Applications of Exosomes in Breast Cancer

Subjects: Oncology

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Breast cancer (BC) is the most common type of malignancy which covers almost one-fourth of all the cancers diagnosed in women. Conventionally, chemo-, hormonal-, immune-, surgery, and radiotherapy are the clinically available therapies for BC. However, toxicity and other related adverse effects are still the major challenges. A variety of nanoplatforms have been reported to overcome these limitations, among them, exosomes provide a versatile platform not only for the diagnosis but also as a delivery vehicle for drugs. Exosomes are biological nanovesicles made up of a lipidic bilayer and known for cell-to-cell communication. Exosomes have been reported to be present in almost all bodily fluids, viz., blood, milk, urine, saliva, pancreatic juice, bile, peritoneal, and cerebrospinal fluid.

Keywords: exosomes ; breast cancer ; diagnosis ; drug delivery ; chemotherapy

1. Biomarkers

Exosomes play a crucial role in intracellular communication by directly binding with surface receptors or transferring their contents to another cell [1]. The presence of exosomal RNA was embroiled as proof for the horizontal transfer of genetic information between different cell types [2]. Valenti et al., 2006 and Whiteside et al., 2013 demonstrated that exosomes can transfer cellular RNA as well as miRNA which indicated that the tumor exosomes showed some functional effects including the suppression of the mRNA which codes for signal transduction components within the T-cell [3][4]. Exosomes secreted from cancer cells show a higher number of RNA due to the higher production of mRNA and miRNA and thus the miRNA may reflect the parental tumor signature. As a result, miRNA expression profiling could be used as a biomarker in diseases, including some cancers specifically in those cancers that lack specific molecular biomarkers.

Baroni et al., 2016 observed that cancer cell-secreted miR-9 could be carried by the exosomes to the healthy fibroblast cells, and thus the uptake of miR-9 can convert the healthy fibroblast into cancer-associated cells, which further lead to increased cell mortality of breast cancer cells [5]. Recently, Shen, et al., 2021 observed elevated levels of exosomal miR-7641 by using qRT-PCR and microarray in the plasma of patients suffering from breast cancer, which is considered a potential diagnostic marker in breast cancer. They further demonstrated that the elevated levels of exosomal miR-7641 could promote tumor growth in vivo [6]. In another study, Hannafon et al., 2016 observed an elevated level of exosomal miR-21 and miR-1246 in plasma of breast cancer patients. This identification indicated their potential as a biomarker in breast cancer [7]. The higher levels of miRNA in breast cancer patients also represented chemo resistance. To confirm this, Liu et al., 2021 isolated exosomes from MCF-7 cells which contained miR-9-5p. It was observed that MCF-7/tamoxifen caused miR-9-5p inhibited apoptosis in cancer cells and increased the cell resistance to tamoxifen treatment [8].

Recently, Hirschfeld and co-workers performed a comparative study in 69 breast cancer patients vs. healthy humans. From the study, four highly expressed urine biomarkers (miR-424, miR-423, miR-660, and let7-i) were identified in breast cancer patients, which represented 100% specificity and 98.6% sensitivity [9]. The high levels of long non-codingRNAs (lncRNA) and non-protein coding RNA (DANCR) are considered potential biomarkers in breast cancer. Shi et al., 2022 have discovered an elevated level of both lncRNA and DANCR in breast cancer patients as compared to healthy patients. An analysis in a large group of BC patients is needed to further confirm the role of serum level of exo-lncRNA and DANCR [10]. Apart from the biological investigation Liu et al., 2021 performed a comprehensive bioinformatics analysis to discover the highly expressed miRNA by gene expression omnibus. It was observed that the exosomes, tissues, and cells showed upregulated levels of miR-21-5p. Furthermore, from the characteristic analysis, it was also confirmed that miR-21-5p could be effectively differentiated in BC patients and healthy people with 87.7 sensitivity and 93.3% specificity [11].

Exosomal miRNA was also identified in serum, plasma of breast cancer patients, and in vitro cell culture that potentially helped in the early detection of breast cancer. Nevertheless, the physiognomies of circulating tumor cells and cell-free DNA (cf-DNA) related to cancer cell DNA are still unclear as compared to exosomal tumor biopsies. Additionally, cf-DNAs carry mutations distinctively of the consistent tumor cells. However, the clearance of circulating DNA is usually observed in

the kidney or liver, indicating the steadiness and pathogenicity of circulating DNA. Therefore, further investigation is indispensable to discover the most targeted and promising set of miRNAs which is highly correlated with solid tumor RNA.

