Interplay between Wnt signaling molecules and exosomal miRNAs in breast cancer (Review)

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Abstract. Breast cancer (BC) is the most common malignancy in women worldwide. Wnt signaling is involved in tumorigenesis and cancer progression, and is closely associated with the characteristics of BC. Variation in the expression of exosomal microRNAs (miRNAs) modulates key cancer phenotypes, such as cellular proliferation, epithelial-mesenchymal transition, metastatic potential, immune evasion and treatment resistance. The present review aimed to discuss the importance of Wnt signaling and exosomal miRNAs in regulating the occurrence and development of BC. In addition, the present review determined the crosstalk between Wnt signaling and exosomal miRNAs, and highlighted potential diagnostic biomarkers and therapeutic targets.

Contents

1. Introduction

Breast cancer (BC) is the most common malignancy among women worldwide, with an heterogeneous nature resulting from various risk factors, such as endogenous and exogenous estrogen exposure, lifestyle choices, dietary habits and exposure to toxic environmental elements, such as heavy metals and chemicals (1,2). In total, ~15% of BC cases can be attributed to genetic susceptibility and genetic factors (3). Notably, research has revealed a substantial discrepancy in the 5-year survival rates between patients with advanced invasive BC (representing 24% of cases with distant metastasis) and those with early-stage BC, with a 99% survival rate (4). In addition, some patients with cancer may benefit from monotherapies, such as hormone therapy, immunotherapy or chemotherapy; however, the effectiveness of these therapies may diminish over time, and some patients may become resistant (5). Thus, the development of novel therapeutic targets is crucial for the treatment of BC.

In addition to regulating cell proliferation and cell fate during embryonic development and tissue homeostasis, Wnt signaling determines cell polarity (6,7). Notably, Wnt is a secreted glycoprotein within this pathway (8). Diverse intracellular signaling pathways may be activated by these interactions, which may intersect or function independently (9). Collectively, an integrin gene, Int-1, and a segmental polarity gene, Wingless, form the term 'Wnt' (10,11). Wnt-1, formerly known as the Int-1 oncogene, has been recognized as the integration site for the mouse mammary tumor virus (MMTV) (10). In addition, BC was the first tumor to be associated with Wnt signaling. Results of previous studies demonstrated that Wnt signaling is involved in multiple aspects of cancer, including proliferation (12,13), metastasis (14,15), immune regulation (16,17), therapeutic resistance (18) and phenotype shaping (19). Moreover, a number of inhibitors targeting components of the Wnt signaling pathway exhibit potential in the treatment of cancer (20). Thus, the present review demonstrated the interaction between exosomal microRNAs (miRNAs) and proteins in signaling cascades, demonstrating their role in BC and in mechanisms of the Wnt signaling pathway.

Exosomes are nano-sized vesicle structures ranging from 50-150 nm. These are derived from endosomes and are present in diverse tumor cells (21,22). Numerous proteins and lipids are present in these vesicles, in addition to miRNA (23). A variety of model systems have been used to demonstrate that cancer cells secrete extracellular vesicles, and these subsequently metastasize from primary tumors to the circulatory system (24). Research focused on exosomal miRNAs have

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demonstrated their role in cellular and molecular biology (25). Notably, miRNAs are endogenous small RNAs that are 20-24 nucleotides in length. In tumor cells, miRNAs play a crucial regulatory role in various signaling pathways within exosomes (26). Cancer-specific exosomal miRNAs exhibit distinct expression patterns and play a significant role in the progression of the disease, highlighting their potential as biomarkers of cancer (27). Notably, BC tissue expresses altered exosomal miRNAs both before and after invasion (28,29). Thus, through studying the functional role of exosomal miRNA in BC, a novel theoretical basis may be developed to understand its etiology.

