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REVIEW OPEN ACCESS

The Role of Beta-Catenin and the Wnt Signalling Pathway in Breast Cancer Initiation, Progression and Metastasis: A Literature Review

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Abstract:
Introduction: Breast cancer (BC) is a complex disease with significant global health implications and is characterized by heterogeneity in molecular profiles and biomarker expression. The Wnt/β-catenin pathway plays a pivotal role in BC progression, with aberrant Wnt signaling contributing to increased tumorigenicity, metastasis, and therapeutic resistance, particularly in aggressive subtypes, such as triple-negative breast cancer (TNBC) and HER2-negative BC.
Methods: This review synthesizes recent literature on β-catenin and Wnt signaling dysregulation in BC, focusing on the triple-negative and HER2-negative subtypes. Key studies emphasizing molecular mechanisms and therapeutic implications were selected from databases such as PubMed and Google Scholar.
Results: Evidence indicates widespread Wnt/β-catenin pathway dysregulation across multiple breast cancer subtypes. This dysregulation often leads to enhanced proliferation, metastatic potential, and resistance to therapy. In triple-negative disease, nuclear β-catenin accumulation correlates strongly with aggressiveness. Additionally, crosstalk with pathways like PI3K/AKT and HER2 further augments oncogenic behavior.
Discussion: In BC, dysregulation of the Wnt/β-catenin pathway can lead to abnormal β-catenin accumulation and activation of oncogenic genes, contributing to tumor growth, metastasis, and resistance to therapy. The Wnt pathway, which is crucial for normal cellular processes, is frequently dysregulated in BC and contributes to increased tumorigenicity, metastasis, and therapeutic resistance. This review presents findings that demonstrate the intricate interactions between Wnt/ β-catenin signaling and other critical pathways, including PI3K/AKT and HER2, and elucidates how these interactions contribute to the progression of breast cancer. It addresses the impact of genetic mutations on the Wnt/β-catenin signaling pathway in BC, highlighting how these alterations contribute to tumor progression, metastasis, and therapeutic resistance, along with examining the role of its homolog, γ-catenin.
Conclusion: This review includes insights from recent literature on the molecular mechanisms underlying Wnt dysregulation and suggests future research directions to improve therapeutic strategies for BC. By understanding the intricate role of Wnt signaling in BC, we aimed to identify novel targets and develop more effective treatments for this challenging disease.

Keywords: breast cancer; beta-catenin; Wnt pathway; dysregulation; metastasis; tumorigenicity; gamma-catenin

Introduction

Breast cancer (BC) remains a significant health challenge and the second leading cause of cancer-related deaths among women worldwide. In 2022, approximately 2.3 million women were diagnosed with BC, resulting in approximately 670,000 deaths globally [1]. This disease is marked by its heterogeneity, characterized by a range of molecular profiles and biomarker expression that can predict prognosis and guide treatment strategies. Molecular marker profiling is a critical component in categorizing BC into its intrinsic subtypes and is essential for diagnosis. An overview of these subtypes, including receptor status & clinical characteristics, is summarized in Table 1 [2-6].

The genetic landscape of BC is primarily shaped by somatic mutations, with approximately 85-90% of cases resulting from spontaneous mutations in genes such as *PIK3CA* [7]. About 30-45% of these cases harbor *PIK3CA* mutations [8, 9]. In contrast, familial BC, accounting for 5-10% of cases, is often associated with BRCA1 and BRCA2 mutations, inherited in an autosomal dominant manner [10]. Mutations in genes such as *TP53*, *BRCA1*, *BRCA2*, and *PIK3CA* disrupt normal cell cycle regulation and DNA repair mechanisms, thereby contributing to carcinogenesis [11, 12]. Although these genetic alterations occur across multiple subtypes, key differences in receptor status and clinical characteristics are summarized in Table 1. These mutations span a wide range of BC subtypes but frequently impact common pathways, such as the Wnt signaling pathway. This pathway plays a crucial role in tissue morphogenesis during development and tissue homeostasis