2. Drug Delivery in Breast Cancer

Exosomal drug delivery gained a lot of interest over the past decades because of the various advantages, *viz.,* biocompatibility, low toxicity, high stability, long-circulating half-life, and tissue targetability. In addition to being natural in origin, they can also be used to deliver both hydrophilic and hydrophobic small molecules and macromolecules such as nucleic acids and proteins.

2.1. Exosomal Delivery of Small Molecules

Exosomes have been used as a drug delivery system for the delivery of several small molecules of both hydrophilic and hydrophobic nature. In several cases, exosomal delivery leads to a higher accumulation of drugs at targeted sites. Exosomal delivery also improves the stability of small molecules and increases their stay in systemic circulation which further improves the pharmacokinetics and thus the therapeutic efficacy. In the previous studies, here were able to deliver different natural and synthetic compounds such as withaferin A, anthocyanidins, curcumin, paclitaxel, and docetaxel using cow milk-derived exosomes [12][13][14][15][16]. The drug loading was completed using simple incubation which also showed a sustained release profile over time. It was also observed that the exosomes loaded with withaferin A and paclitaxel exhibited lower IC_{50} values as compared to free drugs in MDA-MB-231 breast cancer cells. In addition, exosomes also demonstrated improved anti-tumor activity of tested compounds in vivo in tumor-bearing mice. Exosomes loaded with withaferin A exhibited a significantly higher inhibitory effect on tumors as compared to free withaferin A [13]. In previous work, here have also successfully formulated paclitaxel-loaded exosomes derived from bovine milk to treat lung cancer. The paclitaxel-loaded exosomes showed significantly higher tumor inhibition in comparison with free paclitaxel in a xenograft model. Additionally, in comparison with free paclitaxel, the paclitaxel-loaded exosomes exhibited remarkably lower systemic and immunogenic toxicities [12]. Toffoli et al., 2015 delivered doxorubicin by using exosomes that were derived from MDA-MB-231 and HCT-116 cell lines. However, in both in vitro and in vivo studies, the exosomal doxorubicin showed the same effect as free doxorubicin but the cardiac toxicity was found to be reduced by exosomal doxorubicin compared to free doxorubicin [17]. On other hand, exosomal delivery of chemotherapeutic agents has improved the ferroptosis in TNBC [18]. Yu et al., 2019 successfully delivered erastin loaded exosomes into MDA-MB-231 cells, however, the surface-modified exosomes with folate have shown more cellular uptake as compared to unmodified erastin loaded exosomes [18].

2.2. Exosomal Delivery of Biologics

“Mother Nature” has beautifully loaded a variety of miRNA and other biologics into the exosomes and they are believed to deliver this cargo to the recipient cells. This information ignited the scientific community to explore if the exogenous genetic material/biologics can also be loaded and successfully delivered to the cells to have the desired therapeutic efficacy in different disease conditions. Many successful reports came into the public domain which confirmed the successful loading and then gene silencing by using milk exosomes from different sources, including bovine raw milk. Among the different genetic materials, siRNA is a class of double-stranded RNAs that could regulate the expression of specific genes by causing mRNA excision or restraining mRNA translation. However, siRNAs are not therapeutically stable and tend to degrade quickly while in the systemic circulation, which makes it very difficult to deliver these siRNAs to the target cell. There is siKRAS loaded into milk-derived exosomes was protected from enzymatic degradation and able to inhibit the tumor growth in lung tumor xenografts [19]. Alvarez-Erviti et al., 2011 first delivered siRNA by using exosomes as a delivery vehicle. In this study, they used the mouse dendritic cell-derived exosomes and loaded them with siRNA of the BACE1 gene [20]. Recently Munagala et al., 2021 successfully delivered wild-type p^{53} p^{DNA} to mice and H1299 cells. Interestingly they observed high expression of the P^{53} gene in vitro [21]. On the other hand, McAndrews et al., 2021 delivered CRISPR/Cas9 to target mutant $Kras^{G12D}$ to suppress the proliferation and inhibit tumor growth [22]. Similarly, Sheykhhasan et al., 2021 efficiently delivered miR-145 into breast cancer cells via exosomes to explore the role of miR-145 in metastasis and apoptosis. In this study, the mesenchymal stem cell-derived exosomes were used for loading miR-145. The exosomes showed enhanced inhibition of metastasis and increased apoptosis in breast cancer cells [23]. In a recent study, Xu et al., 2021 successfully delivered antisense oligonucleotide via exosomes to analyze their cellular uptake study in MDA-MB-231 and HepG2 cell lines. Antisense oligonucleotide-loaded exosomes showed enhanced HepG2 cell uptake as compared to the free oligonucleotide. It is worth mentioning that exosomes also possess an ability to bypass the blood-brain barrier (BBB), hence, exosomes can also be used to deliver entrapped therapeutic moieties to the CNS which may be a good opportunity to target the breast cancer metastasized to the brain [24]. In another study, Lee et al., 2011 overexpressed the major histocompatibility complex (MHC) class II protein in murine melanoma cell lines

