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Review

Revolutionizing treatment for triple-negative breast cancer: Harnessing the power of exosomal miRNAs for targeted therapy

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ABSTRACT

Triple-negative breast cancer (TNBC) represents a challenging and aggressive form of breast cancer associated with limited treatment options and poor prognosis. Although chemotherapy is a primary therapeutic approach, drug resistance often hinders treatment success. However, the expanding knowledge of TNBC subtypes and molecular biology has paved the way for targeted therapies. Notably, exosomes (extracellular vesicles) have emerged as crucial carriers of tumorigenic factors involved in oncogenesis and drug resistance, facilitating cell-to-cell communication and offering potential as self-delivery systems. Among the cargo carried by exosomes, microRNAs (miRNAs) have gained attention due to their ability to mediate epigenetic changes in recipient cells upon transfer. Research has confirmed dysregulation of exosomal miRNAs in breast cancer cells compared to healthy cells, establishing them as promising biomarkers for cancer diagnosis and prognosis. In this comprehensive review, we summarize the latest research findings that underscore the diagnostic and prognostic significance of exosomal miRNAs in TNBC treatment. Furthermore, we explore contemporary therapeutic approaches utilizing these exosomal miRNAs for the benefit of TNBC patients, shedding light on potential breakthroughs in TNBC management.

1. Introduction

Triple-negative breast cancer (TNBC) comprises 15–20 % of other types of breast cancer and indicates more aggressive biological features, poorer prognosis, and absence of targeted treatments than other subtypes [1,2]. TNBC is characterized by deficiency of human epidermal growth factor receptor 2, estrogen receptor, and progesterone receptor expression [3,4]. Since there is no targeted treatment for TNBC patients, chemotherapy with platinum or non-objective chemotherapy (alone or in combination) are only available systemic treatments, which offer restricted Therefore, an effective targeted delivery system is essential for the treatment of TNBC. Despite outstanding progressions in breast cancer detection and treatment, early diagnosis is still a serious challenge that requires further investigation to substitute modern diagnostic and prognostic instruments [5]. Recent advances in research have led to the identification of specific biomarkers for cancer that can precisely forecast clinical outcomes and treatment responses for primary breast cancer [6]. In this regard, recent studies have indicated up- and downregulation of some microRNAs (miRNAs) in cancer cases provide a sign for breast cancer early diagnosis [7,8]. Thousands of miRNAs are known to play a key regulatory parts in different biological events, such as cell proliferation, differentiation, and apoptosis [9,10]. Exosomes are extracellular vesicles of 30–100 nm that have an endosomal origin, containing lipid, proteins, microRNAs (miRNAs) and mRNAs, secreted from different cells, such as immune cells, epithelial cells, and tumor cells [11,12]. Exosomes are crucial for transmission within the cells,

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leading to maintenance of cellular homeostasis [13,14]. According to evidence, cancer-related exosomes can stimulate the survival of tumor, tumor development and assisting the creation of a tumor-inducing niche by promoting angiogenesis, altering the extracellular matrix, and disabling the immune cells' activity [15–17]. Among the bioactive components of exosomes, miRNAs have gained considerable notice due to their modifying role in gene expression [18]. Exosomal miRNAs have multifaceted effects in tumor initiation and development and reveals diverse types of expression in healthy and cancer-diagnosed cases, which are considered as hopeful cancer biomarkers to apply in clinical trials [19,20]. A latest research by Stevic et al. revealed a system of dysregulated exosomal miRNAs with particular expression patterns in the exosomes of $HER2^{+}$ and TNBC cases, which also correlated with clinicopathological parameters and pathologic complete response (pCR) in each breast cancer subtype [21]. A profound insight of certain miRNA subtype profiles has issued perception in recognizing hopeful therapeutic approaches and concluding tumor development, especially for aggressive TNBC subtypes.

This review will make a summary of the latest findings on the ground of the most favorable results considering the diagnostic and prognostic benefit of exosomal miRNAs in TNBC treatment. In addition, this review will bring out possible modern curative practices of these exosomal miRNAs for TNBC cancer long-sufferers.