2. Overview of Wnt signalling

In 1973, genetic research using *Drosophila melanogaste*r revealed the components of the Wnt signaling pathway (30). In 1982, Nusse *et al* (10) demonstrated that the mouse Wnt1 gene promotes the occurrence and development of mammary carcinomas in MMTV (10). Subsequently, numerous studies have demonstrated that the Wnt signaling pathway exerts a significant impact on human tumors. For example, the deletion of genes associated with rectal cancer leads to excessive activation of Wnt signaling, thereby promoting tumor development (30). Results of a previous study also revealed that Wnt-dependent systemic inflammation drives BC metastasis when p53 is lost (31). Notably, 19 Wnt genes have been identified in the human genome, and these encode secreted lipoglycoproteins (32). These lipoglycoproteins play a fundamental role in controlling cell size, intercellular communication, embryonic development and stem cell self-renewal (33). In addition, Wnt signaling pathways are divided into three types; namely, i) canonical Wnt signaling pathways, ii) Wnt-planar cell polarity (PCP) signaling pathways, and iii) Wnt-Ca^{2+} signaling pathways (34). Canonical Wnt signaling transduction, also known as Wnt/β-catenin protein signaling, is the most well-established pathway. This pathway is induced by Wnt1, Wnt2, Wnt3a, Wnt8b, Wnt10a and Wnt10b (35). β-catenin proteins are the core components of canonical Wnt signaling, and these bind to the cytoplasmic tail of E-cadherin to achieve intercellular adhesion (36,37). The inhibition of canonical Wnt signaling has been identified as an effective approach in inhibiting the advancement of gastric cancer (38). Moreover, Wnt-PCP signaling is triggered by Wnt4, Wnt5a, Wnt5b, Wnt7b and Wnt11 (39,40). Research into the Ca^{2+}-Wnt signaling pathway is lacking; however, this plays a key role in determining cell fate (41), cancer progression (42,43) and inflammatory response (44) during early embryogenesis. Fzd2 and Wnt5a are the main initiators of the Wnt-Ca^{2+} signaling pathway (45). Results of a recent study revealed that a non-canonical Wnt signaling pathway contributes to the establishment of a cancer stem cell niche in cancer-associated fibroblasts (CAFs) (46). In summary, Wnt signaling plays an important role in the occurrence and development of tumors.

3. The role of canonical Wnt in BC development and therapy

The present review focused on canonical Wnt signaling (Fig. 1). Results of a recent study demonstrated that canonical Wnt signaling enhanced melanocyte regeneration; however, this suppressed the invasion, migration and proliferation of melanoma cells (13). In the absence of Wnt signaling, β-catenin binds to cytoplasmic complexes containing casein kinase-1-alpha (CK1Alpha), glycogen synthase kinase-3-beta (GSK3β), axis inhibitor (Axin) and adenomatous polyposis colon proteins (47). This process enhances the phosphorylation of β-catenin and its association with β-transducing protein repeat sequence protein, leading to the ubiquitination of β-catenin and its subsequent breakdown by the proteasome. Results of a recent study revealed that inhibition of Wnt signaling promotes apoptosis of human colorectal cancer cells (48). When Wnt signaling is activated in response to Wnt binding to Frizzled, the Dishevelled (DSH) protein is activated (49). Activated DSH protein enhances the phosphorylation of GSK3β, thereby leading to inhibition of this protein. This results in the accumulation of free unphosphorylated β-catenin in the cytoplasm, which is subsequently transported to the nucleus. Prior to Wnt signaling transduction, lymphoid enhance factor (LEF) and T-cell factor (TCF) bind to specific sequences of the promoter/enhancer region of the target gene and, together with Groucho and HDAC, inhibit gene expression in the nucleus. Wnt signaling leads to elevated levels of β-catenin in the nucleus, which binds to TCF/LEF and promotes alterations in transcriptional mechanisms, resulting in the activation of several target genes. In addition, KDM2A promotes the degradation of TCF/LEF transcription factors, which regulate canonical Wnt signaling (50). The transfer of proteins from the E-cadherin-binding pool to the cytoplasmic pool increases the amount of free β-catenin available to activate target genes. Interactions between β-catenin and histone acetyltransferase CBP (CREb-binding protein), chromatin remodeling SWI/SNF complexes, and the binding of BCL-9 to Pygopus (Pygo) and BRG1 mediate transcriptional activation. Notably, results of a previous study revealed that the Wnt/β-catenin/BCL-9 signaling pathway impacts the proliferation of multiple myeloma cells (51). CHIBBY directly interacts with the C-terminal region of β-catenin; thus, inhibiting β-catenin-mediated transcriptional activation through competitive binding with LEF1.