in various organs [13]. The role it in BC is of particular interest because of its implications for tumor growth and metastasis. Mutations affecting the Wnt pathway, including (epi)genetic changes and alterations in Wnt/*CTNNB1* signaling, have been linked to the initiation, progression, and maintenance of different BC subtypes [13]. Upregulation of the Wnt-β-catenin pathway (WP) is one of the genetic salient features of triple-negative breast cancer (TNBC), and this signaling pathway is associated with metastasis in TNBC [14]. The collective frequency of alterations in WP genes among breast invasive carcinomas was 21% compared to 56% in the PAM50 Basal [14]. This suggests that targeting the Wnt pathway may hold promise as a therapeutic strategy for BC treatment and requires further investigation. It is rarely mutated in other types of cancer, apart from medulloblastoma and colorectal cancer, making its role in BC and β-catenin particularly interesting [15]. The three established Wnt pathways – Wnt/β-catenin, Wnt-planar cell polarity (PCP), and Wnt–Ca2+ – have common elements, but serve different functions in the progression of BC [16].

Table 1. Overview of Intrinsic BC Subtypes

Subtype	ER Status	PR Status	HER2 Status	Proliferation Rate/Mitotic Index	Prognosis	Percentage of Cases	Other Characteristics
Luminal A	Positive [2, 3]	Positive [2, 3]	Negative [2, 3]	Low [2, 3]	Better prognosis [2, 3]	Approximately 40% [2, 3]	Slow-growing; hormonal therapy responsive [2, 3]
Luminal B	Positive [2, 3]	Variable [2, 3]	Positive or Negative [2, 3]	High [2, 3]	Slightly worse prognosis than Luminal A [2, 3]	Approximately 20% [2, 3]	Faster growing; may respond to chemotherapy and hormonal therapy [2, 3]
HER-2 Positive	Negative or Weakly Positive [2, 3]	Negative or Weakly Positive [2, 4]	Positive [2, 4]	High [2, 4]	Variable prognosis [2, 4]	Approximately 15% [2, 4]	Aggressive; responds to HER2-targeted therapies [2, 4]
TNBC	Negative [2, 5]	Negative [2, 5]	Negative [2, 5]	High [2, 5]	Poor prognosis [2, 5]	Approximately 15% [2, 5]	Aggressive; limited targeted therapy options [2, 5]
Basal-like	Negative [6]	Negative [6]	Negative [6]	High [6]	Poor prognosis [6]	Overlaps with TNBC [6]	Express basal markers; aggressive behavior [6]

In the absence of Wnt signaling, β-catenin is phosphorylated and targeted for degradation [18]. When signalling is activated, this degradation is inhibited which allows β-catenin to accumulate in the cytoplasm and translocate to the nucleus, where it interacts with TCF/LEF transcription factors to activate target genes involved in cell proliferation and survival [19]. As illustrated in Figure 1, once Wnt ligands bind to Frizzled and LRP5/6 receptors, the β-catenin destruction complex is inhibited, facilitating nuclear translocation and the subsequent activation of oncogenic pathways. For the purposes of this review, we will focus on the canonical Wnt pathway, with an emphasis on β-catenin. Understanding the underlying genetic and signaling abnormalities in BC is crucial for the development of effective treatments. *CTNNB1* (catenin β-1, also known as β-catenin) has a dual role in cells. It is the key effector of Wnt/*CTNNB1* signaling, acting as a transcriptional co-activator of TCF/LEF target genes, and is crucial for cell adhesion as a component of cadherin-based adherens junctions [20]. There are two functional pools of *CTNNB1*, a transcriptionally active pool and an adhesive pool. The balance and interplay between these pools have long been studied and debated, particularly during epithelial–mesenchymal transition and in response to Wnt stimulation [20]. This dynamic behavior of *CTNNB1* adds complexity to its role in BC. Although there is some controversy surrounding the role of the Wnt signaling pathway in BC development, new research has emerged regarding this pathway as a target for therapeutic interventions and its self-mutating ability through the *CTNNB1* signaling pathway [20]. This review outlines important discoveries regarding the relationship between Wnt signaling and BC and explores

current obstacles, methods, and possibilities for improving BC therapeutic interventions by manipulating the Wnt signaling pathway and analyzing its impact on various cell lines. It also highlights metaplastic BC, a rare invasive subtype characterized by the differentiation of the neoplastic epithelium into squamous cells and/or mesenchymal-like elements [21]. The homolog of β-catenin, γ-catenin, will also be explored as a next step towards future therapeutic treatments and comparisons within the Wnt pathway, as well as more targeted therapeutic options for BC [22].

