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REVIEW ARTICLE

Therapeutic Potential Targeting Cancer Stem Cells to Treat Breast Cancer

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ABSTRACT: Breast cancer has become the most common type of cancer worldwide since 2021. Despite recent advances in therapies, many patients with breast cancer experience tumor relapse and drug resistance, which are believed to attribute to breast cancer stem cells (CSCs), a small population of cells within breast cancer. Therefore, eradicating breast CSCs represents a promising therapeutical strategy to prevent cancer reoccurrence and drug resistance. Current studies have shown that breast CSCs arise from normal mammary stem cells/progenitor cells or differentiated mammary cells. Multiple key signaling pathways have been discovered and implicated in breast CSCs' self-renewal and differentiation, including Wnt/β-catenin signaling. In this article, I review the recent progress in breast CSC's biological studies and therapeutics by targeting breast CSCs' biomarkers and the Wnt/β-catenin signaling pathway.

KEYWORDS: breast cancer; cancer stem cells; Wnt; β-catenin; treatment; signaling pathway.

Introduction

According to the World Health Organization, breast cancer became the most prevalent cancer worldwide as of 2021, accounting for 12% of all new annually diagnosed cancer.[1] Based on the expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (HER2), breast cancer is generally classified into four subtypes: luminal A (ER+/PR+/Her2-), luminal B (ER+/PR+/Her2+), Her 2+ enriched (ER-/PR-/Her2+) and triple negative (ER-/PR-/Her2-).[2] Among the four subtypes, luminal A breast cancer is the most prevalent but the least aggressive, whereas triple-negative breast cancer (TNBC) is the most aggressive and challenging to treat.[3] Distinct therapies have been devised for each subtype of breast cancer; however, many breast cancer patients eventually experience tumor relapse and drug resistance.

CSCs are a very small subpopulation of cells within a tumor, and they can self-renew and differentiate into heterogeneous cancer cells.[4] The CSCs, first reported in acute myeloid leukemia, play a significant role in the advancement of cancer research.[5] Accumulative studies have demonstrated that CSCs account for tumor initiation, progression, and recurrence.[6-8] Recently, intensive efforts have been made to research breast CSCs with the hope of treating breast cancer by eradicating breast CSCs. Here, I summarize the recent progress in breast CSCs' studies and drug development to treat breast cancer, focusing on targeting the Wnt/β-catenin signaling.

Discussion

Current Models of Breast CSCs' Origin:

Breast CSCs play a fundamental role in breast cancer initiation, progression, reoccurrence, and drug resistance, and the cellular origin of breast CSCs remains controversial. Two well-accepted models, namely the hierarchical and stochastic models, have been proposed (Figure 1). In the hierarchical model, breast CSCs are believed to originate from mammary stem cells/progenitor cells that acquire sequential genetic mutations.[9] For example, Liu *et al*. demonstrated that the CD44+/CD24− cell markers expressed on normal mammary progenitor cells resemble the CD44+/CD24− lineage found on breast CSCs, suggesting that breast CSCs arise from the mammary stem cells/progenitor cells.[10] In contrast, it is postulated in the stochastic model that breast CSCs are derived from the differentiated mammary cells, which undergo de-differentiation and gain stem-like properties with enrichment of breast CSCs when exposed to damaging environmental factors such as chemotherapy and radiotherapy, leading to genetic alterations.[11,12] Those two CSCs' models can explain cancer recurrence and chemoresistance well, and currently, it remains unknown which model represents the true biological origin of CSCs.

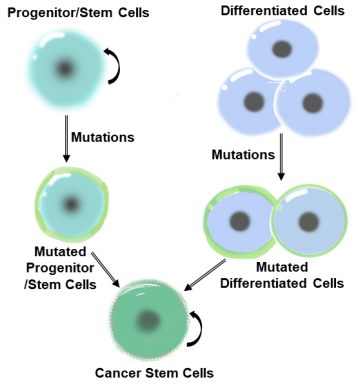

Figure 1: Current Models for the Origin of CSCs: (A) Hierarchical Model and (B) the Stochastic Model. In the hierarchical model, mutations occur in the normal stem/ progenitor cells, and the mutated stem/progenitor/ cells take advantage of the self-renewal ability to become the CSCs. Conversely, the differentiated cells acquire mutations in the stochastic model and then dedifferentiate into the CSCs.