2. Pathogenesis of TNBC

TNBC is known as the most frequent type of invasive and heterogenic subtype of breast cancers, which is specialized through early recurrence, high cell proliferation, poor cellular differentiation and poor prognosis [22,23]. Surelli T et al. have been shown that, TNBC is often invasive with numerous fatality percentage than other breast cancers [24]. Also, various clinical trials and epidemiological researches have indicated that 10–15 % of all breast cancers includes TNBC [25]. Lehmann and et al. have demonstrated that TNBC can be categorized into six subtypes with the help of gene-expression metanalysis profiling data; basal-like 1, basal-like 2, immunomodulatory, mesenchymal-like, mesenchymal stem-like, and luminal androgen-receptor (AR) expressing. Besides, they suggested different types of TNBC require different treatments, and there was no evidence that TNBC vary between different ethnic groups of women [26]. In addition, based on the received date of the Surveillance, Epidemiology, and End Results (SEER) of California database reveals that the rate of TNBC in African-American female is higher than other ethnics in different stage of life [27]. Another study by examining the distribution of molecular subtypes of invasive tumors in different geographical regions in Nigeria and Senegal have stated that TNBC was the most noticeable cancer type in woman, particularly, basal-like TNBC [28]. The results of a large case study including 1216 woman of Soweto, South Africa with breast cancer was compatible with the reported higher rate in African-American female; the number of TNBC was frequent in women between age 50–59 and was more common in African women rather than other ethnics' women [29]. In general, the epidemiological data reports that although TNBC is not limited to a particular age or ethnic group, but has a elevated frequency and contributes to poor survival in African women with cancer background; yet, further epidemiologic data is necessary to support these results. According to the studies, the most important factors associated with higher risk of TNBC comprise higher parity and the lack or short period of breastfeeding, obesity and susceptibility to DNA damage or mutations in BRCA1 and BRCA2 genes [30–32]. The immune microenvironment in the breast is affected by these factors, leading to adverse inflammation which cause cancer-related mutations or non-successful omission of mutated cells [33–35]. According to a meta-analysis of case-case and case control studies, women obesity is certainly linked with the TNBC likelihood comparing to non-obese women [32]. In addition, Gaudet et al. reported a non-significant direct association between Body Mass Index (BMI) and TNBC among women younger than 55 years in a participated analysis of potential researches [36]. Obesity is one of the important factors that lead to an increase in serum and tissue inflammatory cytokines such as IL6, IL8, and TNF-α which have role in activating several signaling pathways contributing to cell proliferation, metastasis, and invasion which are known as aggressive cancers' hallmarks, like TNBC [37,38]. Most of the evidence is from studies conducted in the United States, reporting a constructive link between higher parity and likelihood of TNBC, and a negative relation between breastfeeding extent and TNBC possibility. The population-based, case-control study indicated a notable trend between longer breastfeeding period and reduced chance of TNBC occurrence [39]. Shivani S et al. have showed that there is a direct correlation between higher parity and the absence or short period of breastfeeding with the risk of TNBC in women with invasive breast cancer. The incidence of TNBC risk in the absence or short duration of breastfeeding may be due to not undergoing terminal differentiation of progenitor cells in breast tissue, which usually occurs with long-term breastfeeding and leads to the continuous accumulation of progenitor cells that are susceptible to tumorigenesis [30]. It is noteworthy that one of the important factors that has a crucial role in the development of one of the TNBCs subset is deficiencies in double-stranded DNA repair, because of germline or somatic mutations in BRCA1 and other genes involved in HR [40]. In this regard, it has been indicated, germline mutations in BRCA1or BRCA 2 are related to nearly 20 % of TNBCs and somatic alterations that decrease these genes' activity which happens almost in 40 % of TNBCs [31,41]. In addition to mutations in BRCA1 or BRCA2 genes, other genes associated with DNA repair functions, including BARD1, PALB2, and RAD51D, have been investigated to enhance the risk of TNBC [42,43]. Interestingly, a limited number of highly recurrent mutated genes such as TP53 and PIK3CA have been shown in most TNBCs, suggesting their role in primary tumorigenesis [44,45].