Results of previous studies demonstrated that activation or silencing of the Wnt signaling pathway impact epithelial-mesenchymal transition (EMT)-dependent metastasis, the immune microenvironment and the resistance of BC (52-54). Notably, cells undergo EMT during the differentiation of epithelial cells into mesenchymal cells (55). EMT is an important feature of BC, and plays a key role in triple negative BC (56). Thus, research is focused on regulating EMT for the treatment of BC (57). Li *et al* (58) demonstrated that activation of Wnt signaling enhanced the invasion and metastasis of BC (58). Notably, a number of intrinsic EMT-transcription factors (TFs) are mechanically activated by Wnt/catenin signaling, epidermal growth factor (EGF)/fibroblast growth factor (FGF)-receptor tyrosine kinase signaling and Notch signaling. These pathways also initiate changes in the expression of genes, including E-cadherin and ZO-1. In addition, the aforementioned pathways may activate N-Cadherin, MMPs, integrins and fibronectin (59). EMT-TFs expressed by Wnt regulate BC morphogenesis, including lamellipodia formation, and directly secrete MMPs, resulting in their migration and invasion (60). Results of a previous study revealed that

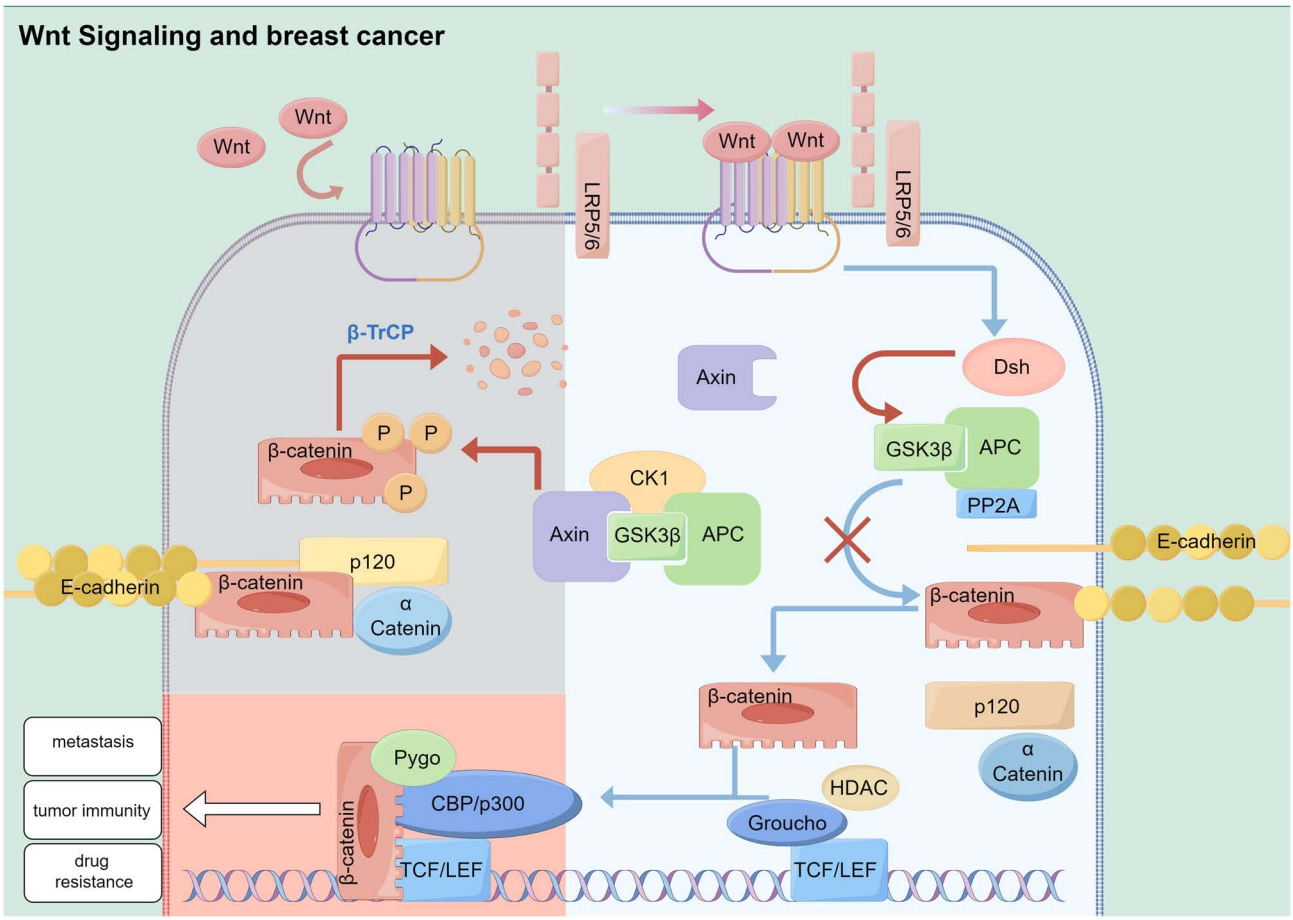

Figure 1. The role of canonical Wnt signaling in BC. Left: An inactive Wnt/catenin pathway is characterized by a 'destruction complex', which phosphorylates catenin for ubiquitination and proteolytic degradation. Right: The active catenin pathway. The destruction complex formation does not occur, resulting in nuclear translocation of β-catenin. In addition, the levels of BC metastasis, tumor immunity and drug resistance are impacted. APC, adenomatous polyposis coli; axin, axis inhibitor; CBP, cAMP response element-binding protein; GSK3β, glycogen synthase kinase-3β; TCF, transcription factor; BC, breast cancer.

