

## Review Article

# Exosome-mediated cell-cell communication in tumor progression

Zhuo Wan<sup>1</sup>, Xiaotong Gao<sup>1</sup>, Yan Dong<sup>1</sup>, Yingxin Zhao<sup>1</sup>, Xutao Chen<sup>3</sup>, Guodong Yang<sup>2</sup>, Li Liu<sup>1</sup>

<sup>1</sup>Department of Hematology, Tangdu Hospital, Fourth Military Medical University, Xi'an 710038, Shaanxi, China;

<sup>2</sup>Department of Biochemistry and Molecular Biology, Fourth Military Medical University, Xi'an 710032, Shaanxi, China; <sup>3</sup>Department of Implantation, School of Stomatology, Fourth Military Medical University, Xi'an 710032, Shaanxi, China

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**Abstract:** Exosomes, which are 30-150 nm lipid bilayer vehicles, have been recognized as one of the most crucial components of the tumor microenvironment. Exosomes transfer specific lipid, nucleic acids, proteins and other bioactive molecules from the donor cells to the recipient cells. Accumulating evidence has suggested that cancer cells and the tumor associated stromal cells can release and receive exosomes, inside of which the components and amounts are greatly changed. Pioneering studies have revealed that these exosomes play essential roles in tumor progression. Here we summarize the recent advances in this field, by focusing on the exosome biogenesis in the cancer condition, and their biological function in angiogenesis, metastasis and chemo-resistance of tumor. The review would not only provide a summary of this field, but also insights and perspectives on exosome-based strategies in cancer diagnoses, prevention and therapy.

**Keywords:** Tumor microenvironment, exosome, metastasis, chemoresistance, proliferation

### Introduction

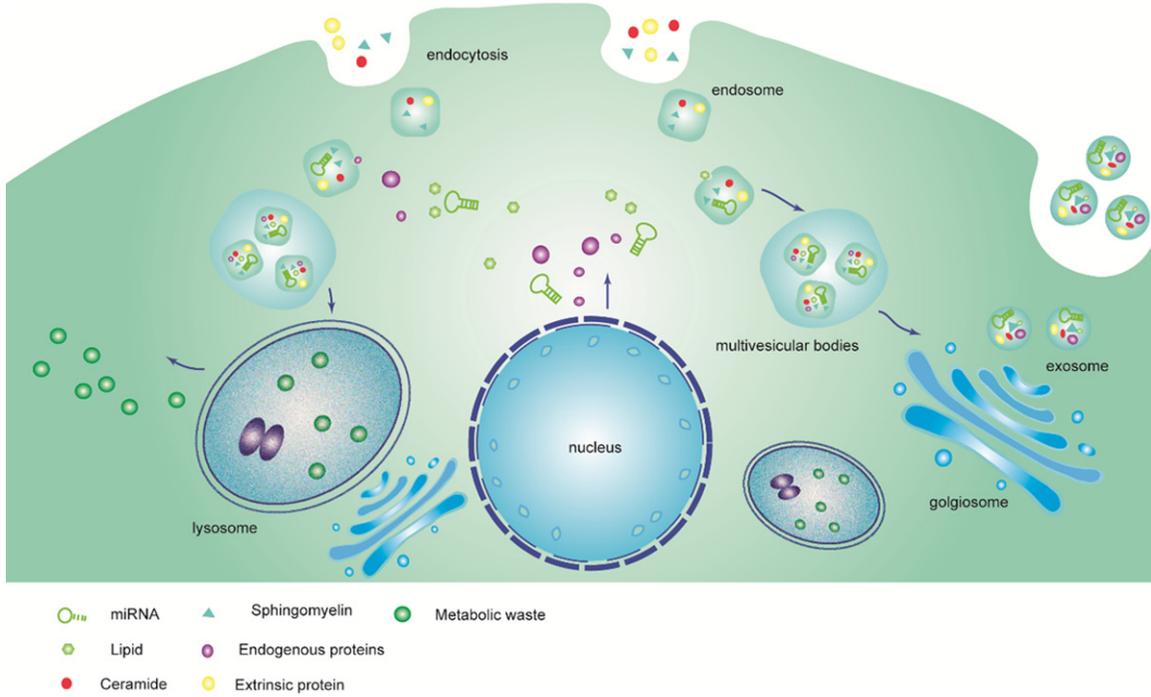
Cancer is the second leading cause of death in the world, and becomes a major public health problem [1]. Tumor microenvironment acts importantly in the cancer progress, not only promote malignant cell growth but also protect the tumor cells from the chemotherapeutic drugs. Previous studies mainly focus on the cytokines and chemokine in tumor microenvironment. However, accumulating evidence suggests that exosomes also play a critical role in local and remote cell-cell communication in cancer, emerging as an essential part of tumor microenvironment.