3. Therapeutic approaches for TNBC

TNBC is one of the most aggressive cancers and due to its histochemical and molecular characteristics; most of the current treatment opportunities for it are limited. Chemotherapy has been reported as one of the main systemic treatment options for TNBC, although optimal chemotherapy regimens have not yet been established [46]. Differences in clinical outcomes report that TNBC subtypes respond differently to neoadjuvant therapy; a subset of TNBCs are more susceptible to chemotherapy, however, a large number show drug resistance or are intrinsically less sensitivity [47]. In the neoadjuvant and metastatic setting, platinum-based chemotherapy has been connected with enhanced levels of pathologic complete response (pCR),but no difference in overall survival (OS) was reported [48]. In the recently published create-x trial, after standard neoadjuvant chemotherapy including anthracycline, taxane, or both, the addition of adjuvant capecitabine therapy played an important role in prolonging disease-free survival (DFS) and OS [49]. Resistance to chemotherapy is an important obstacle to successful cancer therapy, especially in metastatic conditions, which accounts for 90 % of treatment failure [50]. Preclinical information reported that upregulation of ABC transporters, especially multidrug-resistant protein-1 (ABCC1/MRP1), breast cancer resistance protein (ABCG2/BCRP) and multidrug-resistant protein-8 (ABCC11/MRP8) considerably increase resistance to chemotherapy drugs that indicate the main part of popular TNBC treatment [51,52]. Fouzia Guestini et al. have indicated that downregulation of ABCG2 through the inhabitation of growth hormone receptor (GHR) significantly increased the sensitivity of TNBC cells to chemotherapy [53]. Accumulating data show that one of the main reasons for TNBC recurrence is chemotherapy-resistant cancer stem cells (CSCs) [54]. Inhibition of factors critical for CSCs maintenance has been proposed as a new therapeutic strategy to increase the sensitivity of TNBC cells to chemotherapy [55]. A study has shown that radiotherapy after surgery has a remarkable survival benefit for TNBC patients [56]. Studies show that

easy recurrence of TNBC indicates resistance to radiotherapy, which is associated with up- or down-regulation of multi gene-targets. the combination of zinc-finger ZRBA1 as a combined EGFR/DNA targeting molecule and radiation increases the radiation sensitivity by enhanced DNA damage, detained DNA repair procedure, and the blockade of EGFR in a TNBC model [57]. Up-regulation of The Maternal Embryonic Leucine Zipper Kinase (MILK) has been reported as the powerful forecaster of radio resistance and elevated local recurrence in TNBC compared with non-TNBC. It has also been indicated that knockdown of MELK induces radiosensitivity and significantly delays tumor growth both in vitro and in vivo in various models [58]. Immunotherapy is not beneficial to breast cancer patients due to modest tumor mutational burden (TMB), but a subset of TNBC with high TMB and high Tumor Infiltrating Lymphocytes (TILs), has offered a chance to the improvement of TNBC-targeting immunotherapies. The results obtained from clinical trials show that the inhibition of Immune checkpoint inhibitors (ICI) in TNBC, especially in metastatic setting, is almost promising. ICI-based combination therapies were the major treatment strategy; combining ICI with Poly (ADP-ribose) polymerase (PARP inhibitors), cancer vaccines or natural killer (NK) cells therapy has great potential to enhance clinical benefit in TNBC [59,60]. In particular, the existence of TILs in a subset of TNBC has boosted expectation for immunotherapy targeting the programmed death receptor 1 (PD-1) pathway, which is often employed by tumors to escape the immune response [61]. For instance, the combination therapy of PD1/PD-L1 blockades with chemotherapy (atezolizumab plus nab-paclitaxel) have indicated hopeful leads to metastatic and early-stage TNBC [62].

