pathway and stability of β-catenin while inducing upregulation of runt-related transcription factor 2 (RUNX2) and inhibiting the activation of GSK3, facilitating aggressive progression of tumors and the enhancement of cancer cell invasiveness. Specifically, HIF-1α stabilizes the structure of β-catenin and enhances its transcriptional activity; on the other hand, it upregulates the expression of Wnt ligands and receptors, thereby transcriptionally activating Wnt1-inducible signaling pathway protein 3. This activates the Wnt pathway, facilitating tumor growth, metastasis and angiogenesis (112). Concurrently, HIF-2α reprograms normal cells into a SC-like phenotype by activating the Wnt signaling pathway in BC cells and induces chemotherapy resistance (113). This not only drives metabolic reprogramming and maintains stemness of BC cells but also enhances glycolysis and glutaminolysis through the Wnt/β-catenin pathway, ensuring the survival of cancer cells under extreme hypoxic conditions (114-120). Hypoxia-induced RUNX2 upregulates RNA binding motif protein 5-antisense RNA 1, preventing the degradation of β-catenin and promoting the formation of β-catenin-TCF4 transcription complex, thereby amplifying the effect of the Wnt/β-catenin pathway and accelerating tumor progression (121). Hypoxic conditions inhibit the activation of GSK3, decreasing the phosphorylation and subsequent degradation of β-catenin, further activating the Wnt/β-catenin pathway, leading to increased expression of snail family transcriptional repressor 1, and enhancing the invasiveness of cancer cells (122). These findings not only reveal the key role of hypoxia in tumor progression but also provide perspective for the development of innovative therapy.

TME acidity. A common characteristic of solid tumors is the acidic metabolic environment, which not only promotes the proliferation of tumor cells, but also serves a key role in resistance to radiotherapy and chemotherapy (123). The acidic TME is primarily shaped by hydrogen ions released from the dissociation of lactate and carbonic acid. Lactate originates from the anaerobic glycolysis of tumor cells, whereas carbonic acid is generated by the reaction of CO_2 with H_2O catalyzed by carbonic anhydrase (CA) (123). In BC, abnormal regulation of CA exacerbates this acidification, further disrupting the internal pH balance of tumors (124). Intracellular acidification triggers the activation of the unfolded protein response and ATP depletion, thereby inhibiting Wnt signaling activity (125). Drugs that induce intracellular acidification (such as mitochondrial complex I) effectively suppress the Wnt signaling pathway, decrease the expression of SRY-box transcription factor 4 and inhibit SC characteristics and activity of BC cells (125). These findings not only reveal the potential of targeting the Wnt pathway in BC treatment but also provide perspective on strategies that exploit the acidic TME. Therefore, modulating the pH of the TME may serve as an innovative adjuvant therapy, laying a foundation for tumor treatment.

4. Association between BC-associated genes and Wnt signaling

In recent years, with the continuous advancement of oncology research, the association between BC-related genes and the Wnt signaling pathway has become a research hotspot in this field (126-128). BC-associated genes, such as BRCA1, BRCA2 and tumor protein P53 (TP53) are associated with the Wnt signaling pathway and serve key roles in maintaining normal physiological function, genomic stability and cell fate determination.

BRCA1 and BRCA2. BRCA genes, mainly BRCA1 and BRCA2, are closely associated with the risk of hereditary BC (129,130). They effectively inhibit excessive cell proliferation and maintain genomic stability by repairing double-stranded DNA breaks (131). In germline BRCA1 mutation carriers, the microenvironment harboring heterozygous BRCA1 mutations may promote BC development by creating a tumor-promoting niche, particularly by affecting the stromal cells residing in the TME (132,133). Wu *et al* (134) reported that in basal-like BC, the Wnt effector Slug epigenetically suppresses BRCA1, resulting in a negative association between Wnt signaling and BRCA1 expression. Furthermore, Wu *et al* (134) indicated that canonical Wnt signaling drives cancer cell EMT and tissue invasion by modulating Slug activity, inhibiting the function of BRCA1 and BRCA2 and rendering breast epithelial cells more vulnerable to etoposide-mediated DNA damage. Li *et al* (135) revealed that BRCA1 deficiency may increase the sensitivity of the active form of β-catenin protein to H_2O_2, thereby decreasing its expression. To the best of our knowledge, however, research on the association between BRCA genes and the Wnt signaling pathway remains limited, and more mechanistic studies are needed (135).

TP53. TP53 gene mutations serve a key role in BC. Transcription factor p53, encoded by TP53, serves a crucial

