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Research Article

A Comprehensive Approach Towards Wnt/β-Catenin Signalling Pathway in Breast Cancer and Drug Resistance

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I N F O

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A B S T R A C T

Breast cancer is recognized as a commonly occurring cancer in women wherein the cancerous growth occurs in the breasts. The current treatment strategies face a significant setback due to the development of resistance against the subjected drug, i.e., after a few treatment cycles, the drug efflux increases as the body becomes resistant to the therapeutics, there by taking a toll on the effectiveness of the treatment. Although various pathways are involved in tumorigenesis, studies revolve across a signalling pathway referred to as the Wnt signalling pathway. The Wnt pathway is responsible for regulating cell proliferation and apoptosis. Activation of the Wnt pathway results in cancer-like conditions. A detailed understanding of the Wnt pathway would help researchers break the concept of drug resistance and develop effective treatment strategies. In this review, the authors will talk about the Wnt Signalling Pathway, its role in breast cancer, the resistance against the therapeutics due to dysregulated Wnt pathway, and the current advancements.

Keywords: Wnt Pathway, β-Catenin, Breast Cancer, Drug Resistance

Introduction

Cancer is a condition where the cells divide abnormally, leading to uncontrolled cell growth.[1] WHO has reported around 10 million deaths across the globe in 2020, in which breast cancer accounts for 2.26 million cases and 6,85,000 deaths.[2] Dysregulation of various signalling pathways influences the development and progression of cancer. Apart from the Hippo Pathway, researchers are diverting their attention toward Wnt Pathway. Wnt Pathway is a signaling pathway responsible for cell proliferation, differentiation, and apoptosis and maintains tissue homeostasis.[3] Studies suggest that the dysregulation of the pathway results in tumorigenesis.[4,5]

The activation of the Wnt Pathway results in elevated levels of β-catenin, a protein responsible for controlling gene expression and the formation of adherens junctions for cell adhesion. The activated pathway results in the interaction between β-catenin and the transcriptional co-activators, leading to increased expression of the Wnt genes.

As the Wnt pathway is responsible for cell proliferation, the increased expression of the Wnt genes is linked to tumorigenesis. Due to the presence of the Wnt pathway in various cancers, it is now being subjected to drug development. Various Wnt pathway inhibitors are being developed to reduce the signalling cascade's activity. Some inhibitors have even proved to have anti-cancer properties,

thereby demonstrating a positive response in tackling the development of resistance against the anti-cancer drugs.[6] However, till date, no inhibitors for breast cancer are approved.[7]

Overview of Wnt/ β-catenin Signalling Pathway

Wnts are recognized as secretory proteins coded by the Wnt genes.[8] These proteins play a role in the folding of peptides to obtain a functional protein.[9] Wnt proteins are further subjected to post-translation modifications, including glycosylation and the addition of the palmitoleate moiety. The palmitoleate moiety is responsible for the binding between the Wnt ligand and its receptor Frizzled, along with the interaction between the cargo receptor and Wnts, which results in the transportation of Wnts from ER to the plasma membrane.[10,11] Wnt proteins interact with the cell surface receptors, responsible for activating the downstream signalling cascade. The 10 Frizzleds (Fzds), along with its coreceptors LRP5/6 are recognized as the primary cell surface receptor. Some other coreceptors are GPR124, Reck, and TMEM59.[11,12]

The Wnt/β-catenin signal pathway or the canonical Wnt pathway revolves around a protein known as β-catenin, which is responsible for cell adhesion and gene transcription regulation. It is a part of the protein complex, which is responsible for the formation of the adherens junction. The increased levels of β-catenin are regulated by a degradation complex that includes glycogen synthase kinase 3 alpha and beta (GSK3α/β), casein kinase 1 alpha (CK1α), AXIN, and APC.[11,14] The absence of Wnt ligands results in the activation of CK1α, which in turn phosphorylates β-catenin at Ser45. GSK3α/β performs another round of phosphorylation at Thr41, Ser37, and Ser33.[15,16]β-transducin identifies the phosphorylated sites of β-catenin and promotes ubiquitination, which ultimately results in proteasomal degradation.[17]