4. Exosomes biogenesis

Exosomes are nano-sized biovesicles that have received rising notice latterly. The exosomes existence in extracellular space was first observed in rat reticulocytes in 1983 [63,64]. Initially, exosomes were secreted from cells to have cellular waste or as a different method of reducing produced waste to protect cellular homeostasis. Moreover, recent data indicate that exosomes have a vital duty in intercellular communication, which is crucial in diverse cellular activity, such as signal transduction, immune response, antigen presentation [64–66]. Many cellular stages should be completed to release exsosomes, such as Intraluminal Vesicles (ILVs), then the cargoes (RNAs, proteins and lipids) are integrated into ILV, after that transport of Multivesicular Bodies (MVBs) to the plasma membrane to release exosomes in the extracellular space [67,68]. Cell-secreted exosomes are created by inside budding of the membrane and ILV creation inside the cell known as primary endosomes. Then, the cargoes fused into ILV through ESCRT-associated or ESCRT-free pathways to form late endosomal encompassing plenty ILVs known as MVBs [67–71]. During the next developmental stage, MVBs either can be delivered to the trans-Golgi network (TGN) for endosome recycling, subjected to degradation by lysosomes or pass through microtubules to merge with the plasma membrane and secrete exosomes by fusion with the cellular membrane with diverse key elements' assistance, such as Rab GTPases and SNARE complexes. Released exosomes are transferred to recipient cells through three different mechanisms; receptor-ligand interactions, direct membrane fusion, endocytosis [69,72]. According to multi-omics studies, exosomes have been considered as small type of the parental cell that own various types of biomolecules such as particular group of proteins, lipids and nucleic acids, which can be selectively taken up by neighboring cells and reprogramming the recipient cells upon their bioactive compound [73]. Exosomes are protein-rich that is relevant to cell penetration, invasion, and merging process, such as tetraspanins, MVB formation proteins such as (eg, Alix, TSG101), proteins that are involved in membrane transport and fusion such as (eg, annexins and Rab), major histocompatibility complex (MHC) proteins (eg, MHC I and MHC II), heat shock proteins (eg, Hsc70 and Hsc90) and cytoskeleton proteins (eg, myosin, actin and tubulin) [74,75]. In addition, exosomes carry various types of lipids, such as cholesterol, sphingomyelin, glycosphingolipid, phosphatidylserine, and ceramide playing a key role in sustaining exosome biogenesis, morphology, and homeostasis regulation in recipient cells [76,77]. Interestingly, exosomes also contain different patterns of nucleic acids including mRNAs and non-coding RNAs such as miRNAs, lncRNAs, circRNAs, ribosomal RNAs (rRNAs) [78–80]. Due to their special characteristics, exosomes are of great biological importance as non-invasive diagnostic biomarkers and therapeutic nanocarriers. It is noteworthy that cancer cells-induced exosomes have a positive associate with tumor progression through increase angiogenesis, adjust the immune system and alter the surrounding parenchymal tissue [81]. In addition, several miRNAs are identified in human peripheral blood micro vesicles proving that cell-free miRNAs are shielded by the extracellular vesicle membrane [82]. Following that, several researches explored exosomal miRNAs as new biosignature for diagnostic and prognostic assessment of cancer cases [83]. On account of the shielding role of exosomes, exosomal miRNAs are safe in blood and body liquids, declaring them as perfect nominee markers for invasive tumors such as breast cancer [84].

5. Exsomal miRNAs in the pathogenesis of cancers

For the first time, miRNAs existence in exosomes was confirmed by Vladi et al. in 2007, suggesting that exosomes carry miRNAs to be delivered to recipient cells and show the relevant useful parts [80]. miRNAs have gained attention because of their modulatory role in gene expression. Growing evidence shows that exosomes, in addition to their function in various physiological events, also play a role in a series of biological functions in tumor occurrence and development. The existence of extracellular microRNAs in the tumor microenvironment (TME) positively affect cancer cells, immune cells, endothelial cells, fibroblasts, and others proceeding to impair the host immune system and leads to the stimulation of metastatic and angiogenic procedures [85–87]. Tumor-derived exosomal miRNAs may could advance cancer development through stimulating of diverse malignant transformation such as angiogenesis, a critical aspect of tumor metastasis. Yi Liu et al. have indicated that exosomal miR-21 produced by altered lung cancer cells, leads to increased angiogenesis via a STAT3-related system, which induces vascular endothelial growth factor (VEGF) generation in recipient cells [88]. Exosomal miR-105, one of the primary detected exosomal miRNAs, which is released by metastatic breast cancer cells, productively destructs tight junctions and the integrity of natural obstacles against metastasis and causes metastasis and vascular permeability in distant organs through targeting ZO-1, a crucial endothelial cell tight junction protein [89]. Exosomal miR-181c improved and released via brain metastatic TNBC cells in vivo, triggers the breakdown of blood–brain barrier (BBB) via reducing 3-phosphoinositide-dependent protein kinase-1 (PDPK1) expression, which causes brain metastasis [90]. It is revealed that high exosomal miR-122 levels facilitates metastasis by suppressing glucose uptake through niche cells by downregulated PKM, a glycolytic pyruvate kinase, and elevating nutrient availability in the premetastatic niche in TNBC cells [91]. Also, lack of X-inactive specific transcript (XIST), a lncRNA, enhances exosomal miR-503 release which stimulates M1 to M2 polarization of microglia through manipulating STAT3 and NFκB pathways. These exosomal miRNAs have been recognized as crucial elements of breast cancer brain metastasis (BCBM) which increasing PD-L1 expression to block local immunity and thereby increasing tumor growth [92]. In particular, miR-20a-5p transported from breast cancer cell-derived exosomes may promote proliferation and migration in TNBC cells and facilitated the osteoclastogenesis via targeting SRCIN1, a Src protein kinase plays a role in modulation of the cell migration [93]. Exosomal miR-210 produced from metastatic cancer cells was involved in interfering elevated angiogenesis from TNBC cells by inhibiting the level of specific target genes [94]. MTN Le et al., have also reported that exosome-secreted miR-200 from metastatic murine and human breast cancer cell lines can modify nonmetastatic cells to develop metastasis [95]. In this regard, exosomal miR-10b derived from