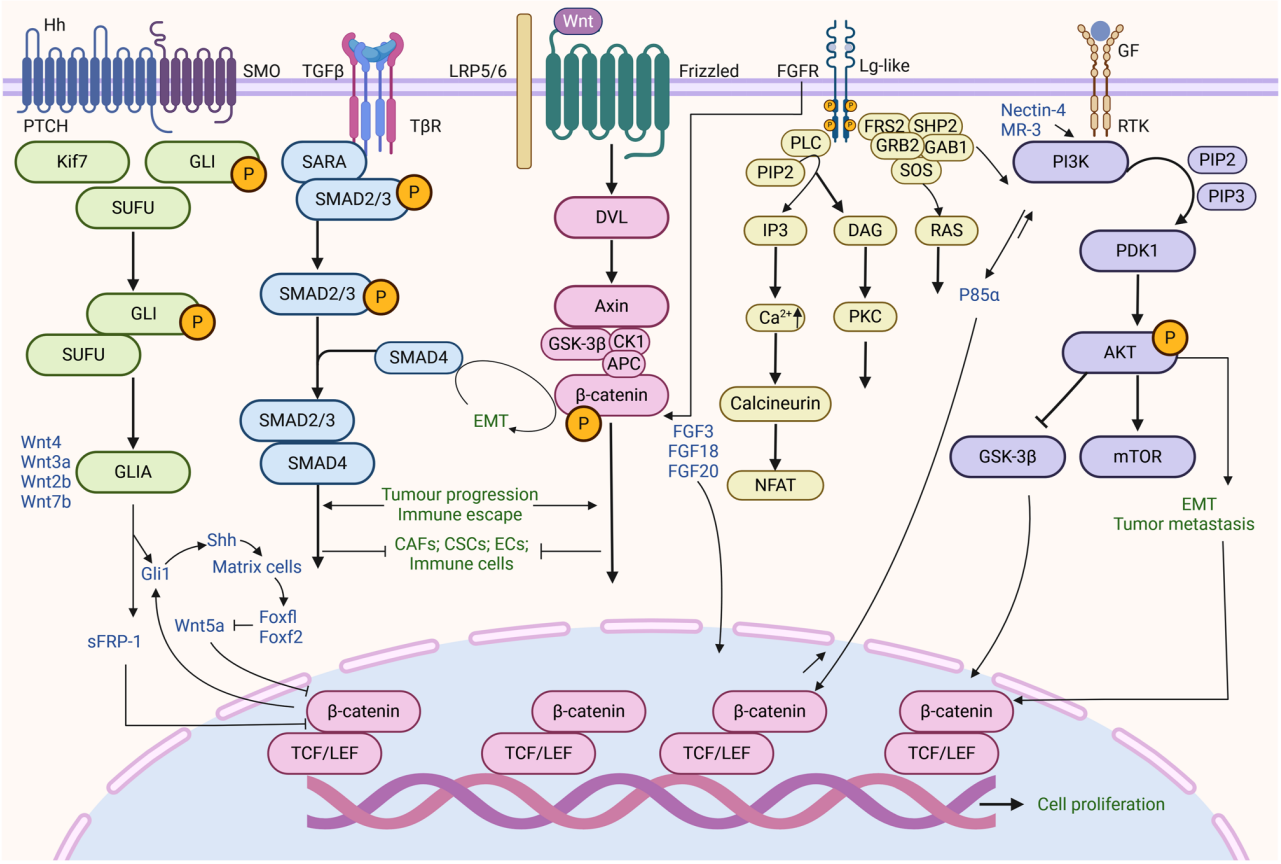

Figure 4. Interaction between the Wnt signaling pathway and other pathways in the breast cancer TME. Wnt signaling interacts with TGF-β, PI3K/Akt, FGF and hedgehog signaling pathways within the TME. TME, tumor microenvironment; FGF, fibroblast growth factor; TGF, tumor growth factor; PI3K, phosphatidylinositol-3 kinase; Hh, hedgehog; PTCH, patched; SMO, smoothened; LRP, lipoprotein receptor-related protein; TβR, transforming growth factor-beta receptor; SARA, Smad anchor for receptor activation; Kif, kinesin family member; GLIA, GLI family zinc finger; SUFU, suppressor of fused; sFRP, secreted frizzled-related protein; Gli, GLI family zinc finger; Shh, sonic hedgehog; TCF/LEF, T-cell factor/Lymphoid enhancer factor; CAF, cancer-associated fibroblast; CSC, cancer stem cell; EC, endothelial cell; EMT, epithelial-mesenchymal transition; DVL, dishevelled; APC, adenomatous polyposis coli; CK, casein kinase; GSK, glycogen synthase kinase; NFAT, nuclear factor of activated T cell; IP3, inositol trisphosphate; PIP, phosphatidylinositol phosphate; PLC, phospholipase C; Lg, ligand; DAG, diacylglycerol; FRS, fibroblast growth factor receptor substrate; SHP, Src homology 2 domain-containing phosphatase; GRB, growth factor receptor-bound protein; GAB, GRB2-associated binder; SOS, son of sevenless; P85α, phosphoinositide-3-kinase regulatory subunit α; MR-3, 3,5,4'-trimethoxystilbene; RTK, receptor tyrosine kinase; GF, growth factor; PDK, phosphoinositide-dependent kinase; EMT, epithelial-mesenchymal transition; mTOR, mammalian target of rapamycin.

role in regulating a series of cellular activities, including cell cycle arrest, apoptosis, metabolic regulation, DNA repair and cellular senescence (136-138). Abnormal activation of the Wnt signaling pathway effectively suppresses TP53 activity, thereby facilitating survival of tumor cells and enhancing their resistance to apoptosis (139). In BC cells, the absence of TP53 promotes the release of key Wnt factors, such as Wnt1, Wnt6 and Wnt7a, but also stimulates TAMs to produce IL-1β, a key inflammatory mediator, through the binding of these factors with frizzled class receptor 7 (FZD7) and FZD9 receptors on the surface of TAMs (140). Moreover, in TP53-deficient basal-like BC tumors, activity of the Wnt signaling pathway is enhanced and is often accompanied by the expression of the non-canonical Wnt signaling mediator receptor tyrosine kinase-like orphan receptor 2 (Ror2). The existence of Ror2 as an alternative Wnt receptor enhances the diversity of Wnt signaling and supports Wnt/β-catenin-independent signaling functions in TP53-deficient model (141). Therefore, the combined inhibition of TP53 and the Wnt signaling pathway may provide effective therapeutic options for patients with BC.