Wnt/β-catenin signaling suppresses antitumor immunity (61). A cancerous breast cell that expresses Wnt signaling may develop strategies to avoid being recognized and destroyed by the immune system (62). To prevent phagocytosis by macrophages, BC cells express CD24 and CD47 through interactions with Siglec-10 and SIRP-α, respectively (63,64). Notably, CD24 directly targets Wnt1, while CD47 indirectly targets SNAI1 and ZEB1 through Wnt signaling in BC (65,66). Therefore, Wnt signaling plays a key role in the immune microenvironment of BC. Metastatic BC is characterized by frequent changes in the TP53 gene (67). The loss of TP53 in BC cells trigger the secretion of Wnt1, Wnt6 and Wnt7a (31). These proteins bind to Fzd7 and Fzd9 on the surface of TAM, stimulating the production of IL-1 by TAMβ. Results of a previous study revealed that mutations in TP53 may lead to drug resistance in BC (68). For example, TP53 mutations are associated with endocrine therapeutic resistance in early luminal BC (69). Wnt-driven systemic inflammation and immunosuppression niches are associated with BC multidrug resistance. Cancer resistance is considered a multifaceted issue, involving tumor heterogeneity, drug efflux/inactivation and activation of survival pathways (70). Results of a previous study demonstrated that inactivation of Wnt signaling leads to BC entering a drug insensitive resting state (71), leading to multidrug resistance. Thus, Wnt signaling is a dynamic and multifaceted process in BC, and Wnt signaling may exhibit potential as a target in the treatment of BC.

4. The function of non-canonical Wnt in BC development

The non-canonical Wnt pathways include the Wnt-PCP signaling pathway and the Wnt-Ca^{2+} signaling pathway. Genetically engineered mice exhibit increased distant metastasis and collective cell migration following Vangl-dependent Wnt-PCP signaling (72). In basal BC, overexpression of the Wnt/PCP protein, VANGL2, is associated with a poor prognosis and an increase in tumor size (73). In addition, results of a previous study revealed that exosomes released by fibroblasts activate Wnt-PCP signaling to drive BC cell invasion (14). Secreted fried-associated protein 2 (SFRP2) is overexpressed in the blood vessels of 85% of human breast tumors, and SFRP2 promotes tumor angiogenesis through the Wnt-Ca^{2+} pathway (74). At present, research is focused on the non-canonical Wnt pathway in BC, and this pathway exhibits potential in further understanding the pathogenesis of BC.

5. The value of exosomal miRNAs in BC

Exosomes are membrane-bound microvesicles that range from 30-150 nanometers in size, and these are secreted into the