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Breast CSC Specific Markers:

Identifying breast CSC-specific markers has dramatically helped the characterization and isolation of breast CSCs. To date, several significant markers have been found to be associated with breast CSCs, including CD44, CD24, and aldehyde dehydrogenase 1 (ALDH1), and combinatorial expression of these markers has been proven to characterize breast CSCs better. In 2003, Al-Hajj *et al*. reported the isolation of breast CSCs expressing cell-surface markers CD44+/CD24-/low from human breast cancer patients, and this cell subpopulation displays great tumorigenic ability.[7] In this study, they showed that approximately 100 cells with CD44+/CD24-/low markers formed tumors in mice, whereas 20,000 cells with alternative markers failed to generate tumors.[7] In addition, the breast CSCs with CD44+/CD24-/low markers can be serially passaged without losing their tumorigenic ability in mice.[7] Subsequently, Ginestier, and colleagues identified a distinct subpopulation of breast CSCs with the expression of the ALDH1+ marker. These cells are capable of self-renewal and generating breast tumors.[13] To figure out the relationship between the two subgroups of breast CSCs (CD44+/CD24-/low cells and ALDH1+ cells), their gene expression profiles were compared, and the result showed that the CD44+/CD24-/low subgroup cells are a mesenchymal and quiescent type of breast CSCs whereas ALDH1+ subgroup cells are an epithelial and proliferative type of breast CSCs.[10,14] These two subgroups of breast CSCs are believed to be two dynamic states of breast CSCs, and one subgroup can be transited to the other subgroup by appropriate signaling regulation.[15,16]

Wnt/β-catenin Signaling in Breast CSCs:

Among multiple signaling pathways implicated in the breast CSCs functions, Wnt/β-catenin signaling is critical (Figure 2). In the absence of Wnt ligands, the cytoplasmic β-catenin is phosphorylated by a "destruction complex" consisting of axin, adenomatous polyposis coli (APC), glycogen synthase kinase 3β (GSK3β) and casein kinase Iα (CKIα).[17] The phosphorylated β-catenin is then degraded by the proteasome, leading to the inactivation of the Wnt/β-catenin signaling pathway.[17] In contrast, Wnt/β-catenin signaling can be activated when Wnt ligands bind to the receptor Frizzled (FZD) and the low-density receptor-related protein 5/6 (LRP5/6).[17] The "destruction complex" with phosphorylation function for β-catenin is then decomposed, and the unphosphorylated β-catenin accumulates and translocates into the nucleus to regulate target gene expression.[4] A recent study has shown that Wnt/β-catenin signaling is highly active in the ALDH+ breast CSCs population and silencing the Wnt in the ALDH+ breast CSCs dramatically decreases their tumor-initiating potential.[18] In addition, the Wnt/β-catenin signaling activation has been reported in various subtypes of breast cancer, including TNBC.[19] The overexpression of Wnt/β-catenin signaling has also resulted in breast tumor formation in transgenic mice and an increased number of stem cells in precancerous mammary glands.[20,21] Vice versa, blocking the Wnt/β-catenin signaling suppresses breast cancer metastasis by inhibiting breast CSCs.[22]

Targeting Breast CSCs' Markers:

As illustrated previously, those common breast CSCs markers CD44, CD133, and ALDH1 are phenotypically and functionally crucial for preserving breast CSCs. Thus, therapeutically targeting these markers may effectively eliminate breast CSCs.