Upon the presence, the Wnt ligands interact with the LRP5/6 coreceptors and FZD receptors at the cell surface, which triggers the β-catenin signal pathway. This interaction promotes the uptake of Dishevelled (DVL). A cytoplasmic protein interacts with the cytoplasmic domains of FZD and adheres to the cell membrane.[18] DVL results in the aggregation of the degradation complex. The phosphorylation of GSK3α/β results in the upregulation of β-catenin. β-catenin travels to the nucleus and interacts with the transcriptional co-activators, i.e., T cell-specific factor (TCF)/ lymphoid enhancer-binding factor (LEF) and other co-activators thereby activating the Wnt genes like c-Myc and cyclin D1, which results in the upregulation of the TCF/LEF gene.[19]

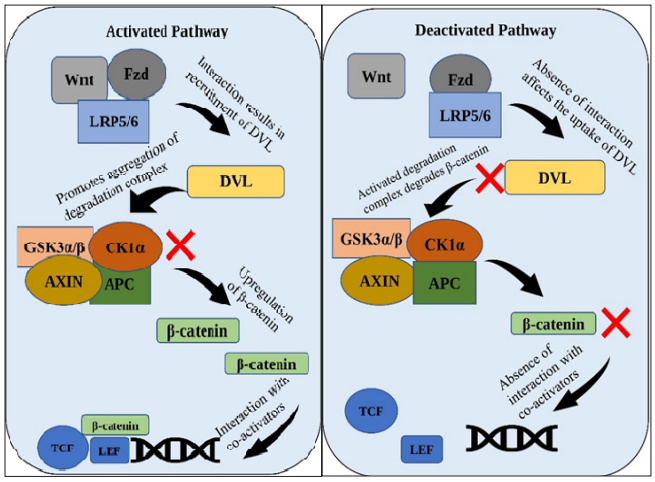

Figure 1.Representation of Wnt/ β-catenin Signalling Pathway or Canonical Pathway

Wnt/ β-catenin Signalling Pathway and Breast Cancer Progression

The down-regulation of the negative regulators of the Wnt signalling results in elevated levels of β-catenin, a crucial characteristic of cancer development and progression. Studies have indicated elevated levels of β-catenin in approximately 50% of breast cancer cases.[20,21] DVL, a protein that prevents the degradation of β-catenin, was found to be elevated in breast cancer.[22] The levels of the negative regulators of the Wnt signalling pathway were found to be downregulated. Frizzled-related protein 1 (FRP1) was detected to be downregulated in 78% of the cases[23], whereas Dickkopf 1 (DKK1), which is another Wnt inhibitor, was found to be downregulated.[24] The mutation, hypermethylation, or loss of heterozygosity resulted in the down-regulation of APC, a tumor suppressor gene, by 36-50% in breast cancer.[25]

Research indicates the role of the activated β-catenin in HER-2 breast cancer and its influence on promoting triple-negative breast cancer.[26] In addition, various studies demonstrate the link between the activation of the Wnt inhibitors and the reduction in tumor growth.[27,29] Therefore, understanding the linkage between Wnt signalling and breast cancer progression can help the researchers improve the current treatment strategies.

Dysregulated Wnt/β-catenin Pathway and Drug Resistance

Drug resistance is a condition encountered wherein the patient starts to develop resistance against the administered drug. Drug resistance is commonly seen in cancer when the patient is subjected to cycles of chemotherapy. ATP-binding cassette (ABC) transporters are responsible for the efflux of drugs from cancer cells. P-glycoprotein and

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breast cancer resistance protein are highly recognized ABC transporters that are responsible for the efflux of anti-cancer therapeutics. PYGO2 falls under the class of co-activators, activate the Wnt pathway, and is responsible for imparting resistance against anti-cancer drugs in breast cancer by elevating the expression of MRD1.[30] Furthermore, the increased expression of ABCG2 is observed upon the elevated expression of Caveolin 1, which results in the development of chemo resistance in breast cancer.[31]

Tamoxifen falls under the category of chemotherapeutics and is used for the treatment of breast cancer. Cytochrome P450 2D6 (CYP2D6) is responsible for converting tamoxifen to endoxifen. The inactivation of CYP2D6 and the reduced Erα expression results in endocrine resistance.[32] The canonical Wnt pathway is involved in imparting resistance against tamoxifen as Wnt3a promotes the resistance of EsR+ breast cancer cells to the subjected treatment.[33] Another factor involves Sox2, which acts as an activator of the Wnt Pathway and is responsible for developing EsR+ breast cancer cells resistant to tamoxifen.[34]