TNBC cells will be absorbed via not-cancerous epithelial breast cells to aid their cell invasion by targeting HOXD10, related to the homeobox protein family [96]. Also, exosomal miR-1246 isolated from TNBC indicated to increase the viability, migration and chemotherapy resistance of not-cancerous cells by targeting CCNG2, an chief cyclin-associated protein kinase [97]. Exosomal miR-1910–3p engaged in development of breast cancer by increasing the propagation and migration in TNBC and ER- and PR-positive breast cancer cells in vitro and in vivo. Moreover, this extensive study indicated exosomal miR-1910–3p decreased myotubularin related protein 3 (MTMR3), triggered the NF-κB signaling pathway and prevented apoptosis [98]. Interestingly, cancer-related lymphatic vessels as a pathway of tumor circulation ease cancer cells spreading in tumor development via three exosomal miRNAs (miR-503–3p, −4269, and 30e-3p) in TNBC cells [99]. The obtained results indicated that exosomal miRNAs may have pivotal roles in controlling tumorigenic transformation, however, additional examination to these parts is essential.

6. Prognostic and diagnostic values of exosomal miRNAs

Although the exact primary molecular mechanisms for packaging of miRNAs in exosomes are not yet fully realized, previous investigation have indicated that exosomal miRNAs could be useful as diagnostic biomarkers of cancer. The up- and down-regulation of exosomal miRNAs has been confirmed in BC cells compared to healthy cells (Fig. 1). In this regard, an extensive study reported that exosomal miRNAs were remarkably relate to clinicopathological and risk factors. They delved into a large group encompassing 435 BC subjects for particular exosomal miRNAs levels and discovered adjusted expression patterns for some of them. A significant up-regulation of exosomal miR-27b and exosomal miR-433 in TNBC subtypes were indicated. Interestingly, the enhanced occurrence of miR-335 and the upregulation of exosomal miR-376c and exosomal miR-382 were indicated in TNBC cases. Their comprehensive data reported the potential of several exosomal miRNAs for TNBC diagnosis [21]. Eichelser reported that circulating (but cell-free) exosomal miR-373 levels were elevated in TNBC than in the luminal subtypes. Elevated level of exosomal miR-373 correlated with downregulated of estrogen receptor (ER) and suppression of camptothecin-induced apoptosis, which is used in cancer chemotherapy. It has also been indicated that serum levels of exosomal miR-373 as new biomarkers are related to TNBC and invasiveness of breast cancer cells [100]. EV-based studies identified miRNA-134 to be both as a biomarker for TNBC and as a potential therapeutic option, inhibiting cell migration and causing resistance to anti-Hsp90 drugs [101]. Another investigation revealed next exosomal miRNA, known as miR-939, which led to downregulation of VE-cadherin in endothelial cells, which was connected to poor prognosis in TNBC sufferers [102]. In addition, different expression levels of several exosomal miRNAs were detected in 27 BC patients and 3 healthy controls. It has been observed that 54 exosomal miRNAs were distinctly expressed in TNBC cases, comprising 20 elevated levels of miRNAs and 34 reduced levels of miRNAs. Some exosomal miRNAs were found to have hopeful prognostic importance as biomarkers for identifying recurrent from non-recurrent breast cancer, which may be used for preventive strategies. In addition to their