(B16F1) by transduction of the CIITA (Class II transactivator) gene. The exosomes were then isolated from the MHC-II overexpressed B16F1 cell containing a large amount of MHC-II and tumor antigen TRP2. It was observed that this Exo-CIITA exhibited a significantly improved anti-tumor immune response through solenocyte proliferation and IL-2 secretion [25].

2.3. Exosome Modification for Targeted Drug Delivery for Breast Cancer

One of the drawbacks of exosomal delivery is that the naturally secreted exosomes in the body can freely move across the extracellular space and biofluids by free diffusion and are randomly internalized into accepter cells. For observing the biodistribution of exosomes, Wiklander et al., 2015 labeled exosomes with DiR dye. It was observed that the exosomes were accumulated in the liver, spleen, kidney, pancreas, and other organs administrated by tail vein which indicated uncontrolled biodistribution of exosomes in vivo [26]. Thus, it was inferred that the delivery of the exosome-loaded drugs to specific targets may require some surface modifications. The modifications are performed in three ways: (1) ligand-receptor binding-based targeted delivery, (2) pH gradient/surface charge-driven targeted delivery and (3) magnetism-guided targeted delivery.

2.3.1. Ligand-Receptor Binding-Based Targeted Delivery

The ligand-receptor binding-based targeted delivery is the most widely reported targeting strategy in which a ligand is attached over the surface of exosomes that recognizes its specific receptor overexpressed on the targeted site or cell. Ligand-receptor binding-based targeted delivery has two types, namely (a) transfection-based ligand overexpression and (b) chemical assembling of ligand on the exosomal surface.

2.3.2. Transfection-Based Ligand Overexpression

Cancer cells are characterized by uncontrolled proliferation, migration, abnormal elevation of cellular metabolisms, and overexpression of certain kinds of proteins and receptors such as epidermal growth receptor factors (EGRF) [27]. Ohno et al., 2012 modified MDA-MB-231 cell lines to express the transmembrane domain (TD) of platelet-derived growth factor receptor (PDGFR) by fusing with the GE11 peptide. PDGFR-TD enhances the expression of GE11 peptide on the surface of the exosome which binds specially to overexpressed EGFR. Afterward, Luciferase-expressing HCC70 cells were transplanted into the mammary fat pads of RAG2–/– mice and the GE11 expressed exosomes loaded with let-7a and labeled with DiR dye were administrated systemically to the RAG2–/– mice. After 24 h of incubation, a large number of accumulated exosomes were observed in the spleen and liver [28]. Based on this study, various other studies were performed to target the exosomes over other overexpressed moieties such as Lamp2b and phosphatidylserine [29][30].

2.3.3. Chemical Assembling of Ligand on Exosomal Surface

Chemical modification is a method that directly places ligands either on the membrane of donor cells or on the surface of the exosomes by using chemical interactions. Functionalization by using covalent bond was supposed to be stable until the functionalized exosomes reached the target site. In line with the hypothesis, it was observed that the folic acid-modified exosomes showed a significant reduction in tumor size as well as immunotoxicity as compared to non-targeted exosomes and available marketed paclitaxel formulation [31]. Wang et al., 2017 first labeled the donor cell membrane chemically with biotin and then labeled exosomes with avidin. Exosomes were then isolated by microfluidic devices and loaded with doxorubicin. These dual targets showed strong targeting abilities towards the liver cancer model [32]. Recently, Li et al., 2020 delivered hyaluronic acid coupled doxorubicin exosomes to CD-44 overexpressed tumor cells, as hyaluronic acid acts as a specific ligand of CD-44 receptor [33].