In order to improve immunotherapy, it is essential to decipher the immune checkpoint inhibitors to understand the effectiveness of immunotherapy. Researchers are currently focussing on PD-1/PD-L1 and CTLA-4, which are active immune checkpoint inhibitors.[35] Wnt signalling directly controls the expression of PD-1/PD-L1 and CTLA-4[36, 37] and down-regulates the tumor immune cycle.[38] β-catenin also play a vital role in the upregulation and stabilization of PD-L1 inhibitor, leading to immune invasion.[39] A detailed understanding of the Wnt pathway would help the researchers understand its influence on the subjected drug, enhancing the effectiveness of chemo and immunotherapy.

Advancements in Targeting the Wnt/β-Catenin Pathway

The Wnt pathway is gaining attention due to its significant role in cancer initiation and progression. Various inhibitors are developed to target different factors involved in the Wnt pathway, such as Porcupine, DVLs, Fzds, etc.[7]

Porcupine inhibitors are recognized for having a role in anti-cancer activity. LGK974 is a type of porcupine inhibitor subjected to phase I clinical trials in patients suffering from triple negative breast cancer.[40] OMP-54F28 is an Fc fusion protein that competes with Fzd8 to interact with the binding sites of Wnt. This competition alters the Wnt–Fzd interactions, which blocks the Wnt signalling cascade.[41]

Inhibitors of Fzds target the Wnt pathway as they prevent the interactions between Wnt and Fzd receptors. Niclosamide is an FDA-approved inhibitor that has entered phase I/II of clinical trials and is expected to be the prominent inhibitor of Fzd.[42] In addition, antibodies are also used to target Fzd, such as OMP-18R5. Out of 10, OMP-18R5 binds to 5 of the Fzds and is a potential drug candidate for breast cancer.[43]

Dvl is another target for regulating the Wnt signalling pathway, although only a few inhibitors are developed for Dvl. Sulindac is an FDA-approved, anti-inflammatory, anti-cancer drug and is a potential candidate for the Dvl inhibitor. The inhibition of Dvl results in the suppression of tumorous growth, thus having anti-cancer effects.[44]

Regulating the levels of β-catenin is another potential target for maintaining the activity of the Wnt signalling pathway. Only a handful of inhibitors are identified till date, two of them being MSAB and NRX-252262.[45,46] These inhibitors can directly regulate β-catenin levels, thereby regulating the activity of the Wnt signalling pathway. Another strategy to regulate the levels of β-catenin is improving the destruction complex. Proteins such as CK1α, GSK-3β, and Axin are potential candidates for enhancing the destruction complex.[47,49]

Table 1.Target Inhibitors for Wnt/ β-Catenin Pathway

Targeted Inhibitor	Development Stage	Targeted Against	References
LGK974	Phase-I	Fzd Receptor	40
Niclosamide	Antihelminth	Fzd Receptor	42
Sulindac	Anti-inflammatory, Anti-cancer	Dvl	44
MSAB	Preclinical	β-catenin	45
NRX-252262	Preclinical	β-catenin	46
CK1α	Antihelminth	β-catenin	47

Conclusion and Future Perspective

Recent years have shown advancements in deciphering the Wnt/ β-catenin pathway indicating its role in breast cancer initiation and metastasis. Understanding the pathway has helped researchers target the Wnt pathway inhibitors as a treatment strategy against the activated pathway in cancer progression. In addition, the inhibitors prove to be promising in developing effective treatment strategies against tumorigenesis. Currently, these molecules are under clinical trials as a treatment strategy for breast cancer.

Although studies indicate the role of the Wnt/ β-catenin pathway in the development and progression of cancer, no effective target inhibitor is approved for the treatment of breast cancer. Furthermore, the progress related to the Wnt pathway remains in its early stages. Therefore, there is a need to understand the signalling pathway regulation in

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cancer progression to break the development of resistance against the anti-cancer drugs and develop novel therapies for cancer treatment.

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