Research Article

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Exosome, is it a Benefit or Harm for Cancer?

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Summary

Exosomes are nanoparticles formed of plasma membrane that surround the genetic information in the form of miRNA. Exosomes provide a mean of cellular communication. Exosomes can affect the neighboring cells or transmitted to distant organs through body fluids. The function of exosomes depend on their origin. Cancer cell derived exosomes contain certain types of miRNA that enhance tumor initiation and metastasis. On the other side exosomes derived from another types of cell like dendritic cells or MSCs can be used for cancer treatment. Loading these types of exosomes with certain miRNA can inhibit tumor growth and increases the chemo sensitivity.

Keywords: Exosomes, miRNA, Cancer and MSCs

Introduction

Exosomes are 40–150-nm plasma membrane-coated vesicles that generate from many types of cells. Exosomes are composed of a lipid bilayer that surround the genetic information of the original cells in the form of RNA, and DNA. The exosomes are produced as a result of inward budding of the plasma membrane to form intracellular endosomes, then further invagination of the intracellular endosomes generates multivesicular bodies (MVBs) containing vesicles with a diameter of 40–150 nm. MVBs then either fuse with lysosomes for degradation of their contents or fuse with the plasma membrane, releasing their contents into the extracellular space in the form of exosomes in a process involving the endosomal sorting complexes required for transport complexes (ESCRT complex) [1].

The biological effects of the exosomes are due to their miRNA content. miRNA are small non-coding RNAs (20–30 nucleotides) that can regulate gene expression. It is believed that selected miRNAs are present within exosomes micro vesicles and in the cells of origin, also some miRNAs are present in the MVs while not detected in the donor cells however, others were present in the cells but not in the MVs. These suggest the presence of a mechanism that controls the sorting of miRNAs within the exosomes. Specific miRNAs are produced only for the purpose of cell–cell communication without inducing a regulatory function in the donor cell [2].

Thus exosomes are an important intercellular communication vehicle, they can affect the neighboring cells or carried by body fluid to distant sites to mediate multiple cellular processes [3]. Furthermore exosomes can be considered an ideal vehicles to protect and deliver molecules to the specific targets due to its nanometer-size, by encapsulating molecules such as enzymes or RNAs within their membranes, exosomes protect them against degradation and facilitate their intracellular uptake via the cellular endocytosis of exosomes [4]. Exosomes circulate for prolonged time periods within the body, it can resist phagocytosis and degradation by macrophages and lysosomal breakdown [5]. Exosomes uptake are favored by acidotic microenvironment, thus exosomes preferentially taken up by cells in injured tissues, as tissue injury is often characterized by tissue acidosis [6]. Exosomes can pass the blood–brain barrier, which is highly impenetrable to many drugs and easily escape from lung clearance [7].

The biological effect of the exosomes depend on nature of the donor cells, cancer cell form excessive amount of exosomes that support cancer development and progression. The immune system can recognize any abnormal or foreign cells and destroy them, however cancer cell secreted exosomes create a state of immune suppression through inhibition of NK cell proliferation and its cytotoxic functions. NKG2D ligand-containing exosomes derived from cancerous cells interact directly with NK cells, leading to a significant reduction in NKG2D expression, resulting in significant defects of NK effector functions together with inhibition of NK cell proliferation [8]. Furthermore, cancer cell derived exosomes express FasL molecule on their surface. After binding of the Fas ligand with the Fas receptor on activated immune cells, the cells trigger apoptosis [9].

Cancer exosomes help tumor progression and metastasis by modulating ECM, through activation of several proteases as MMP by release of HSP90α, in addition such exosomes induce TGF-β1 causing differentiation of fibroblasts into myofibroblasts wich induce the Wnt-PCP signaling pathway, resulting in increased motility and invasiveness of cancer cells [10,11].