5. Interplay of Wnt signaling and other cellular pathways in BC

Somatic genomic aberrations in breast tumors disrupt key signaling networks that regulate cell division, survival and differentiation, highlighting numerous potential biomarkers and therapeutic targets (142). Previous studies have demonstrated crosstalk between the Wnt signaling network and key pathways within the TME, including TGF-β, phosphatidylinositol-3 kinase (PI3K)/Akt, fibroblast growth factor (FGF) and Hedgehog signaling (37,143,144). These signaling networks not only control tumor cell proliferation and migration, but also serve indispensable roles in immune evasion, metabolic reprogramming and therapeutic resistance, which are critical biological processes (145). The association between the Wnt signaling pathway and other core pathways, as well as the underlying biological mechanisms, may serve as potential therapeutic strategies and biomarkers (Fig. 4).

TGF-β signaling pathway. The Wnt and TGF-β signaling pathways, as evolutionarily conserved regulatory mechanisms,

serve crucial roles in embryonic differentiation, tissue homeostasis and pathological processes. Abnormal activation is closely associated with BC progression, increased potential for metastasis and poor clinical prognosis (146,147). The mechanisms by which these pathways influence BC primarily involve driving EMT, inducing immune evasion and maintaining BC cell stemness (148). EMT, as a key mechanism of tumor metastasis, is regulated by the Wnt and TGF-β signaling pathways. TGF-β, acting as a catalyst for EMT, can prompt epithelial cells to transition into invasive mesenchymal phenotypes (149). Concurrently, the Wnt pathway, particularly its β-catenin-activated form, promotes EMT. These two pathways collectively regulate gene expression networks associated with EMT through interactions between β-catenin and SMAD proteins, thereby accelerating the invasion and migration of BC cells (149). In addition to regulation of EMT, the crosstalk between the Wnt and TGF-β signaling pathways amplifies their individual effects in promoting immune evasion. TGF-β signaling activates immune escape mechanisms, while Wnt signaling is involved in immune modulation, especially in promoting immune tolerance (32,150). The maintenance of BCSCs is a component of the functional intersection of Wnt and TGF-β pathways, which are key for tumor development, metastasis and the emergence of therapeutic resistance. The Wnt pathway drives the self-renewal of BCSCs via β-catenin-mediated transcriptional activation, whereas TGF-β enhances the maintenance of BCSCs by promoting stemness (151). More specifically, non-canonical Wnt signaling, by maintaining CSCs in a quiescent state in association with TGF-β signaling, enhances the EMT process, thereby promoting the maintenance and expansion of CSCs (151). Interactions between these pathways provide valuable insight for the development of innovative therapeutic interventions. Compared with the inhibition of a single pathway, targeting both Wnt and TGF-β pathways simultaneously provides a more efficient approach to improving the outcomes of BC treatment (152,153).

PI3K/Akt signaling pathway. The PI3K/Akt pathway plays a pivotal role in regulating core cellular activities, such as proliferation, division, metabolic adaptation, survival and angiogenesis (154,155). The PI3K/Akt and Wnt pathways are associated with tumor biological behaviors through regulating CSC self-renewal, accelerating EMT and metastasis and affecting angiogenesis, thus facilitating progression of BC. In BC, a key factor in the combined action of the Wnt and PI3K/Akt signaling pathways to promote CSC self-renewal is the interaction between β-catenin and the PI3K regulatory subunit p85α, which enhances the catalytic activity of PI3K, thereby triggering the phosphorylation and activation of Akt (156,157). Further research has shown that the PI3K/Akt pathway intersects with the canonical Wnt signaling cascade under the regulation of GSK3β, where Akt phosphorylates and inhibits GSK3β, amplifying the efficiency of Wnt signal transduction and further promoting the self-renewal of CSCs (158-160). In terms of promoting EMT and metastasis, Siddharth *et al* (161) revealed the overexpression of nectin-4 drives Wnt/β-catenin signaling through the PI3K/Akt axis, thereby enhancing the EMT process and promoting metastasis. Simultaneously, the PI3K/Akt signal phosphorylates and activates β-catenin; this upregulates the expression spectrum of genes associated with EMT and enhances its interaction with TCF/LEF transcription factors, thus advancing the EMT process (162). 3,5,4'-trimethoxystilbene can affect E-cadherin levels and nuclear localization of β-catenin by regulating the PI3K/Akt signaling axis and GSK3β, thereby reversing EMT in BC cells (163). In addition, the role of Wnt3a and the PI3K/Akt pathway in angiogenesis has attracted increasing attention (164). Thymoquinone, as an effective inhibitor, simultaneously impairs the normal function of PI3K and Wnt3a signaling pathways, thereby inhibiting angiogenesis (164). Arqués *et al* (165) reported that the combined use of the PI3K inhibitor BKM120 and the Wnt signaling inhibitor LGK974 can decrease tumor progression and metastasis in BC. These findings provide a theoretical and experimental basis for the development of targeted therapeutic strategies for the PI3K/Akt and Wnt signaling pathways and the formulation of personalized treatment plans.