2.3.4. pH Gradient/Surface Charge-Driven Targeted Delivery

The specific physicochemical properties of different tissues and cells play an important role in targeting the exosomes. For example, increased intracellular glycolysis and lactate production creates an acidic environment around the tumors which makes the pH-responsive medication prominent in targeting the tumors. Kim et al., 2018 successfully delivered doxorubicin loaded in i-motif-modified (i-motif-bio) exosomes by using a pH gradient. Interestingly, da-i-motif-bio was efficiently released in acidic pH within one hour [34]. On the other hand, Zhang et al., 2020 prepared doxorubicin-loaded exosomes which were further conjugated with a moiety having a pH cleavage bond that undergoes cleavage in acidic conditions. Moreover, endoperoxides and chlorin e6 (Ce6) were also loaded where the endoperoxides undergo thermal cycloreversion and release singlet oxygen that kills the cancer cells in squamous cell carcinoma [35].

2.3.5. Magnetism-Guided Targeted Delivery

Apart from techniques that use the physicochemical and biological characteristics of specific tissue or cells, targeted drug delivery can be accomplished with the help of some external magnetic forces. Qi et al., 2016 developed a dual-functional exosome-based superparamagnetic nanoparticle cluster to obtain a targeted drug delivery vehicle for cancer therapy. Engineered exosomes exhibit a strong response to an external magnetic field, which enables the exosomes to become separated from the blood and target the cancer cells. In vivo examinations further showed that the exosomes have an attractive capacity to deliver doxorubicin to malignant cells to suppress their further progression [36].

Exosomes served as a natural and novel drug delivery system that can deliver potent anticancer drugs to target tumors. Nevertheless, administering exosomes as a drug delivery system may present a certain disadvantage, because exosomes loaded with protein, miRNA, and nucleic acids may provoke the transformation of healthy cells to cancer-associated cells, thereby leading to tumor development. Therefore, further studies should be concentrating on exact loading mechanisms to exosomes, discovering novel loading methods and isolation methods to produce a large number of exosomes for industrial applicability, and novel technology for delivering exosomes to treat various diseases, including breast cancer, without causing any pharmacological adverse effects and toxic effects caused by endogenous and exogenous exosomes.