Tumor cell proliferation creates a state of local hypoxia, the exosomal protein analysis indicates increased levels of transcripts and proteins including IL-8, VEGF, which are crucial for vessel formation. Also, it was believed that a hypoxic condition increased the ability of cancer

cells to migrate by upregulation of proteins such as IGFB1 and IGFB3 in exosomes. Moreover, increased levels of IL-8, caveolin 1 (CAV1), MMP9 and PDGF in exosomes can be potentially used as an exosomal marker of hypoxia in glioblastoma cancer patients, which is crucial for follow up the effectiveness of therapy.

Exosomes secreted by stromal cells also contribute to tumor drug resistance. BM-MSC-derived exosomes induce multiple myeloma cells resistant to bortezomib through the activation of several survival relevant pathways [12]. Multiple theories suggest that targeting specific functions of exosomes could enhance response to therapies. Exosomes carry a certain types of miRs that transfer a resistance phenotype to sensitive cancer cells by altering cell cycle control and inducing antiapoptosis programs. Removal of these exosomes limits invasive features of cancer cells in addition, removal of HER-2+ exosomes from the blood of patients with HER-2–overexpressing breast cancers improves patient responses to trasuzumab [13].

Since Tumors are formed from heterogeneous populations of cells. This leads to variability in sensitivity and resistance to applied treatment. It was demonstrated that chemo resistant cancer cell can affect the chemosensitive cells when they cocultered together through secretion of exosomes containing miRNAs which involved in the horizontal transfer of chemo-resistance such as (miR-100, miR-222, miR-30a and miR-17) [14].

On the other hand, Tumor irradiation results in the secretion of exosomes, containing survivin, which is a member of the IPA gene family involved in inhibition of the apoptosis signaling pathway. This may enhance the cancer cell survival fraction, which is connected with a poorer outcome for patients [15].

Extracellular vesicles (EVs), including exosomes and microvesicles, are critical mediators of cell to- cell communication in tissue homeostasis and repair, thus can be used as a transfer agents for active biomolecules. Specifically, EVs are natural carriers of microRNAs (miRNAs), protecting their cargo from plasma ribonucleases and delivering their content to recipient cells. In cancer, the expression of miRNAs is dysregulated, Therefore, EVs-mediated miRNA delivery may represent a valuable tool for cancer therapeutic intervention. MicroRNAs may act both as tumor suppressors or oncogenes, consequently different alternative approaches for regulating miRNA expression in tumor tissues have been developed [16].

Since cancer cell derived exosomes are a critical component in tumor development and progression, it can be considered that such exosomes are a novel target for cancer therapy. Suppression of transfer miRs from cancer cells to ECs by the mean of exosomes suppresses angiogenesis and metastasis. Tumor stroma–derived exosomes are implicated in cancer chemo resistance by several mechanisms, mediating drug efflux. The drugs and their metabolites can be encapsulated and exported by exosomes. In addition, exosomes may counteract the effect of antibody drugs by modulating their binding to tumor cells. Lymphoma exosomes carry CD20, which bind therapeutic anti-CD20 antibodies and protect target cells from antibody attack. Exosomes from HER2-overexpressing breast cancer cells express active HER2 and can bind to the HER2 antibody trastuzumab to inhibit its activity [16].

The formation of new blood vessels is necessary for tumor growth and development, angiogenesis is a complex process that involves vascular endothelial substrate degradation, vascular endothelial cell migration and endothelial cell proliferation, also formation of vascular pipeline branches and a new basement membrane. Exosomes contain abundant angiogenic factors that regulate tumor angiogenesis. For example, MSC-derived exosomes promote tumor angiogenesis by increasing VEGF expression in tumor cells and activating ERK1/2 and p38 mitogen-activated protein kinase pathways furthermore placental MSC exosomes promote vascular network formation and improve microvascular endothelial cell migration [17,18]. In cancer stem cells, exosomes derived only from CD105-positive cancer stem cells induce angiogenic phenotype phenotype differentiation of endothelial cells, stimulating their growth and vessel formation and cancer metastasis [19]. However, another studies demonstrate that MSC-derived exosomes inhibited tumor growth and angiogenesis in breast cancer by downregulating the expression of VEGF, which is a pro-angiogenic factor that is frequently overexpressed in cancer through miR-16 [20].