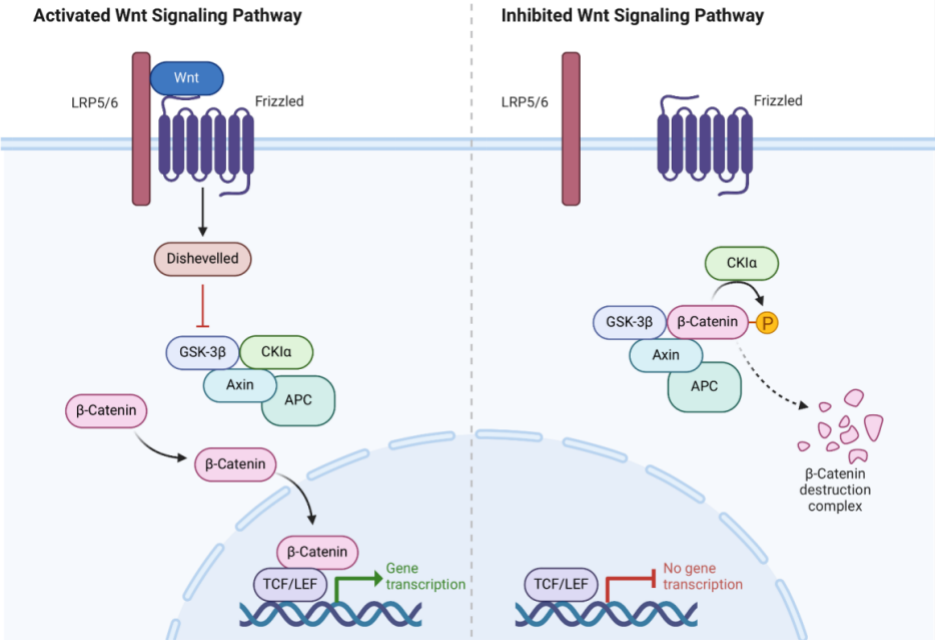

Figure 1. In the canonical Wnt pathway, Wnt ligands bind to Frizzled receptors and LRP5/6 co-receptors, inhibiting the β-catenin destruction complex, which includes proteins such as APC and Axin [17]. This figure was created on BioRender.

Methods

This review was conducted by surveying recent literature on the role of β-catenin and Wnt dysregulation in BC, with a particular focus on their involvement in TNBC and HER2 subtypes. Articles were sourced from databases such as PubMed and Google Scholar using the following keywords "beta-catenin," "gamma-catenin," "breast cancer," "Wnt signaling," "triple negative breast cancer," and "HER2-negative breast cancer." The selection criteria included studies published within the last 10 years, with an emphasis on those providing insights into the molecular mechanisms of β-catenin and hormonal signalling pathways in BC. Review articles, meta-analyses, and primary research papers were included to provide a comprehensive understanding of this topic.