CD44 is a vital breast CSC marker, and direct knockdown

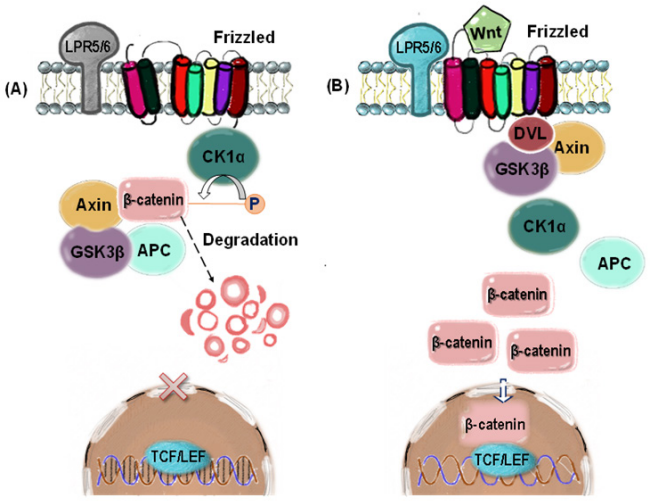

Figure 2: Scheme of the Wnt/β-catenin pathway: (A) In the absence of the Wnt ligand, the signaling process will not get initiated as the cytoplasmic β-catenin is phosphorylated by a "destruction complex" consisting of Axin, APC, GSK3β, and CKIα followed by subsequent proteasome-mediated degradation (Wnt off). (B) In contrast, in the presence of the Wnt ligand, the Wnt binds to the Frizzled family receptors, the signaling pathway is turned on (Wnt on), and a DVL (disheveled) molecule is liberated from the WNT receptor complex. The DVL molecule induces the β-catenin to be detached from the AXIN bound to CK1a, GSK3β, and APC. The β-catenin is then transduced, arrives in the nucleus, and adheres to the TCF/LEF transcription factor protein.

of CD44 effectively reduces breast CSC stemness and increases breast cancer susceptibility to anti-cancer drugs.[23,24] Pham et al. knocked down CD44 with lentivirus particles in breast CSCs, which resulted in the loss of their stemness.[23] The breast CSCs with the CD44 knockdown showed lower tumorigenic potential, altered the cell cycle, and similar gene expression profiles to the non-breast CSCs. For instance, expression of crucial genes related to stemness, metastasis, and anti-tumor drug resistance in breast CSCs, such as Myc and EGFR genes, have sharply reduced in breast CSCs with CD44 knockdown.[23]

In addition, as CD44 is a major cell membrane receptor for hyaluronic acid (HA), multiple anti-tumor drugs take advantage of such interaction between CD44 and HA by coating anti-tumor drugs with HA nanoparticles so that they can effectively bind to and kill the breast cancer cells expressing CD44.[25, 26] Lapatinib and rapamycin coated with HA nanoparticles, for example, can be effectively delivered to CD44+ breast CSCs, leading to dramatic breast CSC apoptosis.[25,27]

Moreover, ALDH1 is another breast CSC marker in Her 2+ enriched and triple negative (ER-/PR-/Her2-) breast cancer cells. The activity of ALDH1 is positively correlated to stemness in breast CSCs.[28] Hence, targeting ALDH1

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can be a promising therapy to kill breast CSCs for cancer treatment. Withaferin A, derived from the roots of Withania somnifera plants, has been reported to lower ALDH1 activities, inducing the death of the breast CSCs and shrinking breast tumor size.[29]

Targeting Wnt/β-catenin Signaling:

As Wnt signaling activation is implicated in breast CSCs' self-renewal and tumorigenesis, targeting Wnt signaling represents a potential therapy for breast cancer by targeting breast CSCs. Recently, numerous Wnt signaling inhibitors have been identified, some of which have gone into clinical trials.[30]

In a high-throughput screening of Wnt signaling inhibitory molecules, Liu and colleagues identified that LGK974 (also known as WNT974), a small molecular chemical, dramatically inhibits Wnt/β-catenin signaling by targeting porcupine, a Wnt pathway associated acyltransferase.[31] The preclinical result has demonstrated that LGK974 is well-tolerated and displays strong efficacy in rat breast cancer models, and later LGK974 was moved into clinical trial.[31] In 2011, an open-label phase I clinical trial of LGK974 was initiated to treat a variety of malignancies, including breast cancer (NCT01351103), and the preliminary result was recently released, showing that LGK974 was generally well tolerated but exhibited a limited anti-tumor activity.[32]