Exosomes released from stem cells also contribute to tumor metastasis. through facilitating epithelial-mesenchymal transition and the induction of stem-like properties that allow cancer stem cells to increase their survivability through the circulation (64). It is believed that MSC-derived exosomes deliver miR-221 to HGC-27 cells, which facilitated the proliferation and migration of these cells (65). In addition, MSC-derived exosomes promoted Wnt signaling pathway activation to facilitate the migration and proliferation of the breast cancer cell line MCF-7 The Wnt signaling pathway is characterized by the nuclear accumulation of β-catenin, which is involved in tumor development Dysregulation of miR-140 has an important role in regulating the transition of DCIS to invasive ductal carcinoma (IDC) [21]. As the tumor grade increases, miR-140 is progressively down regulated and plays a significant role in the stem cell regulatory pathways. Down regulation of miR-140 leads to higher CSC populations and breast cancer progression by removing tumor suppressive pathways. In addition to miR-140, miR-29a and miR-21are also involved in tumor growth and metastasis through induction of stem cell like properties [22]. On the other side, certain studies believed that MSC-derived exosomes transferred specific miRNA that enforces the gap junction-through dependent and contact-independent manner. miR-124 and miR-145 decrease the luciferase activity of their respective reporter target genes, including small carboxy-terminal domain phosphatase 1 (SCP-1) and sex-determining region Y-box 2 (Sox2), and decrease the migration of glioma cells and the self-renewal of glioma stem cells.Additionally, BM-MSC-derived exosomes overexpress miR-23b, which induces a dormant phenotype through suppressing a target gene, myristoylated alanine-rich C-kinase substrate, which encodes a protein that promotes cell cycling and motility [23].

As a delivery system, exosomes are widely used as vehicles for various tumor therapeutic cargos. The lipid bilayer membrane of exosomes forms a natural protective shelter and a sustained release capsule for various anti-cancer drugs. It has been reported that chemotherapeutic drug-loaded exosomes specifically targeting CSCs has much improved anti-tumor effects when compared to free drugs in animal tumor models. For example, doxorubicin is a common chemotherapeutic drug to treat hematological malignancies and many types of solid tumors and sarcomas. In a colon adenocarcinoma mouse model, exosome-delivered doxorubicin shrank tumor size much more efficiently than did free or liposome-delivered

doxorubicin [24]. Furthermore, using αv integrin-specific iRGD peptide presenting exosomes to deliver doxorubicin dramatically enhanced the anti-tumor effect in αv integrin-positive breast cancer cells in animals compared to free drug administration [25].

Paclitaxel is another widely used antimitotic chemotherapeutic drug for various tumor therapy [26]. Paclitaxel can be loaded into exosomes by sonication, and these loaded exosomes have 50 times more cytotoxicity than free paclitaxel for drug resistant cancer cells *in vitro*. T[27]. This indicates that exosome-encapsulated paclitaxel can directly target drug resistant CSCs. Moreover, prostate cancer cell-derived exosomes loaded with paclitaxel also have enhanced cytotoxicity to autologous cancer cells [28].

Exosomes-loaded withaferin A showed a much stronger anti-tumor effect compared to free drugs in human lung cancer xenograft mouse model [29]. Exosomes loaded with celastrol, a triterpenoid derived from plants also showed stronger anti-tumor effect compared to free celastrol in human lung cancer cell xenograft model [30,31].

As miRNAs are frequently detected in exosomes isolated from either cell culture medium or bodily fluids , Most of these miRNAs are functionally involved in exosome-mediated cell-cell communication, and the anti-cancer properties. miR-146b-enriched exosomes efficiently transfer miR-146b into glioma cells, inhibiting their proliferation, and reducing glioma xenograft growth in rats [32]. EGFR-specific binding peptide GE11 can guide Let-7a-containing exosomes to EGFR-positive cancer cells, which dramatically inhibited EGFR-positive human breast cancer cell growth in a xenograft mouse model Moreover, exogenous miRNA-143-loaded exosomes significantly reduced osteosarcoma cell migration [33,34].