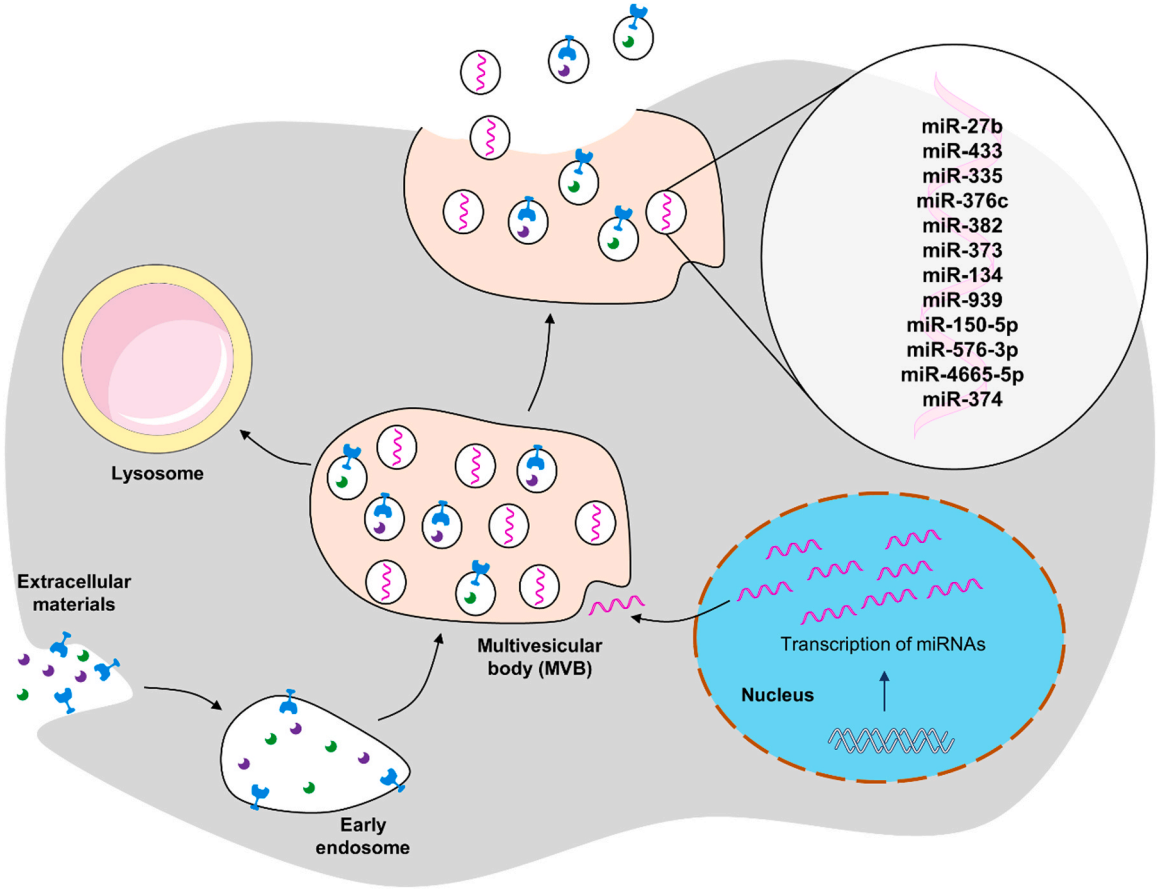

Fig. 1. Schematic illustration of the biogenesis of exosomes-carrying miRNAs. In the nucleus, miRNA genes are transcribed by RNA polymerase II to form mature miRNAs. Mature miRNAs are incorporated into the RNA-induced silencing complex (RISC) and are able to bind to their target mRNAs, leading to their degradation or translational repression. Exosomes are formed in the endosomal compartment of the cell, where intraluminal vesicles (ILVs) are formed by inward budding of the endosomal membrane. MVBs containing ILVs can either fuse with lysosomes for degradation or be secreted from the cell as exosomes. Exosomes are then taken up by recipient cells, where they can transfer their cargo, including miRNAs, to regulate gene expression.

diagnostic significance, prognostic exosomal miRNAs are capable of anticipating recurrence in TNBC patients. In this regard, the up-regulated of miR-150–5p, miR-576–3p, miR-4665–5p were indicated to identify recurrent from non-recurrent TNBC [103]. Moreover, exosomal miR-374 rate were connected to larger tumor size in TNBC patient [21]. These results put forward that exosomal miRNAs can be considered as potential biomarkers for TNBC.