Vantictumab (OMP18R5) is a humanized monoclonal antibody targeting the Frizzled receptor to inhibit the Wnt/β-catenin.[33] The Phase I clinical trial of Vantictumab in 37 breast patients, was recently completed, and the final result has not been released yet (NCT01973309). Two additional Phase I studies of Vantictumab in patients with solid tumors have revealed that Vantictumab suppressed target gene expression of the Wnt/β-catenin pathway and was tolerated at 2.5 mg/kg for one intravenous injection every three weeks. In contrast, a clinical trial with further dose escalation is ongoing (NCT01345201).[33]

Disheveled (DVL) plays a decisive role in the transduction of Wnt signals from the Frizzled receptor to the downstream of Wnt signaling. Therefore, it is a feasible target to modulate Wnt signaling. Shan *et al*. identified a small molecular compound, NSC668036, which binds to the Dvl to inhibit Wnt/β-catenin signaling by interrupting the interaction between Frizzled receptor and Dvl.[34] In a succeeding study, Shan *et al*. identified six new compounds exhibiting improved binding affinity over NCS668036.[35]

Tankyrase is an important enzyme involved in the Wnt/β-catenin signaling, and it stimulates Axin degradation for Wnt/β-catenin activation through the ubiquitin-proteasome pathway.[36,37] So far, several small-molecule Tankyrase inhibitors have been developed to inhibit the Wnt/β-catenin signaling. Chen *et al*. testified that a Tankyrase inhibitor, IWR-1, stabilizes Axin to block the Wnt/β-catenin signaling.[38] Subsequently, another Tankyrase inhibitor, XAV939, is discovered, and it functions similarly to IWR-1.[36] Recently, several new Tankyrase inhibitors have been identified, including WIKI4 and G007-LK.[39,40]

Wnt/β-catenin signaling can also be regulated by microRNAs (miRNAs). Isobe *et al*. reported that one miRNA, miR-142, dramatically activated the Wnt/β-catenin signaling through decomposing the "destruction complex" and knockdown of miR-142, effectively suppressed formation by breast CSCs, and slowed down breast cancer growth *in vivo*.[41] Furthermore, Liu *et al*. reported that another miRNA, miR-1, can down-regulate breast CSC stemness, proliferation, and migration by binding to the Frizzled seven receptor and Tankyrase-2 to inhibit Wnt/β-catenin signaling.[42]

In summary, considerable efforts and advances have been made to develop drugs by targeting the Wnt/β-catenin signaling pathway with small molecules, antibodies, and miRNAs which have shown beneficent effects on the treatment of breast cancer. However, to date, no Wnt signaling-related drugs have been officially approved by FDA for clinical usage.

■ Conclusion

Years of scientific research have revealed that breast CSCs play vital roles in cancer relapse and drug resistance. Thus far, several breast CSCs markers have been identified, including CD44, CD133, and ALDH1, and therapeutically targeting these markers have been shown to induce breast CSC apoptosis and shrink tumor growth.[23-27] The Wnt/β-catenin signaling is one of the key pathways involved in breast CSCs self-renewal and differentiation. Several potential drugs have been developed to target the abnormal activation of the Wnt/β-catenin signaling at multiple levels with small molecules, antibodies, and miRNAs. Preclinical studies and clinical trials have indicated that targeting the Wnt/β-catenin pathway represents a promising strategy for treating breast cancer. However, as Wnt/β-catenin signaling is also essential to normal cell proliferation and tissue homeostasis, it remains challenging to effectively fix the dysregulated Wnt/β-catenin pathway in breast CSCs, while being safe enough not to damage the normal cell functions and tissue homeostasis. Nevertheless, our understanding of the Wnt/β-catenin pathway continues to improve in both physiology and pathology, and several potential drugs are under clinical trials. Therapeutic agents targeting Wnt/β-catenin signaling may be developed to treat breast cancer in the near future effectively.

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Yu Tianyue is G11, a high school student from Shanghai, China. For her future career, she wants to be a pharmacist who produces the most economical drugs to rescue people's lives. Hence, through this review article, she dives deep into a highly promising medical solution to the breast cancer.