MiR-122-transfected MSCs derived from adipose tissue can produce miR-122 loaded exosomes. These miRNA-loaded exosomes can deliver miR-122 into hepatocellular carcinoma cells to increase their sensitivity to chemotherapeutic agents through altering genes such as cyclin G1, a disintegrin, metalloproteinase domain-containing protein 10 (ADAM10), and insulin-like growth factor receptor 1. Furthermore, miR-122-loaded exosomes dramatically reduced human hepatocellular carcinoma growth in xenograft mice MiR-134-enriched exosomes can reduce breast cancer cell migration, invasion, and enhance their chemosensitivity through suppressing transcription 5B, heat shock protein 90, and Bcl-2 MSC-derived exosomes loaded with anti-miR-9 are able to reverse the expression of multidrug transporters in drug resistant glioblastoma multiforme cells, leading to an enhanced sensitivity to temozolomide treatment [35-37].

Using exosomes to silence genes in tumor cells by loading them with siRNAs provides a new target for cancer therapy. Delivery of siRNA against RAD51 via exosomes dramatically inhibited the proliferation of human breast cancer cells and caused their death *in vitro* [38]. Exosome-mediated transfer of siRNA against c-Myc can efficiently silence c-Myc and activate the pro-apoptotic protein caspase-3 in mouse lymphoma cells [39]. Exosomes can also deliver PLK-1 siRNA into bladder cancer cells to silence PLK-1, reducing their proliferation [40].

Cancer stem cells is a type of cancer cells with stem like properties that responsible for chemo resistance and cancer recurrence. The cell surface marker CD44 is highly expressed in high tumorigenic and metastatic hepatocellular CSCs, and Anti-CD44 antibody-coated liposomes can deliver doxorubicin directly to CSCs positive for this marker [41]. The anti-CD44 antibody itself can induce the apoptosis of CD90+ hepatocellular carcinoma stem cells, moreover, an anti-CD44 antibody-coated exosome could directly induce CSC death, along with their drug delivery role [42]. Therefore, other CSC markers like CD133, CD24, epithelial cell adhesion molecule (EpCAM), and CD200, can also be used as targeting candidates to improve the exosome-mediated CSC targeting efficiency. multiple-antibody coated exosomes will need to be engineered to improve their CSC targeting efficiency and to reduce the side effect on normal cells;as multipule surface marker are expressed on the surface of CSC, the normal cells may present one CSC cell surface marker, but not several of those expressed on CSCs. furthermore, exosomes can also target CSC specific signal pathways. as Wnt, Notch, Hippo, Hedgehog, NF-κB, and TGF-β pathways are crucial to maintain the CSC capacities such as self-renewal, differentiation, tumor initiation, and drug resistance Using exosomes loaded with inhibitors, miRNAs, or siRNAs to target these pathways can be considered an alternative way to achieve CSC targeting [43].

Since many promising results have been achieved *in vitro* and in animal models, some clinical trials have been done using exosomes for cancer patient treatment. For example the immune response was activated and disease progression was slowed in a small number of exosome-treated non-small cell lung cancer patients, moreover, exosomes with interferon-γ (IFN-γ) treatment have enhanced immune activation and tumor suppression effects also IFN-γ-DC-derived exosomes were capable of boosting NK cell-mediated anti-tumor immunity in advanced non-small cell lung cancer patients [44,45]. Thirty two percent of participants experienced stabilization for more than 4 months [46]. An ascite-derived exosomes combined with GM-CSF treatment was revealed induction of beneficial tumor-specific antitumor cytotoxic T lymphocyte response [47].

Conflict of interest

All authors declare that no conflict of interest

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