References

1. Camussi, G.; Deregibus, M.C.; Bruno, S.; Cantaluppi, V.; Biancone, L. Exosomes/microvesicles as a mechanism of cell-to-cell communication. Kidney Int. 2010, 78, 838–848.
2. Yuan, A.; Farber, E.L.; Rapoport, A.L.; Tejada, D.; Deniskin, R.; Akhmedov, N.B.; Farber, D.B. Transfer of microRNAs by embryonic stem cell microvesicles. PLoS ONE 2009, 4, e4722.
3. Valenti, R.; Huber, V.; Filipazzi, P.; Pilla, L.; Sovena, G.; Villa, A.; Corbelli, A.; Fais, S.; Parmiani, G.; Rivoltini, L. Human Tumor-Released Microvesicles Promote the Differentiation of Myeloid Cells with Transforming Growth Factor-B–Mediated Suppressive Activity on T Lymphocytes. Cancer Res. 2006, 66, 9290–9298.
4. Whiteside, T.L. Immune modulation of T-cell and NK (natural killer) cell activities by TEXs (tumour-derived exosomes). Biochem. Soc. Trans. 2013, 41, 245–251.
5. Baroni, S.; Romero-Cordoba, S.; Plantamura, I.; Dugo, M.; D'ippolito, E.; Cataldo, A.; Cosentino, G.; Angeloni, V.; Rossini, A.; Daidone, M. Exosome-mediated delivery of miR-9 induces cancer-associated fibroblast-like properties in human breast fibroblasts. Cell Death Dis. 2016, 7, e2312.
6. Shen, S.; Song, Y.; Zhao, B.; Xu, Y.; Ren, X.; Zhou, Y.; Sun, Q. Cancer-derived exosomal miR-7641 promotes breast cancer progression and metastasis. Cell Commun. Signal. 2021, 19, 1–13.
7. Hannafon, B.N.; Trigoso, Y.D.; Calloway, C.L.; Zhao, Y.D.; Lum, D.H.; Welm, A.L.; Zhao, Z.J.; Blick, K.E.; Dooley, W.C.; Ding, W. Plasma exosome microRNAs are indicative of breast cancer. Breast Cancer Res. 2016, 18, 1–14.
8. Liu, J.; Zhu, S.; Tang, W.; Huang, Q.; Mei, Y.; Yang, H. Exosomes from tamoxifen-resistant breast cancer cells transmit drug resistance partly by delivering miR-9-5p. Cancer Cell Int. 2021, 21, 1–15.
9. Hirschfeld, M.; Rücker, G.; Weiß, D.; Berner, K.; Ritter, A.; Jäger, M.; Erbes, T. Urinary exosomal microRNAs as potential non-invasive biomarkers in breast cancer detection. Mol. Diagn. Ther. 2020, 24, 215–232.
10. Shi, W.; Jin, X.; Wang, Y.; Zhang, Q.; Yang, L. High serum exosomal long non-coding RNA DANCR expression confers poor prognosis in patients with breast cancer. J. Clin. Lab. Anal. 2022, e24186.
11. Liu, M.; Mo, F.; Song, X.; He, Y.; Yuan, Y.; Yan, J.; Yang, Y.; Huang, J.; Zhang, S. Exosomal hsa-miR-21-5p is a biomarker for breast cancer diagnosis. PeerJ 2021, 9, e12147.
12. Agrawal, A.K.; Aqil, F.; Jeyabalan, J.; Spencer, W.A.; Beck, J.; Gachuki, B.W.; Alhakeem, S.S.; Oben, K.; Munagala, R.; Bondada, S. Milk-derived exosomes for oral delivery of paclitaxel. Nanomed. Nanotechnol. Biol. Med. 2017, 13, 1627–1636.
13. Munagala, R.; Aqil, F.; Jeyabalan, J.; Gupta, R.C. Bovine milk-derived exosomes for drug delivery. Cancer Lett. 2016, 371, 48–61.
14. Aqil, F.; Kausar, H.; Agrawal, A.K.; Jeyabalan, J.; Kyakulaga, A.-H.; Munagala, R.; Gupta, R. Exosomal formulation enhances therapeutic response of celastrol against lung cancer. Exp. Mol. Pathol. 2016, 101, 12–21.
15. Aqil, F.; Munagala, R.; Jeyabalan, J.; Agrawal, A.K.; Gupta, R. Exosomes for the enhanced tissue bioavailability and efficacy of curcumin. AAPS J. 2017, 19, 1691–1702.
16. Munagala, R.; Aqil, F.; Jeyabalan, J.; Agrawal, A.K.; Mudd, A.M.; Kyakulaga, A.H.; Singh, I.P.; Vadhanam, M.V.; Gupta, R.C. Exosomal formulation of anthocyanidins against multiple cancer types. Cancer Lett. 2017, 393, 94–102.