FGF signaling pathway. FGFs are involved in controlling a broad range of cellular functions, including SC survival, proliferation, programmed cell death inhibition, drug resistance and angiogenesis (166,167). The FGF signaling pathway interacts with the Wnt pathway and regulates the transcriptional activity of target genes. Members of the FGF family activate the Wnt pathway through various mechanisms, such as inducing β-catenin modification and promoting the phosphorylation of low-density LRP6, and these pathways exhibit synergistic oncogenic effects in mouse mammary tumor virus (MMTV)-induced tumors. FGF family members FGF18 and FGF20 promote Wnt pathway activation via β-catenin-TCF/LEF-dependent transcription (168,169). Activation of FGF receptors induces tyrosine phosphorylation-mediated modification of β-catenin, leading to the detachment of β-catenin from adherens junctions and a decrease in its N-terminal serine/threonine phosphorylation levels. By blocking the proteasomal degradation pathway of β-catenin, this mechanism enhances the self-reinforcing loop of the canonical Wnt signaling pathway (170-172). Additionally, FGF signaling promotes the phosphorylation of LRP6 mediated by cyclin Y/vertebrate homolog PFTK, further activating the Wnt pathway during the G2/M transition of the cell cycle (173). The interaction between Wnt-1 and FGF3 was initially detected in tumors induced by MMTV (174,175). FGF3, as an oncogene, triggers the occurrence of ~40% of MMTV infection-dependent tumors with Wnt-1. MMTV insertional mutagenesis studies have demonstrated that simultaneous activation of Wnt and FGF signaling components is one of the most common genetic alterations in breast tumors (176,177). Overactivation of the Wnt and FGF signaling pathways is considered a potential molecular marker for predicting the response of BC to next-generation eukaryotic initiation factor 4A RNA helicase inhibitors (178). Therefore, the interaction between Wnt and FGF signaling in the BC TME is a dynamic and complex process that affects the behavioral patterns of tumor cells and promotes BC progression.

Hedgehog signaling pathway. The Hedgehog signaling cascade is a highly conserved process in evolution and serves a crucial role in cell differentiation, tissue development,

homeostasis and EMT (179). Within the complex network of tumor biology, the crosstalk between the Wnt and Hedgehog signaling pathways primarily occurs through the transcription factor Gli1-mediated control of secreted frizzled-related protein 1 (sFRP-1) and sonic hedgehog (Shh) expression, and Gli1 exerts a synergistic impact with β-catenin, shaping the progression of BC. Specifically, the key transcription factor Gli1 in the Hedgehog pathway mediates crosstalk with the Wnt pathway by regulating the negative regulator sFRP-1 in the Wnt signaling pathway (180). When the function of sFRP-1 is compromised, the canonical Wnt pathway is abnormally activated, leading to disorders in the signaling network (180). The regulatory role of Gli1 is not limited to sFRP-1 but also involves other members of the Wnt family, such as Wnt2b, Wnt4 and Wnt7b. Furthermore, Gli1 upregulates the expression of the secreted Hedgehog Shh, which transmits paracrine signals to the surrounding stromal cells, triggering biological effects. Upon receiving the Shh signal, stromal cells upregulate the expression of forkhead box F1 (Foxf1) and Foxf2, thereby inhibiting the production of Wnt5a in the stroma and indirectly regulating the activity of β-catenin (181). There is an association between nuclear Gli1 and β-catenin activity. The expression of exogenous constitutive nuclear β-catenin can enhance the activity of Gli1 reporter genes, indicating that the sustained activation of Wnt signaling can enhance the transcriptional efficacy of Gli (182). Arnold *et al* (183) reported that the co-elevation of nuclear Gli1 and β-catenin activity is associated with the progression of TNBC stage and poor clinical prognosis (183). Concurrent activation of the Hedgehog and Wnt pathways is also associated with a decline in recurrence-free and overall survival rates in patients with TNBC (183). Thus, the synergistic activation of the Wnt and Hedgehog pathways may serve as an important biomarker for the progression and therapeutic response of BC, providing avenues for optimizing clinical treatment plans and improving the prognosis of patients with BC.

6. Clinical advantages of regulating the Wnt signaling pathway in BC

While exploring the complex mechanisms of the TME, abnormal regulation of the Wnt signaling pathway has been identified as a key element in tumor progression, affecting angiogenesis, immune evasion and metastasis (184). In addition, the Wnt signaling pathway affects the efficacy of anti-HER2 therapy, chemotherapy and immunotherapy, influencing the success of BC treatment and patient prognosis. For example, in HER2-overexpressing BC cells, Wnt3 overexpression activates the Wnt/β-catenin signaling pathway, which not only leads to the transactivation of EGFR and promotes an EMT-like transformation but may also be a key cause of trastuzumab resistance (185,186). This signaling pathway may regulate CD36 levels, prompting resistant mesenchymal CSCs to transition to a treatment-sensitive epithelial state, thereby affecting lapatinib resistance (187,188). *In vitro* studies by Xu *et al* (189) have shown that β-catenin expression is associated with chemoresistance in TNBC, as β-catenin knockdown can restore the sensitivity of TNBC cells to doxorubicin- or cisplatin-mediated cell death. Shetti *et al* (190) reported that the combination of low-dose paclitaxel and XAV939 (a Wnt signaling inhibitor) can inhibit EMT and angiogenesis by inducing apoptosis and suppressing Wnt signaling, demonstrating its therapeutic potential for TNBC. Upregulation of CSC-related Wnt signaling and activation of β-catenin signaling in PD-L1-high TNBC suggest that selective Wnt/β-catenin inhibitors may decrease resistance and re-sensitize TNBC to anti-PD-L1/anti-CTLA-4 monoclonal antibody immunotherapy (191-195).