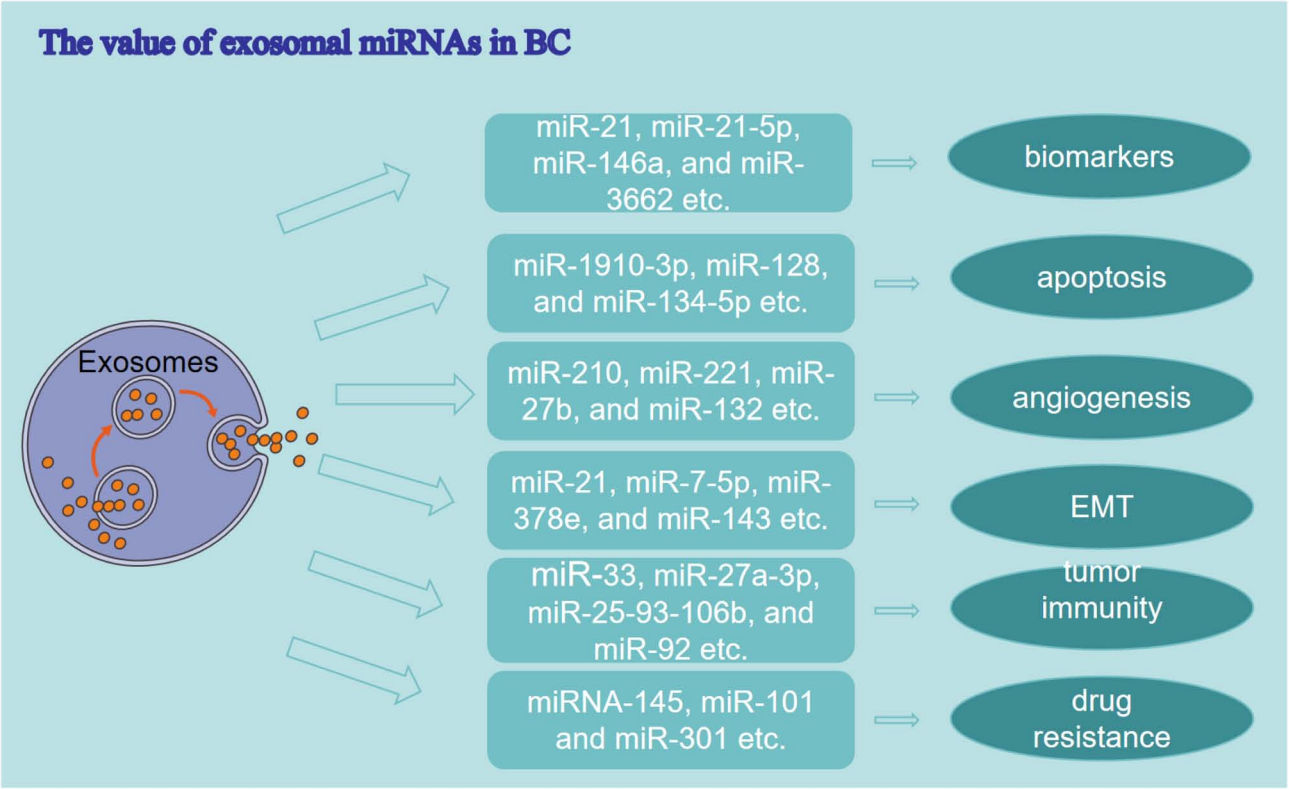

Figure 2. Schematic demonstrating the roles of exosomal miRNAs. miRNA, microRNA; EMT, epithelial-mesenchymal transition; BC, breast cancer.

extracellular environment by all cells, including prokaryotes and eukaryotes. Exosomes contain a diverse array of miRNAs, mRNA, proteins, lipids and other substances (75). They play a crucial role in facilitating intercellular material exchange and information transmission. miRNAs accelerate mRNA degradation or inhibit mRNA translation through interactions with the 3'-untranslated region of target mRNAs. This regulation of post-transcriptional gene expression in recipient cells has been observed in various models (23). Abnormal expression or mutations in miRNAs are associated with a range of tumors, including BC, where they function as oncogenes or tumor suppressors (76,77). However, miRNAs are inherently unstable. Exosomes, with a phospholipid bilayer membrane structure, provide stability to miRNAs via protection from enzymatic degradation (78). Therefore, exosomal miRNAs are valuable for understanding the pathogenesis of malignant tumors. Extensive research has demonstrated that exosomal miRNAs exhibit potential as biomarkers and therapeutic targets in BC (Fig. 2).

Exosomal miRNAs as potential biomarkers. A biomarker quantifies a normal biological or pathological process, or an impact of a therapeutic intervention (79). Exosomal miRNAs exhibit potential as biomarkers in the prediction, diagnosis and prognosis of BC (80). The present study demonstrated that serum exosomal miR-21 may be used as a biomarker for the early detection and diagnosis of BC (81). Moreover, the plasma exosomal miR-21-5p has also been identified as a potential biomarker for the diagnosis of BC (82). Li *et al* (83) demonstrated that exosomes miR-3662, miR-146a and miR-1290 exhibit potential in predicting disease, and these may be used as biomarkers for diagnosis and treatment. Through monitoring exosomal miRNAs, BC occurrence, recurrence, prognosis and responses to common therapies can be predicted.

Exosomal miRNAs and apoptosis. Apoptosis plays a key role in promoting tumor occurrence. Exosomal miRNAs play a significant role in the apoptosis of BC cells, exhibiting abnormal expression patterns in patients (84). Notably, BC cells release exosomes containing miR-1910-3p, which inhibits apoptosis and facilitates tumor development through the transfer of miR-1910-3p to target cells (85). In addition, Wei *et al* (86) revealed that miR-128 is specifically sorted into exosomes and enhances the proliferation of MCF-7 cells through targeting the Bax gene. Bax plays a key role in the inhibition of apoptosis. A previous study identified exosomal miR-134-5p as a potential therapeutic target for BC, as it promotes apoptosis through inhibiting the PI3K/AKT pathway (86).