17. Toffoli, G.; Hadla, M.; Corona, G.; Caligiuri, I.; Palazzolo, S.; Semeraro, S.; Gamini, A.; Canzonieri, V.; Rizzolio, F. Exosomal doxorubicin reduces the cardiac toxicity of doxorubicin. Nanomedicine 2015, 10, 2963–2971.
18. Yu, M.; Gai, C.; Li, Z.; Ding, D.; Zheng, J.; Zhang, W.; Lv, S.; Li, W. Targeted exosome-encapsulated erastin induced ferroptosis in triple negative breast cancer cells. Cancer Sci. 2019, 110, 3173–3182.
19. Aqil, F.; Munagala, R.; Jeyabalan, J.; Agrawal, A.K.; Kyakulaga, A.-H.; Wilcher, S.A.; Gupta, R.C. Milk exosomes-Natural nanoparticles for siRNA delivery. Cancer Lett. 2019, 449, 186–195.
20. Alvarez-Erviti, L.; Seow, Y.; Yin, H.; Betts, C.; Lakhal, S.; Wood, M.J. Delivery of siRNA to the mouse brain by systemic injection of targeted exosomes. Nat. Biotechnol. 2011, 29, 341–345.
21. Munagala, R.; Aqil, F.; Jeyabalan, J.; Kandimalla, R.; Wallen, M.; Tyagi, N.; Wilcher, S.; Yan, J.; Schultz, D.J.; Spencer, W. Exosome-mediated delivery of RNA and DNA for gene therapy. Cancer Lett. 2021, 505, 58–72.
22. McAndrews, K.M.; Xiao, F.; Chronopoulos, A.; LeBleu, V.S.; Kugeratski, F.G.; Kalluri, R. Exosome-mediated delivery of CRISPR/Cas9 for targeting of oncogenic KrasG12D in pancreatic cancer. Life Sci. Alliance 2021, 4.
23. Sheykhhasan, M.; Kalhor, N.; Sheikholeslami, A.; Dolati, M.; Amini, E.; Fazaeli, H. Exosomes of mesenchymal stem cells as a proper vehicle for transfecting miR-145 into the breast cancer cell line and its effect on metastasis. BioMed Res. Int. 2021, 2021, 5516078.
24. Xu, H.; Liao, C.; Liang, S.; Ye, B.-C. A Novel Peptide-Equipped Exosomes Platform for Delivery of Antisense Oligonucleotides. ACS Appl. Mater. Interfaces 2021, 13, 10760–10767.
25. Lee, Y.S.; Kim, S.H.; Cho, J.A.; Kim, C.W. Introduction of the CIITA gene into tumor cells produces exosomes with enhanced anti-tumor effects. Exp. Mol. Med. 2011, 43, 281–290.
26. Wiklander, O.P.; Nordin, J.Z.; O'Loughlin, A.; Gustafsson, Y.; Corso, G.; Mäger, I.; Vader, P.; Lee, Y.; Sork, H.; Seow, Y. Extracellular vesicle in vivo biodistribution is determined by cell source, route of administration and targeting. J. Extracell. Vesicles 2015, 4, 26316.
27. Aaronson, S.A. Growth factors and cancer. Science 1991, 254, 1146–1153.
28. Ohno, S.-I.; Takanashi, M.; Sudo, K.; Ueda, S.; Ishikawa, A.; Matsuyama, N.; Fujita, K.; Mizutani, T.; Ohgi, T.; Ochiya, T. Systemically injected exosomes targeted to EGFR deliver antitumor microRNA to breast cancer cells. Mol. Ther. 2013, 21, 185–191.
29. Limoni, S.K.; Moghadam, M.F.; Moazzeni, S.M.; Gomari, H.; Salimi, F. Engineered exosomes for targeted transfer of siRNA to HER2 positive breast cancer cells. Appl. Biochem. Biotechnol. 2019, 187, 352–364.
30. Longatti, A.; Schindler, C.; Collinson, A.; Jenkinson, L.; Matthews, C.; Fitzpatrick, L.; Blundy, M.; Minter, R.; Vaughan, T.; Shaw, M. High affinity single-chain variable fragments are specific and versatile targeting motifs for extracellular vesicles. Nanoscale 2018, 10, 14230–14244.
31. Kandimalla, R.; Aqil, F.; Alhakeem, S.S.; Jeyabalan, J.; Tyagi, N.; Agrawal, A.; Yan, J.; Spencer, W.; Bondada, S.; Gupta, R.C. Targeted Oral Delivery of Paclitaxel Using Colostrum-Derived Exosomes. Cancers 2021, 13, 3700.
32. Wang, J.; Li, W.; Zhang, L.; Ban, L.; Chen, P.; Du, W.; Feng, X.; Liu, B.-F. Chemically edited exosomes with dual ligand purified by microfluidic device for active targeted drug delivery to tumor cells. ACS Appl. Mater. Interfaces 2017, 9, 27441–27452.
33. Li, D.; Yao, S.; Zhou, Z.; Shi, J.; Huang, Z.; Wu, Z. Hyaluronan decoration of milk exosomes directs tumor-specific delivery of doxorubicin. Carbohydr. Res. 2020, 493, 108032.
34. Kim, J.Y.; Song, J.; Jung, H.; Mok, H. I-motif-coated exosomes as a pH-sensitive carrier for anticancer drugs. Appl. Biol. Chem. 2018, 61, 599–606.
35. Zhang, Q.; Xiao, Q.; Yin, H.; Xia, C.; Pu, Y.; He, Z.; Hu, Q.; Wang, J.; Wang, Y. Milk-exosome based pH/light sensitive drug system to enhance anticancer activity against oral squamous cell carcinoma. RSC Adv. 2020, 10, 28314–28323.
36. Qi, H.; Liu, C.; Long, L.; Ren, Y.; Zhang, S.; Chang, X.; Qian, X.; Jia, H.; Zhao, J.; Sun, J. Blood exosomes endowed with magnetic and targeting properties for cancer therapy. ACS Nano 2016, 10, 3323–3333.