7. Exosomal MicroRNAs as cancer therapeutics

miRNAs play a crucial role in tumor progression, which is why therapeutic miRNAs are considered for FDA approval [104–106]. miRNAs can offer desired clinical usage, none of miRNA drugs have progressed to phase III clinical trials, as several phase II trials were ceased ahead of schedule because of severe side effects. Similar to traditional systemic drugs, miRNAs can be enveloped in liposomes, nanoparticles, and micelles; transferring these miRNAs as influential effector molecules may cause serious side effects without precise potent target [106,107]. Despite the response to initial treatments in primary breast tumors, after months, the tumors show strong resistance to initial treatments. Therefore, to control this resistance, exosomal miRNAs and exosomes carrying other molecular cargoes have been proposed be examined [108]. For instance, Mingli Han et al. have proved that miR-567 delivery via exosomes decrease the resistance of breast cancer cells to trastuzumab. In this regard, exosome-mediated miR-567 was tested against HER2-enriched that played a key role in reversing trastuzumab resistance via directly targets autophagy-related 5 (ATG5), a vital protein for autophagy implementation, which is associated with carcinogenesis [109]. Moreover, shikonin is a naphthoquinone derived from the conventional Chinese medicine, inhibits MCF-7 development through the inhibition of exosome secretion. The exosomes targeted by shikonin contained miR-128, which downregulates Bax expression level in MCF-7 receiver cells and prevents cell proliferation [110]. Studies reveal that exosomes are involved in drug resistance. In this regard, it has been shown that miR-222 secreted by exosomes of breast cancer cells leads to increased resistance to adriamycin while cancer cells transfected with miR-222 suppressors lost resistance [111]. Interestingly, the crucial exosomal component miR-221/222 enhances tamoxifen resistance in recipient ER-positive breast cancer cells through the downregulating p27 and ERα [112]. Exosomal miR-100 restricted angiogenesis via regulating the mTOR/HIF-1α/VEGF signaling axis in breast cancer cells in vitro [113]. The studies show that exosomal miRNAs' level reduced in breast cancer cells. It is also indicated that loss of exosomal miR134 in cells correlates with enhanced cellular aggressiveness while upregulation of exosomal miR-134 remarkably restricted TNBC cell proliferation, cellular migration and invasion and elevated cisplatin-triggered apoptosis through inhibiting STAT5B to decrease Hsp90 and Bcl-2 levels [101]. Overexpression of exosomal miR-770 in combination with doxorubicin restricted the chemo-resistance, invasion metastasis in TNBC cell lines through modulation of apoptosis and modification of EMT pathway and tumor microenvironment. This study showed that exsosomal miR-770, a promising tumor inhibitor, precisely reduces STMN1 level, a stathmin family phosphoprotein, which is known as a tumor inducer in many cancers [114]. miR159 and doxorubicin by targeting exosomal for TNBC treatment significantly decreased TCF7 and MYC expression in tumors and manifested better anticancer effects, with no sides effects; it was a potential anti-cancer combination therapy [115]. Exosomal miR-3182 remarkebly suppressed cell proliferation and migration and promoted apoptosis in TNBC cells by inhibiting mTOR and S6KB1 genes. This study suggested that exosomal miR-3182 could be crucial therapeutic element in TNBC therapy [113]. These studies help to deeply study exosomal miRNAs' function in BC metastasis, drug resistance and treatments progression based on exosomal miRNAs.