Exosomal miRNAs and angiogenesis. In hypoxic environments, the secretion of exosomal miRNAs by cancer cells is upregulated to modulate tumor angiogenesis, a critical and dynamic process in the progression of tumorigenesis (87). Exosomal miR-210 enhances angiogenesis through the modulation of vascular remodeling-associated genes, Ephrin A3 and PTP1B, consequently influencing the development of BC and the dissemination of hypoxic BC cells to adjacent tissues (88). Results of previous studies demonstrated that exosomal miRNAs play a significant role in promoting vascular survival through the regulation of FGF, vascular endothelial growth factor (VEGF), EGF and angiopoietin-1, ultimately contributing to the progression and metastasis of BC (89,90). In patients with

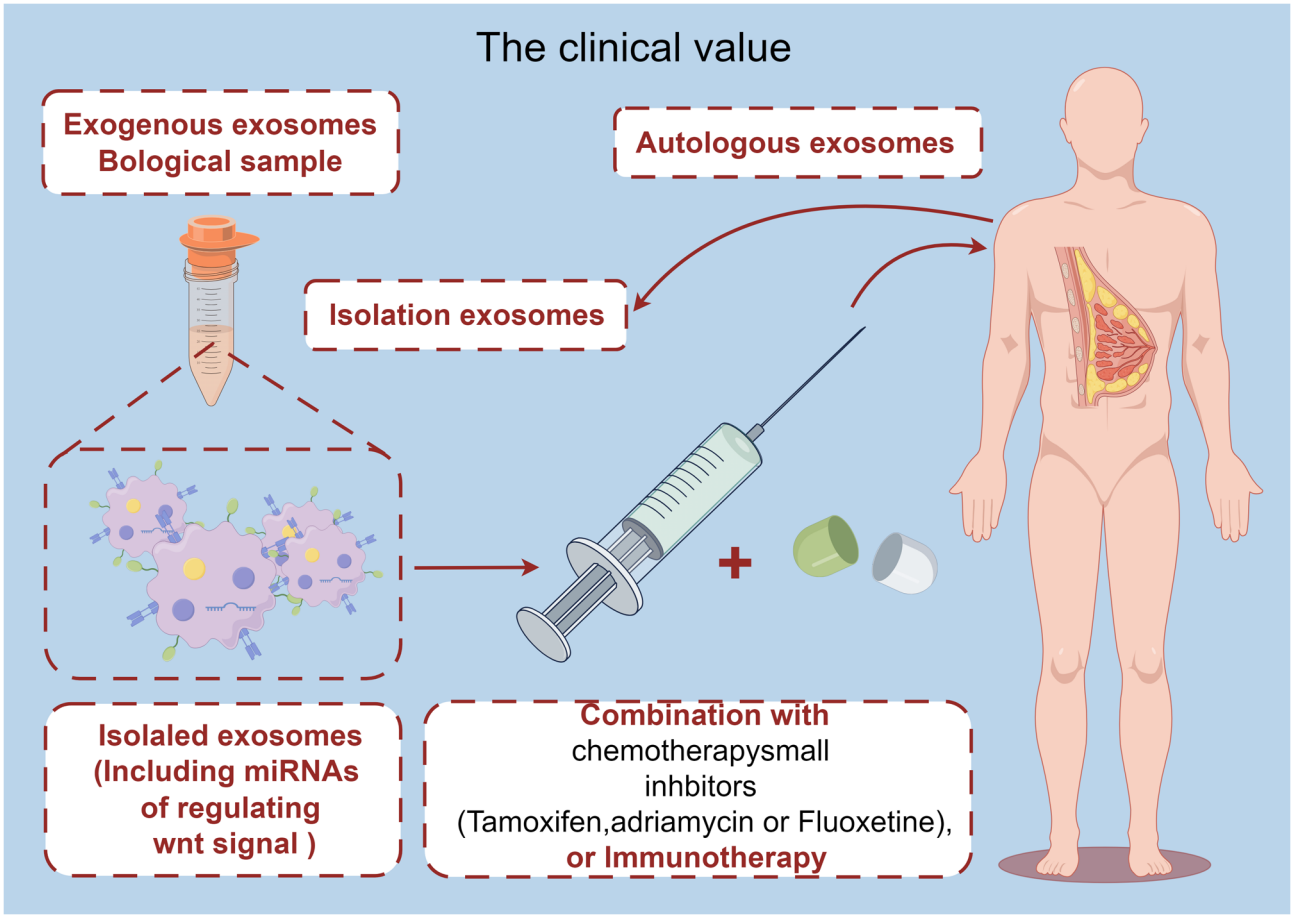

Figure 3. Schematic demonstrating the value of exosomal miRNAs in clinical practice. miRNA, microRNA.