Results

Aberrant β-Catenin Activity

Aberrant β-catenin activity within the Wnt/β-catenin pathway is a phenomenon observed across various subtypes of BC, significantly influencing tumorigenesis and metastatic characteristics [23]. For instance, studies have demonstrated that aberrant activation of the Wnt/β-catenin pathway occurs in a substantial proportion of BC cases, with reports indicating its presence in up to 60% of basal-like BC cases [42]. Also, in ER+BC, exemplified by the MCF-7 cell line, enhanced β-catenin signaling is associated with increased proliferation and survival signals [24]. This dysregulated pathway contributes to the stem cell phenotype in basal-like/TNBC cells, impacting tumor growth both *in vitro* and *in vivo* [24]. Whole genome sequencing (WGS) and transcriptomic analyses have revealed that the main role of Wnt signaling is in BC growth and metastasis [16]. Recent studies have emphasized its function in managing the immune microenvironment of BC, preserving stem cell properties, providing therapeutic resistance and impacting the tumor phenotype [16]. Wnt signaling has been implicated in breast cancer metastasis by promoting primary and metastatic tumor growth through various mechanisms, including the induction of epithelial-mesenchymal transition (EMT) [25]. Dysregulated β-catenin activity in BC cells, including ER+ BC, TNBC, and basal-like BC, leads to activation of downstream target genes associated with cell proliferation, invasion, and metastasis [28]. The interaction of β-catenin with transcription factors of the TCF/LEF-1 family results in the upregulation of oncogenic genes, such as c-Myc and cyclin D1, promoting tumorigenesis and tumor progression [29]. In TNBC, aberrant Wnt/β-catenin signaling contributes to the aggressive nature of this subtype, enhancing cell proliferation, invasion, and metastasis [30].

Triple-Negative Breast Cancer

β-Catenin dysregulation is especially prominent in TNBC, as seen in the MDA-MB-231 cell line, and plays a significant role in the aggressive and metastatic behavior of these tumors [14].This specific cell line has been extensively studied to understand the implications of aberrant Wnt signaling in TNBC. This nuclear accumulation of β-catenin leads to increased tumorigenesis by enhancing cell proliferation, migration, and chemoresistance in TNBC cells both in mouse models and *in vitro* [32]. Moreover, mutations in key tumorigenesis driver genes such as *TP53*, *PIK3CA*, and *PTEN* are frequently observed in TNBC [31], and these genetic alterations may interact with Wnt/β-catenin signaling pathways, potentially contributing to the dysregulation of β-catenin and the aggressive phenotype of TNBC.

Interaction of Wnt/β-Catenin with PI3K/AKT and HER2 Pathways

The PI3K/AKT pathway, which is essential for cell survival, growth, and metabolism, is frequently altered in BC, with aberrations occurring in approximately 70% of cases [35]. Hyperactivation of PI3K due to *PIK3CA* mutations can lead to increased β-catenin activity in estrogen receptor-positive (ER+) BC while suppressing it in ER-negative BC [35]. Studies have shown that *PIK3CA* mutant ER+ BC exhibits enhanced Wnt/β-catenin signaling, including up-regulation of Wnt target genes and other components such as transcriptional regulators, receptors, and ligands associated with the Wnt pathway [36]. This enhanced Wnt/β-catenin signaling in *PIK3CA* mutant ER+ BC suggests a shift towards promoting β-catenin activity, which can influence various cellular processes related to cell proliferation and survival [37]. In contrast, the HER2 pathway, commonly overexpressed in HER2-positive BC, influences β-catenin activity and contributes to tumor progression [38].

Mutations in Basal/Luminal Lineage

A study using in vitro BC cell lines, which included luminal A, luminal B, HER2+/ER−, and basal-like BC cells, analyzed the subcellular localization of β-catenin. The study found that in all subtypes, membrane-associated β-catenin was linked to poorer patient outcomes related to tumor growth [42]. The use of genetically engineered mouse models and lineage-tracing approaches has been instrumental in studying the behavior of mammary stem and progenitor cells. The Wnt/β-catenin pathway activation may be an early event in breast neoplasia and may be driven, at least in part, by HER2/neu expression, suggesting a potential link between Wnt regulation and different BC subtypes [44]. A study focused on signalling nodes of mammary gland development found that in mouse models, dysregulation of β-catenin signaling within a specific subset of luminal cells, which have alveolar progenitor marker profiles and functional characteristics, leads to the development of tumors of mixed lineage [45]. This finding is significant because it aligns with the understanding that basal-type hormone receptor-negative BC in humans is believed to originate from luminal progenitors [46].