Developing therapeutic strategies targeting both the canonical and non-canonical Wnt signaling pathways is key for advancing precision medicine and genome-based disease therapy. Wnt pathway inhibitors, including porcupine (PORCN) and LRP5/6 inhibitors, frizzled receptor antagonists, tankyrase inhibitors and natural compounds may be used to target the Wnt signaling pathway in the BC TME (Fig. 5). These inhibitors not only modulate the complex signaling network within the TME but also suggest that precise intervention in the Wnt pathway may provide new avenues for BC treatment.

PORCN inhibitors. PORCN, a member of the membrane-bound O-acyltransferase family, catalyzes the palmitoylation of Wnt ligands, a key step that allows Wnt ligands to be secreted, and effectively activates the Wnt signaling pathway, thereby regulating fundamental physiological functions, such as cell differentiation, proliferation, migration and apoptosis (196-201). To intervene in the palmitoylation of Wnt proteins within the endoplasmic reticulum, PORCN inhibitors effectively prevent the secretion of Wnt proteins and curb the abnormal accumulation of β-catenin to restore normal cell proliferation and signal transduction (202,203). In a preclinical study of BC mice, the PORCN inhibitor GNF-6231 showed strong antitumor activity, stimulating a notable tumor response (204). Similarly, another PORCN inhibitor, LGK974, not only blocks the secretion of Wnt proteins, but also effectively inhibits the activation of Wnt signaling (205). In a preclinical study of epithelial ovarian cancer, LGK974 in combination with paclitaxel demonstrates synergistic antitumor effects (206). In BC models induced by Wnt signaling, such as the MMTV model, LGK974 also performs well at doses tolerable to animals, achieving tumor regression while decreasing the phosphorylation levels of LRP6 and the expression of Axin2 (207,208). LGK974 has entered phase I clinical trials, and its potential as a monotherapy in combination with PDR001 for the treatment of Wnt signaling-driven cancer, including TNBC, is being evaluated (207,209). The aforementioned trials aim to assess the clinical efficacy and safety of LGK974 and to propose innovative strategies for Wnt signal inhibition in BC treatment (30).

LRP5/6 inhibitors. LRP5/6, a key co-receptor in the Wnt signaling pathway, plays a key role in the β-catenin-mediated canonical signal transduction process. Alkalescel, initially recognized as an antimicrobial potassium ionophore, inhibits phosphorylation of LRP5/6 and promotes its degradation, thereby inhibiting BC cell proliferation and inducing apoptosis (210). Salinomycin can downregulate LRP5/6 expression, further decreasing the transmission of Wnt signaling (211,212). By contrast, niclosamide acts on LRP6 by blocking its phosphorylation and downregulating its protein