BC, miR-221, miR-27b and miR-132 enhance angiogenesis through modulating the angiogenic properties of VEGF (91,92). However, several exosomal miRNAs have been identified as inhibitors of tumor angiogenesis. Notably, exosomal miR-16 inhibits angiogenesis in BC cells through the direct regulation of VEGF expression (93). Overall, exosomal miRNAs play a role in modulating the progression of BC via angiogenesis.

Exosomal miRNAs and EMT. EMT facilitates the acquisition of metastatic capabilities by epithelial cells, serving as a crucial prerequisite for metastasis. Results of a previous study demonstrated that exosomes released by CAFs transfer specific miRNAs, including exosomal miR-21, miR-378e and miR-143 to BC cells, promoting EMT characteristics (94). Yan *et al* (95) further elucidated that CAF-derived exosomal miR-18b induces EMT, invasion and metastasis in BC through targeting TCEAL7 to activate the NF-κB signaling pathway. Wang *et al* (96) demonstrated that exosomal miR-181d-5p derived from CAFs promotes the proliferation, invasion, migration and EMT of BC cells through regulating CDX2 and HOXA5 genes (96). Thus, targeting CAF-derived exosomal miR-18b and miR-181d-5p may exhibit potential in the treatment of BC. In addition, miR-103-107 may inhibit miRNA biosynthesis through targeting the Dicer gene in BC, resulting in enhanced EMT and metastatic characteristics in epithelial tumor cells (97).

Moreover, exosomal miRNAs exhibit anticancer properties in BC through the inhibition of EMT. For example, miR-34a, a transcriptional target of p53, suppresses the aggressiveness of BC cells through targeting EMT and the zinc finger transcriptional inhibitor, Snail (98). In addition, exosomal miR-16-5p attenuates EMT via downregulation of EPHA1 and NF-κB signaling pathways, ultimately impeding the proliferation, invasion and migration of BC cells (99). Moreover, miR-7-5p exhibits differential expression levels in various invasive BC cell lines. miR-7-5p inhibits EMT through targeting RYK and decreasing the phosphorylation of JNK, thereby reducing the metastasis of BC (100).

Exosomal miRNAs and tumor immunity. Exosomal miRNAs play a significant role in mediating the communication between BC cells and immune cells, thereby influencing immune regulation. Results of previous studies demonstrated the involvement of exosomal miRNAs in modulating the polarization of macrophages and the secretion of proinflammatory cytokines (101,102). Specifically, M1 macrophages exhibit a pro-inflammatory phenotype, characterized by the expression of cytokines, such as IL-12. This may contribute to the destruction of cancer cells. On the other hand, M2 macrophages produce anti-inflammatory cytokines, such as IL-10, thus promoting tumor progression (103). BC is characterized by the presence of tumor-associated macrophages (TAMs), predominantly displaying the M2 phenotype (104). Results of previous studies demonstrated that BC-derived exosomal miR-16 and miR-33 inhibit the M1 polarization of TAMs,

through suppressing the expression of epigenetic factors, while simultaneously stimulating M2 polarization (102,105). This mechanism ultimately facilitates the advancement of metastatic BC. Previous research has focused on the miRNA-mediated inhibition of mRNA translation in the regulation of endoplasmic reticulum stress and immune evasion in human tumors. Specifically, in the context of endoplasmic reticulum stress, BC exosomes containing miR-27a-3p, miR-25-93-106b and miR-92 enhance the expression of PD-L1 in macrophages, thereby facilitating immune evasion (106,107). These findings suggest that targeting exosomal miRNAs may exhibit potential in the treatment of BC.