8. Drawbacks and future perspective

Despite the great progressions in exosomal miRNAs in cancer diagnosis and prognosis, some drawbacks and limitations should be overcomed before moving exosomal miRNAs to the clinical trials [116]. Firstly, isolation of tumor cell-derived exosome is a complex and difficult process because the body's biological fluids are enriched with exosomes with various origins. Secondly, despite the exosomal miRNAs isolation techniques, there is no standard protocol for exosome separation and identification because the purity and quality of exosomes depends to diverse procedures. Thirdly, most of the existing separation methods are complex and time-consuming and have disadvantageous; therefore, a reproducible, rapid and high-performance selective separation technique should be considered. Finally, the main problem that needs to be addressed is that several researches have conduct the analysis of exosomal miRNAs in small-scale sample, while large-scale studies are needed for desirable evaluation and verifying of the data. On the other hand, different types of BC have their own clinicopathological characteristics, therefore the use of exosomal miRNAs in the diagnosis, prognosis and prediction of the outcome of BC treatment may have uncertain feasible differences in different types of BC, especially TNBC. Further investigations may partially resolve the specificity problem by revealing exosomal miRNAs variation in all BC subtypes. Due to microarray and next-generation sequencing techniques, significant improvements reported in the investigation of exosomal miRNAs in TNBC cases. Such advances require skillful experts to examine complicated bioinformatics data. In this regard, they should have been used a broad group of patients. To improve the efficiency of exosomal miRNAs in TNBC diagnosis, it has been proposed to develop an in situ multi-miRNA simultaneous detection construct relying on a biosensor importation into exosomes and their hybridization with complementary miRNA targets before initiating the fluorescence signals. Using such biosensors' application in exosomal miRNAs recognition in serum samples can effectively specify TNBC cases and assist TNBC early diagnosis [117]. However, the potential of exosomal miRNAs in TNBC treatment goes beyond diagnosis. Future research in this area should explore novel strategies for leveraging exosomal miRNAs as a targeted therapeutic approach for TNBC patients. This could involve investigating the specific mechanisms through which exosomal miRNAs exert their effects on TNBC cells and tumor microenvironments. Moreover, optimizing the delivery of exosomal miRNA-based therapeutics to tumor sites and assessing their efficacy in preclinical and clinical settings will be essential steps in translating these findings into tangible treatments. Notably, it is necessary to observe the patient situation, disease stage, its specification and development, the suitable sampling size, and storage method, as well as exosome identification and examining techniques. Furthermore, it may offer an understandable diagnosis pattern and prognosis effect. Also, improvements in software background, professional investigation procedures, and bioinformatics can give hopeful insight. Not to mention that it is necessary to observe the patient situation, disease stage, its specification and development, the suitable sampling size, and storage method, as well as exosome identification and examining techniques. Furthermore, it may offer an understandable diagnosis pattern and prognosis effect. Also, improvements in software background, professional investigation procedures and bioinformatics can give hopeful insight. According to progresses in modern and delicate technologies, including next-generation sequencing, exosomal miRNAs recognition provides new and deeper understanding of advancement in therapeutic responses in breast cancer.

9. Conclusion

TNBC accounts for 15–20 % of BCs and also for an excessive number of BC-related death. The poor results are consistent with the innate aggressiveness of TNBC, which is enhanced because of not having enough targeted therapies [118–121]. One of the important steps to

increase and improve the survival of cancer sufferers is early diagnosis. Despite extensive and promising advances, discovering precise biomarkers is also essential. According to extensive evidence, the role of miRNAs in nearly all kinds of cancer has been reported, and dysregulated expression of miRNAs have an important part in cancer origination, development, and metastasis [122]. Recently, microRNA (miRNA) profiling has been employed in an effort to detect TNBC subtypes and to discover biomarkers for TNBC therapy [123,124]. Exosomes are efficient and stable miRNA carriers found in body fluids. There are marked differences in exosomal miRNA expression patterns in TNBC cells compared to their normal counterparts. Exosomal miRNA has attracted more attention due to several important factors, which can be considered as a cancer biomarker [125]. Among the important factors is that miRNAs in cancer have great delicacy and specificity in diagnosis and because of the exosomes existence in many biological fluids, their accessibility is very high [126]. In this review, we highlighted an overview of exosomal miRNAs in TNBC. Specifically, we reviewed their crucial functions in tumorigenesis and tumor development, therapeutic applications of exosomal miRNAs and potential biomarkers value of exosomal miRNAs. In this regard, it has been noted that exosomal miRNAs were highly enhanced in TNBC, leading to proliferation and migration in TNBC cells and facilitated angiogenesis, including miR-21, miR-105, miR-181c, miR-122, miR-503, miR-20a-5p, miR-210, miR-200, miR-10b, miR-1246 and miR-1910–3p. Moreover, the upregulation of exosomal miRNAs has been confirmed in TNBC cells compared to healthy cells and be considered as potential biomarkers for TNBC, including miR-27b, miR-433, miR-335, miR-376c, miR-382, miR-373 and miRNA-134. It is noteworthy that exosomal miRNAs in combination with chemotherapy drugs or alone play a key role in limiting chemo-resistance, invasion metastasis, including miR-567, miR-128, miR-100, miR-503, miR-770, miR-770, miR159. Overall, it is expected that further investigation on exosomal miRNAs will open a new insight on non-invasive cancer diagnosis and create an opportunity for future research using these potential biomarkers. Exosomal miRNA-associated responses approves of further investigation in TNBC as the findings may provide countless opportunities for targeted breast cancer therapies in the future.

Compliance with ethical standards

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

No data was used for this study.

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Parts of the figure were drawn by using pictures from Servier Medical Art. Servier Medical Art by Servier is licensed under a Creative Commons Attribution 3.0 Unported License (https://creativecommons.org/licenses/by/3.0/).

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