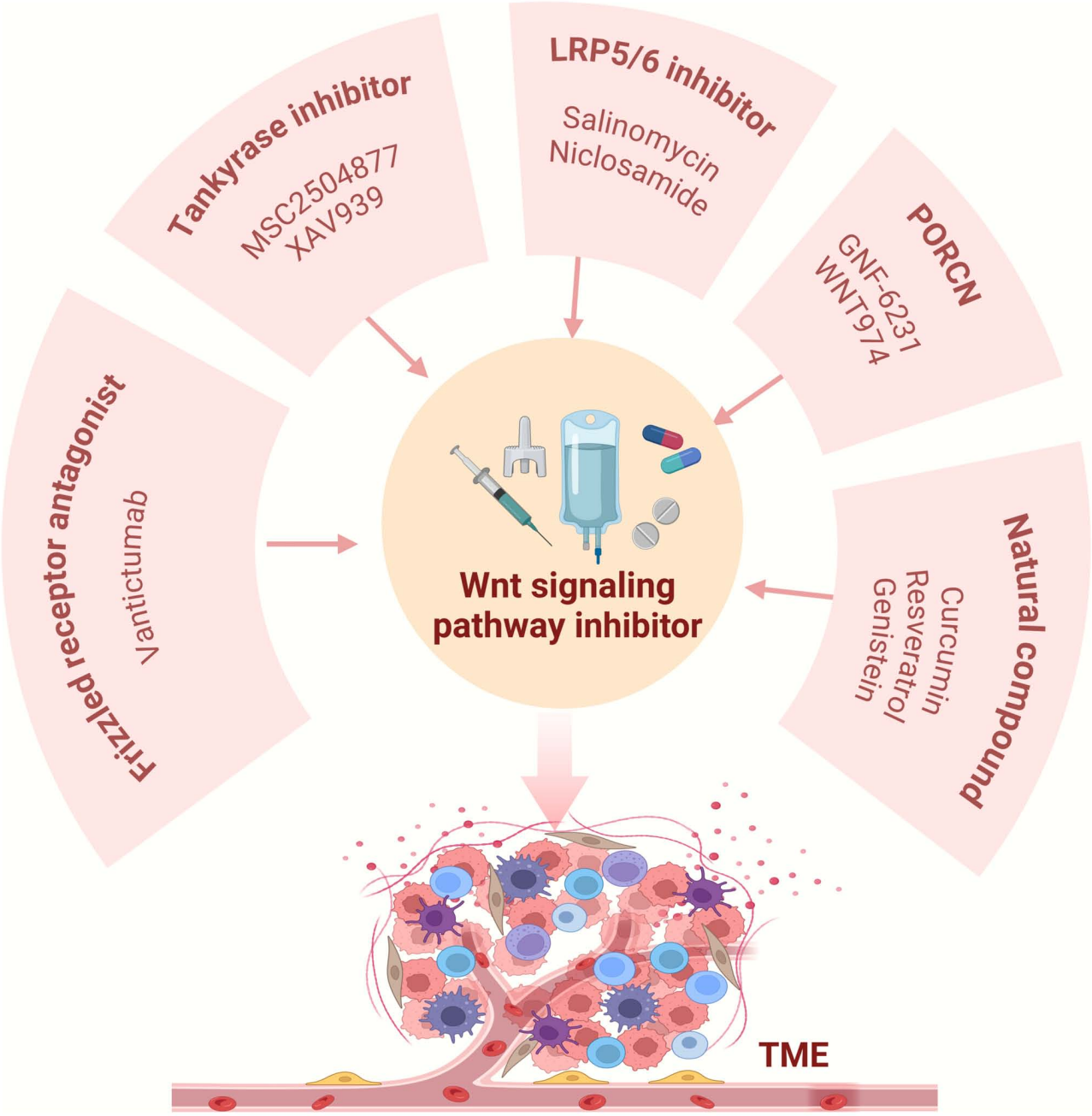

Figure 5. Drugs targeting the Wnt signaling pathway in breast cancer. Therapeutic strategies for inhibiting the Wnt pathway include PORCN and LRP5/6 inhibitors, frizzled receptor antagonists, tankyrase inhibitors and natural compounds. LRP, lipoprotein receptor-related protein; PORCN, porcupine; TME, tumor microenvironment.

synthesis. In BC cell models, niclosamide inhibits cellular proliferation and promotes apoptosis without affecting DVL2 expression (213,214). Research on BC cells has confirmed that niclosamide could inhibit tumor sphere formation in non-obese diabetes/severe combined immunodeficiency mice, promote apoptosis and effectively curb tumor growth, providing support for its application in CSC-directed therapy (215). Furthermore, using a mouse BC model, Ye *et al* (216) reported that niclosamide decreases tumor cell proliferation, migration and invasion, while promoting apoptosis and decreasing tumor weight. These findings demonstrate the mechanisms of action of LRP5/6 inhibitors and provide insights for BC treatment strategies.

Frizzled receptor antagonists. Vantictumab is a fully human IgG2 monoclonal antibody that selectively targets frizzled receptors and effectively disrupts the canonical Wnt signaling pathway (217). Preclinical experiments involving human cancer cell cultures and patient-derived BC xenograft models have shown that vantictumab not only impedes tumor progression but also exhibits enhanced antitumor efficacy when combined with paclitaxel compared to monotherapy (217,218). Sequential treatment with vantictumab and paclitaxel induces mitotic cell death, decreases tumor proliferation and decreases CSC numbers. Vantictumab decreases the number of CSCs and downregulates the expression of EMT-associated genes (219).

Table I. Natural compounds affecting the Wnt signaling pathway in the breast cancer tumor microenvironment.

Compound	Origin	Mechanism of action	(Refs.)
Monotheca buxifolia leaf methanol	*M. buxifolia*	Gene regulation targeting Wnt/β-catenin signaling	(224)
Ursolic acid	Fruit	Upregulation of Wnt antagonist SFRP4 mediated cancer stem cells through Wnt	(254)
Echinacoside	Cistanche and echinacea	Inhibition of Wnt/β-catenin signaling	(255)
Jatrophone	Coral plant		(256)
Oudemansiella raphanipes	Black termite mushroom	Inhibition of macrophage polarization and Wnt/β-catenin signaling	(257)
Prodigiosin	Polybacteria	Inhibition of Wnt/β-catenin signaling and decrease of cyclin D1 expression	(258)
γ-tocotrienol	Vitamin E	Inhibition of proliferation, EMT and Wnt/β-catenin signaling pathways	(259)
Rottlerin	Kamala tree	Inhibition of Wnt/β-catenin and mTORC1 signaling	(260)
Diallyl trisulfide	Garlic	Inhibition of Wnt/β-catenin pathway activation	(261)
Garcinol	Guttiferae	Reverses dysregulation of EMT phenotype and Wnt signaling pathway	(262)
Limonin	Rubiaceae and neem	Binding to Wnt3a inactivates the Wnt/β-catenin pathway	(263)
Epigallocatechin gallate	Green tea	Induction of HBP1 transcription suppressor to block Wnt signaling	(264)
Schisandrin A	*Schisandra chinensis*	Overactivation of the Wnt signaling	(265)
Daurisoline	*Menispermum dauricum*	Inhibition of Akt/mTOR and Wnt/β-catenin signaling pathways	(266)
Genistein	Soybean	Downregulation of β-catenin and inhibition of Wnt1	(267)
Resveratrol	Grape skin and berries	Decreased β-catenin and cyclin D1, inhibited Wnt/β-catenin pathway	(268)
Vogonoside	*Scutellaria baicalensis Georgi*	Inhibition of activation of Wnt/β-catenin pathway	(269)
Matrine	*Mallotus philipinensis*	Inhibition of Wnt/β-catenin signaling	(270)
Shikonin	*Lithospermum erythrorhizon*	Increased levels of GSK-3β and decreased levels of β-catenin	(271)
Tannins	*Syzygium guineense*	Inhibition of Wnt3a and decreased β-catenin levels	(272)
Saikosaponin D	*Radix bupleuri*	Inhibition of β-catenin signaling	(273)
Inotodiol	*Inonotus obliquus*	Downregulated expression of β-catenin and its downstream targets	(274)
Curcumin	Curcuma longa	Inhibition of Wnt/β-catenin activity	(275)
Diosgenin	Steroidal saponin	Promotes dysregulation of the Wnt/β-catenin pathway	(116)
Lycorine	Short-tube lycoris	Regulates EMT and β-catenin signaling	(276)
Astragalus polysaccharide	*Astragalus membranaceus*	Inhibition of Wnt/β-catenin signaling pathway	(277)