Exosomal miRNAs and drug resistance. Primary breast tumors often respond well to initial treatment, and develop drug resistance after a few months (70). At present, research is focused on exosomal miRNA-mediated drug resistance mechanisms in BC cells (108). Results of a previous study highlighted that modulation of exosome miRNA expression may impact the responsiveness of BC cells to hormonal treatments, targeted therapies and chemotherapeutic agents via diverse signaling pathways (109). BC is categorized according to hormone receptor expression, with ~70% of BC cases being labelled as estrogen receptor-positive. These cases are treated with anti-estrogen drugs, such as tamoxifen or fluoxetine; however, cells may develop resistance. Notably, exosomal miR-101 and miR-301 may cause BC cells to become resistant to tamoxifen, through the inhibition of PTEN (110). Exosomal miR-221 and miR-222 increase the therapeutic resistance of sensitive MCF7 BC cells to tamoxifen through downregulation of p27 and ERα targets. Exosomal miR-221/222 also promote BC cell resistance to fluoxetine through dysfunction of TGF-β and β-catenin signaling networks; thus, impacting the survival of patients with ER-positive BC (111,112). Results of a previous study revealed a high correlation between changes in exosomal miRNA expression and adriamycin resistance. For example, upregulation of miR-145 may sensitize BC to doxorubicin chemotherapy (113). In conclusion, exosomal miRNAs may exhibit potential as targets for increasing the chemosensitivity of BC.

6. Crosstalk between exosomal miRNAs and Wnt signaling

The role of exosomal miRNAs in the regulation of Wnt Signaling. Exosomal miRNAs may impact various aspects of tumor progression through regulation of Wnt signaling. Patients with recurring BC exhibited significantly lower levels of exosomal miR-18a-5p (114). Results of a recent study demonstrated that exosomal miR-18a-5p promotes the EMT and metastasis of nasopharyngeal carcinoma cells through activating the Wnt/β-catenin signaling pathway (115). In addition, the migration and invasion of BC cells are promoted via the downregulation of exosomal miR-7-5p through WNT signaling (100). In addition, exosomal miR-1260b promotes cell invasion through the Wnt/β-catenin signaling pathway (116). miRNA-1260b also plays a role in promoting tumor invasion in BC (117). Exosomal miR-10527-5p inhibits migration, invasion, lymphangiogenesis and lymphatic metastasis via Wnt/β-catenin signaling (118). In cancer cells, exosome-derived miR-375 targets DIP2C and regulates Wnt signaling, thus promoting osteoblastic metastasis (119). Li *et al* (120) revealed that exosomal miR-92a promotes cytarabine resistance through activating the Wnt/β-catenin signaling pathway (120). In conclusion, exosomal miRNAs may influence tumor progression through regulating Wnt signaling.

Wnt signaling may impact the expression of exosomal miRNAs. Results of previous studies highlighted that activation of Wnt/β-catenin signaling may impact the expression of exosomal miR-301a and promote resistance to radiation (121,122). In addition, Wnt signaling impacts the release of exosomal miR-454 to maintain the biological properties of cancer stem cells through BC cells (123). Exosomal miR-1323 is involved in cervical cancer progression and resistance to radiation, which may exhibit potential in the treatment of cervical cancer (124). In addition, the chemosensitivity of bladder cancer cells was increased via Wnt/β-catenin pathway-mediated downregulation of exosomal miR-148b-3p in CAFs (125). In conclusion, the release of miRNA in exosomes may be influenced by the activation or deactivation of Wnt signaling. Thus, regulation of Wnt signaling may regulate the expression of exosomal miRNAs in BC.

7. Conclusions

At present, research is focused on the role of exosomal miRNAs in BC. Results of previous studies highlighted the involvement of multiple exosomal miRNAs in various aspects of BC progression, including apoptosis regulation, cell metastasis, tumor immunity, drug resistance and modulation of Wnt signaling pathways. Thus, targeting multiple biological processes of exosomal miRNAs may exhibit potential in the treatment of BC (Fig. 3). At present, the use of exosomal miRNAs is limited due to difficulties in batch isolation and the extraction of exosomes. However, further investigations into the role of exosomal miRNAs and Wnt signaling pathways in BC may enhance the current understanding of the pathogenesis of BC, and aid in the development of exosomal miRNA-based therapies. In conclusion, exosomal miRNAs and Wnt signaling exhibit potential as effective diagnostic and therapeutic targets for BC. Further investigations into the regulatory mechanisms of exosomal miRNAs in Wnt signaling are required for the development of novel diagnostic and therapeutic targets in BC.

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Authors' contributions

HL organized the manuscript and produced the figures. XL completed the exosome section of the manuscript. WD

provided the outline of the present review and completed the 'Conclusions' section of the manuscript. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

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Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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