Metaplastic BC and β-Catenin Mutations

Although there is still controversy surrounding the aberrant activity of β-catenin, there are subtypes for which there is greater confirmation of Wnt activation than others. One of these subtypes is metaplastic breast cancer (MpBC). MpBC is a rare and aggressive subtype characterized by diverse histological features [47]. Research on spindle lesions has demonstrated that aberrant β-catenin expression is often observed in metaplastic carcinomas, indicating that Wnt canonical pathway activation is present [47]. Studies have shown that aberrant β-catenin expression is often observed in MpBC, indicating activation of the Wnt/β-catenin pathway. However, mutations in *CTNNB1*, the gene encoding β-catenin, are not commonly found in MpBC [47]. This suggests that β-catenin dysregulation in MpBC may result from mechanisms other than direct mutations, such as alterations in upstream Wnt signaling components or downregulation of β-catenin degradation processes.

Significance of CTNNB1 Mutations

Mutations in *CTNNB1* are relatively rare in breast cancer [20]. Despite this, aberrant activation of the Wnt/β-catenin pathway is commonly observed across multiple subtypes, including TNBC and basal-like breast cancer [42, 47]. This indicates that mechanisms other than *CTNNB1* mutations contribute to Wnt pathway dysregulation in breast cancer. Such mechanisms may include overexpression of Wnt ligands, downregulation of Wnt antagonists, or mutations in other pathway components [28]. For example, one study observed that β-catenin/Wnt pathway activation is predominantly found in TNBC/basal-like BC, is associated with poor clinical outcomes, and is unlikely to be driven by *CTNNB1* mutations in BC [47]. This conclusion was further supported by the finding that none of the 28 selected BC cell lines exhibited *CTNNB1* mutations [47], indicating a lack of natural mutations in *CTNNB1*.

Role of γ-Catenin

In addition to β-catenin, γ-catenin (also known as plakoglobin) is another crucial member of the catenin family that is involved in cell adhesion and Wnt signaling pathways [48]. β-catenin and γ-catenin share structural and functional similarities, influencing cell-cell adhesion and gene expression regulation [48]. Altered expression of γ-catenin can affect β-catenin stability and function, indicating a complex interplay between these proteins in cancer biology [49]. Specifically, γ-catenin has been observed to undergo selective downregulation at metastatic sites, suggesting that it might play distinct roles in metastatic lesions compared with primary tumors [49].

Discussion

Aberrant β-Catenin Activity

The dysregulation of specific Wnt signaling pathways has significant implications for various BC subtypes as a result of altered activity of downstream regulators, such as β-catenin. Identifying similarities and differences between the Wnt pathway in its regular and aberrant functioning is crucial for developing targeted therapeutic interventions for the various subtypes of BC. The fact that the aberrant β-catenin activity is observed in a substantial proportion of BC tumors highlights its potential as a universal therapeutic target across multiple subtypes. The relationship between aberrant β-catenin activity and Wnt dysregulation showcases the critical role of Wnt signaling in driving the aggressive behavior and metastatic potential of TNBC and other breast cancer subtypes [27].

Triple-Negative Breast Cancer

The interplay between aberrant β-catenin activity and Wnt dysregulation in TNBC cells highlights the critical role of Wnt signaling in driving the aggressive behavior and metastatic potential of this subtype. However, it is important to note that while this dysregulation is prevalent in TNBC, the degree of its impact may vary among individual tumors and can be influenced by other molecular alterations and pathways involved in tumorigenesis. Thus, while the association is strong, it is not absolute for every TNBC case. Understanding the molecular alterations associated with Wnt signaling in TNBC is essential for developing targeted therapeutic strategies aimed at modulating Wnt signaling and inhibiting the oncogenic effects of dysregulated β-catenin in TNBC.

Interaction of Wnt/β-Catenin with PI3K/AKT and HER2 Pathways

It is important to recognize that Wnt/β-catenin signaling does not operate in isolation. In many BC subtypes, including TNBC, the interaction of the Wnt/β-catenin pathway with critical signaling pathways, such as the PI3K/AKT pathway, creates a tumor microenvironment conducive to aggressive tumor progression [33]. Understanding how the Wnt/β-catenin pathway interacts with other key signaling pathways in BC is essential for elucidating the complex molecular landscape of TNBC and developing targeted therapeutic approaches tailored to the specific molecular alterations present in this aggressive subtype [34]. Further research on the interactions of these pathways with the Wnt/β-catenin pathway is essential for unraveling the complex molecular landscape of BC.