EMT, epithelial-mesenchymal transition; HBP1, high mobility group box protein 1; SFRP4, secreted frizzled-related protein 4; GSK, glycogen synthase kinase.

Tankyrase inhibitors. Tankyrase regulates Axin stability and directs its degradation through PARsylation (220). In a BC cell culture, XAV939 or small interfering RNA-mediated tankyrase knockdown significantly increases the expression of Axin1 and Axin2 proteins, thereby inhibiting Wnt-induced transcriptional activity (221). Tankyrase inhibitor MSC2504877 exerts G1 phase cell cycle arrest effects in tumor cells, promotes cellular senescence and enhances the efficacy of clinically used CDK4/6 inhibitors, facilitating development of BC treatment (222).

Natural compounds. Natural products are used for the development of anticancer drugs. The use of these naturally derived compounds and their derivatives to modulate the TME and

Table II. Clinical trials related to Wnt signaling pathways.

Drug	Target	Indication	Phase	Completion date	Status	(Refs.)
OMP-18R5	FZD1/2/5/7/8	Locally advanced or metastatic HER2-negative breast cancer	1b	Apr, 2017	Completed	(219)
OMP-18R5	FZD1/2/5/7/8	Locally recurrent or metastatic breast cancer	1	Dec, 2017	Completed	(248)
Foxy-5	Wnt5a	Metastatic breast and colorectal/prostate cancer	1	Nov, 2015	Completed	(249)
Foxy-5	Wnt5a	Metastatic breast and colorectal/prostate cancer	1b	Oct, 2017	Completed	(249)
Sulindac	DVL	Breast cancer	1b	Jan, 2010	Completed	(278)
ROR1R-CAR-T	ROR1	ROR1-positive chronic lymphocytic leukemia, mantle cell lymphoma, acute lymphoblastic leukemia, stage IV non-small cell lung and triple-negative breast cancer	1	Sep, 2021	Terminated	(279)
VLS-101	ROR1	Breast cancer	2	Jun, 2023	Terminated	(280)
NBE-002	ROR1	Advanced solid tumors, advanced cancer, triple-negative breast cancer	1/2	Aug, 2023	Terminated	(281)
UC-961	ROR1	Metastatic or locally advanced, unresectable breast cancer	1b	Feb, 2024	Completed	(282)
CAB-ROR2-ADC	Antibody-drug conjugate against ROR2	Triple-negative breast, head and neck and non-small cell lung cancer/melanoma	1/2	Dec, 2024	Completed	(283)
BI-905677	LRP5/6	Advanced solid tumors	1	Jul, 2022	Completed	(284)
OMP-131R10	RSPO	Advanced solid tumors and metastatic colorectal cancer	1a/b	Mar, 2018	Completed	(285)
ETC-159	PORCN	Solid tumors	1a/b	Oct, 2024	Active, not recruiting	(286)
DKN-01	DKK1	Advanced solid tumors, recurrent non-small cell lung cancer	1	Dec, 2013	Completed	(287)
BC2059	β-catenin	Solid tumors	1/2	Jun, 2028	Recruiting	(288)
PRI-724	β-catenin/CBP	Advanced solid tumors	1a/b	Jun, 2015	Terminated	(289)
LGK974	PORCN	Solid malignancies	1	Jun, 2024	Completed	(290)
E7449	TNK1/2	Advanced solid tumors, B cell malignancy	1/2	Jul, 2015	Completed	(291)
SM08502	CLK	Advanced solid tumors	1b	Oct, 2022	Terminated	(292)
RXC004	PORCN	Solid tumors	1	Sep, 2023	Completed	(293)
Chloroquine	v-ATPase	Solid tumors	1	Dec, 2018	Completed	(294)
CGX1321	PORCN	Advanced solid tumors	1	Mar, 2023	Unknown status	(250)
9-ING-41	GSK-3	Advanced tumors	2	Jan, 2026	Active, not recruiting	(295)

ROR1, receptor tyrosine kinase-like orphan receptor 1; PORCN, porcupine homolog; FZD, frizzled; DVL, disheveled; LRP5/6, low-density lipoprotein receptor-related protein 5/6; RSPO, r-spondin; DKK1, dickkopf-related protein 1; CBP, cyclic AMP response element-binding protein; TNK1/2, tyrosine kinase non-receptor 1/2; CLK, CDC-like kinase; v-ATPase, vacuolar-type H^+-ATPase; GSK-3, glycogen synthase kinase 3.

target the Wnt signaling pathway is becoming a highly promising direction in BC treatment (223-225). Phytochemicals regulate the Wnt signaling cascade, thereby providing options for future drug development (Table I).

7. Conclusion

BC, which poses a threat to lives and safety, has long been a core focus of medical research and clinical practice (226,227). The biological research system of BC is intricate, and the multidimensional network constructed between the Wnt signaling pathway and TME forms a cornerstone in this field of study (228-230). The components of the TME are associated with the Wnt signaling pathway, creating dynamic regulatory network. Immune cells releasing cytokines to regulate Wnt signaling, stromal components influencing signal transmission through chemical induction and secreted molecules directly interacting with key proteins in the pathway affect the proliferation, migration and invasion of tumor cells, and serve a role in promoting immune evasion, metabolic reprogramming and enhancing therapeutic resistance (231,232).

The hallmark features of the TME, such as hypoxia, acidity and mechanical stress, are associated with the Wnt signaling pathway, promoting the continuous progression of tumors (233,234). The Wnt signaling pathway interacts with key signaling networks, such as TGF-β, PI3K/Akt, FGF and Hedgehog, forming a highly interconnected regulatory pattern. Therefore, single-target treatment strategies for the Wnt signaling pathway may be insufficient to inhibit development of tumors. Therefore, developing combination treatment plans that act on multiple key nodes in these signaling networks is key for more effective treatment.

Given the role of the Wnt signaling pathway in the heterogeneous microenvironment of BC and its association with treatment resistance, it has become a key target for identifying novel biomarkers (14,235). By exploring the effector molecules of the Wnt signaling pathway and the association between Wnt signaling activity and patient prognosis, more precise predictive biomarkers can be developed (236,237). For example, cyclin D1 is upregulated following activation of the Wnt pathway and may promote the proliferation of BC cells (238). Ras GTPase-activating protein-binding protein 1 (G3BP1) induces β-catenin by inactivating GSK-3β, thereby increasing the proliferation of BC cells. Blocking the interaction between G3BP1 and GSK-3β inhibits cell proliferation (239). Platelet-activating factor, a co-factor of β-catenin, can induce Wnt signaling, promote the proliferation of BC cells and increase the expression levels of CSC markers (240,241). The downregulation of autophagy-related protein 4A leads to decreased expression of β-catenin, cyclin D1 and MYC proto-oncogene protein c-Myc, which impacts the autophagy process and enhances the chemosensitivity of tamoxifen in BC. Deficiency of fibrous sheath interacting protein 1 promotes autophagy, resulting in decreased Wnt/β-catenin activity and influencing drug sensitivity in TNBC (242). Kallistatin, a tissue kallikrein-binding protein and a unique serine proteinase inhibitor, inhibits the proliferation, migration, invasion, and tumor progression of BC cells by blocking the Wnt/β-catenin signaling pathway and inducing autophagy (243). Additionally, the genetic background of patients, such as the mutation status of BRCA1/2, may influence Wnt signaling activity, thereby providing a basis for the development of personalized treatment strategies.

In studies exploring the relationship between the Wnt signaling pathway and tumor cell death, it has been confirmed that the Wnt signaling pathway is not only closely related to the apoptosis and autophagy processes of breast cancer cells, but also associated with disulfidptosis, a specific type of cell death caused by disulfide accumulation (244,245). Wnt signaling activation not only promotes tumor cell self-renewal but also modulates serine peptidase inhibitor, clade B, member 6B (SERPINB6B) to decrease immune cell death and interfere with T cell-mediated tumor lysis (246). Specifically, SERPINB6B suppresses pyroptosis and immune recognition, thereby inhibiting apoptosis of immunogenic cells at metastatic sites and facilitating tumor dissemination (246). However, knowledge gaps persist in the context of the BC TME, particularly regarding the interaction between Wnt signaling and other tumor cell death modalities such as disulfidptosis, ferroptosis, autophagy and pyroptosis. Future studies should integrate multidisciplinary approaches, including genomics, proteomics, bioinformatics, high-throughput screening technology and precision medicine strategies, to systematically investigate the crosstalk between Wnt signaling and tumor cell death mechanisms and identify novel therapeutic targets and clinically actionable biomarkers.

Small-molecule inhibitors and natural compounds regulate Wnt pathway activity, effectively inhibiting the proliferation and migration of tumor cells, while accelerating apoptosis (247). Existing research indicates that these inhibitors and compounds may have clinical translation and application potential in BC (49). However, despite scientific advancements, the pace of clinical translation is slow, with most Wnt pathway-targeting drugs in phase I clinical trials, constrained by thorough safety validation and preliminary efficacy assessment, and only a few advancing to phase III trials (Table II) (248-250). The clinical safety and efficacy of Wnt-targeting small molecules and natural compounds must be validated to confirm their therapeutic potential where toxicity poses a barrier. For example, salinomycin carries the risk of neurotoxicity, potentially inducing peripheral neuropathy, whereas niclosamide is associated with dose-limiting toxicity, posing a threat to the gastrointestinal system (251,252). Future research should focus on enhancing the clinical safety and efficacy of these compounds, which may be achieved through the optimization of chemical structures or development of innovative drug delivery technology to enhance bioavailability and reduce adverse reactions (253). This may provide more effective and safer treatment options for patients with BC and improve prognosis and overall quality of life.

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Availability of data and materials

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Authors' contributions

CS and RL conceived and designed the study. MS and HZ wrote and edited the manuscript, constructed the figures and performed the literature review. YYu, YYa and HL revised the manuscript. FF and QW constructed figures. All the authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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