Mutations in Basal/Luminal Lineage

Since majority of BC occurs in mammary epithelial cells, it is important to examine the basal and luminal subtypes to identify similar characteristics and to perform comparative analyses between mouse models, in vitro cell cultures, and human breast cancer samples. The finding that membrane-associated β-catenin is linked to poorer patient outcomes across all subtypes [42] is significant and should be further investigated on the basis of of Wnt and different subtypes in mammary tissues. However, it is also important to acknowledge the differences between murine models of BC and human breast neoplasms, including their immune environment, vascularization, and tumor microenvironment [43]. This raises the importance of understanding Wnt signaling heterogeneity in BC and the need for relevant preclinical research models to address this issue. The focus on the complexity of Wnt signaling activation in both normal and diseased states, along with the difficulties in pharmacologically modulating this pathway, underscores the need to map the functional outcomes of Wnt signaling disruptions in breast cancer cell populations. Further research is required in order to elucidate the specific molecular and cellular mechanisms through which deregulated β-catenin signaling in luminal progenitor cells contributes to the development of mixed-lineage tumors.

Significance of CTNNB1 Mutations

Since the literature has demonstrated that a significant portion of carcinomas (TNBC and basal-like phenotype) have been characterized by a loss of E-cadherin expression and epithelial-to-mesenchymal transition [48], canonical Wnt pathway activation can be attributed to factors other than *CTNNB1* activating mutations. These external factors must be explored further. Genetically engineered mouse models are crucial for elucidating the role of Wnt signaling, lineage-specific cells, and genetic mutations in mammary tumorigenesis, although they should be used with caution when investigating mutations in *CTNNB1* and other factors that influence tumor growth and Wnt dysregulation. Mutations in *CTNNB1* are not the only way to aberrantly activate the Wnt pathway so this should be explored further.

Role of γ-Catenin and Future Directions for Therapeutic Interventions

Understanding the differences and interactions between β-catenin and γ-catenin is crucial for a comprehensive view of Wnt signaling dysregulation in BC and could reveal additional therapeutic targets [50]. Targeting of the Wnt/β-catenin pathway offers promising therapeutic opportunities for BC. Strategies include the development of inhibitors that target β-catenin or its interactions with other proteins. Despite their potential benefits, challenges such as the development of selective inhibitors and overcoming resistance mechanisms remain.

Conclusions

The Wnt/β-catenin pathway plays a role in BC development and progression, which requires further investigation. Aberrant Wnt signaling is associated with increased tumorigenicity, metastasis, and therapeutic resistance, particularly in TNBC and HER2 subtypes.

Understanding the distinct patterns of Wnt pathway dysregulation across BC subtypes and cell lines is essential for developing targeted therapeutic interventions. Future research should focus on exploring the role of β-catenin and other Wnt pathway components in BC progression and therapy resistance, with the aim of improving treatment outcomes in BC patients. A focus on γ-catenin for targeted therapies is also worth exploring.

List of Abbreviations
BC: breast cancer
CTNNB1: catenin beta-1
EMT: epithelial-mesenchymal transition
ER: estrogen receptor
ER-: estrogen receptor negative
ER+: estrogen receptor positive
HER2: human epidermal growth factor 2
MpBC: metaplastic breast cancer
PCP: planar cell polarity
PR: progesterone receptor
TNBC: triple-negative breast cancer
WP: Wnt- β-catenin pathway

Conflicts of Interest
The author declares that they have no conflicts of interest.

Ethics Approval and/or Participant Consent
Ethics approval was not required as this study was a literature review that only assessed pre-existing studies and articles.

Authors' Contributions
AM: made contributions to the design of the study, collected and analysed data, drafted the manuscript, and gave final approval of the version to be published.

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