Exosomes are a class of extracellular vesicles defined as 30-150 nm diameter membrane nanovesicles which float on sucrose gradient to a density that ranges from about 1.13 to 1.19 g/ml [2]. Exosomes present with a characteristic cup-shaped morphology under the scanning tunneling microscope [3]. The biogenesis of exosomes could be summarized to four concise processes as described in **Figure 1:**

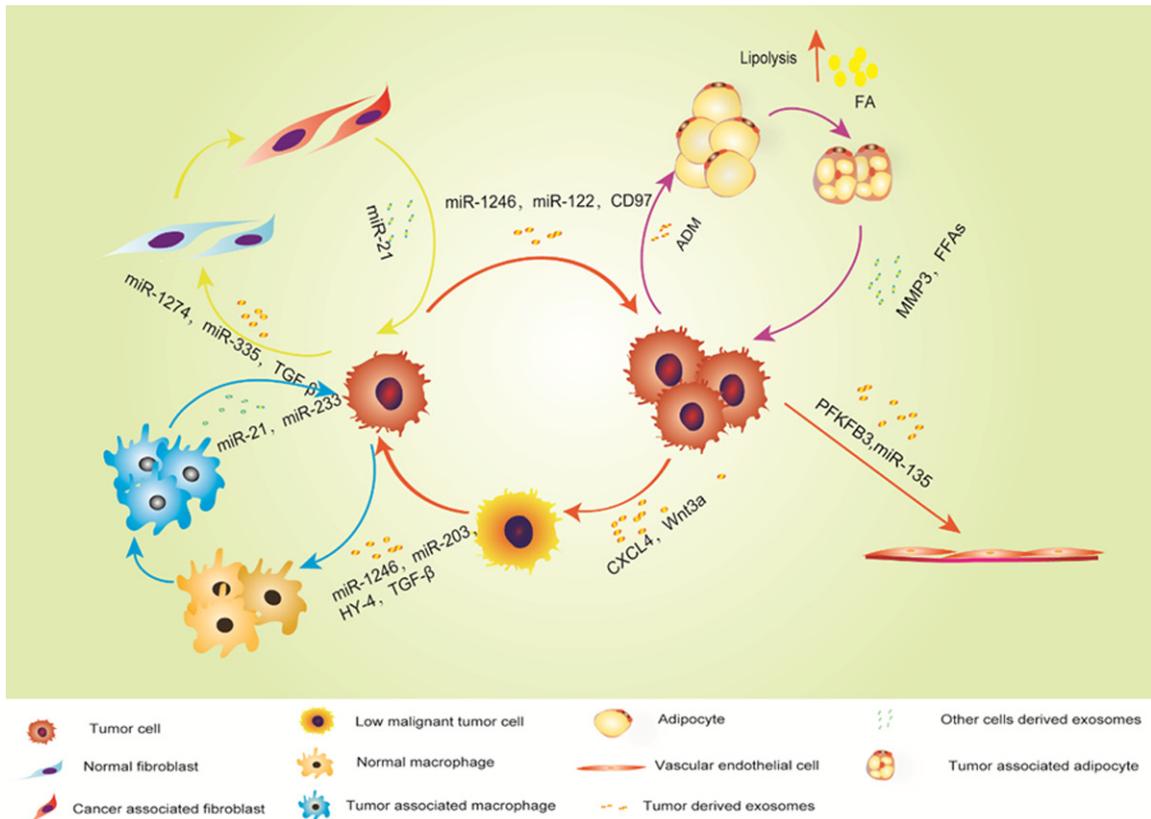
sorting and parceling, Golgi network, lysosomal degradation, and secretion through exocytosis. In the early stage, early endosomes take shape after invagination of the plasma membrane and cell swallowing the intracellular components and extracellular ligands occurs, leading to the accumulation of intraluminal vesicles. In the meanwhile, early endosomes will parcel some specific proteins, lipid and other contents selectively through a number of different pathways, such as endosomal-sorting complexes required for transport (ESCRT). These mature endosomes are named as multivesicular bodies (MVB) [4]. A part of MVB will be degraded by lysosomes, and the other part of MVB will be processed and assembled in the golgiosome. Then the mature MVB will be secreted through exocytosis by cells, which is termed as exosome release [5]. The secretion of exosomes is mainly driven by the Rab-GTPases 27a, 27b, SLP4 and SLAC2B [6].

Exosomes can be secreted by almost all kinds of cells in the cancer, and thus transfer the internal messengers when taken up by proximal

## Function of tumor cells' exosomes and tumor stromal cells' exosomes



**Figure 1.** Four concise processes of exosomes formation: sorting and parceling, Golgi network, lysosomal degradation, and secretion through exocytosis.



**Figure 2.** Tumor cells and tumor associated cells communicate with each other via exosomes.

and distal recipient cells (**Figure 2**). Notably, the biogenesis, secretion and the components of the exosomes are greatly dysregulated. For instance, cancers with advanced malignancy secrete more exosomes than well differentiated cancers [7]. Recent studies have shown that tumor exosomes play important roles in promoting cell survival, distal metastasis and chemoresistance [8]. Roles, and components of the exosomes have been briefly summarized in **Figure 2**. In the following sections, we will describe the detailed progress in these fields.

### **TCexos' roles in the regulation of tumor cells**

#### *TCexos in cancer stem cells' stemness*

Cancer stem cells (CSCs) are a kind of tumor cells with normal stem cell characteristics (found in solid tumors and hematological tumors), which possess substantial potential for clonal tumor initiation, phenotypic plasticity preservation, long-term repopulation and the ability of self-renewal [9]. Unlike other types tumor cells, CSCs can produce tumor cells through self-renewal, differentiation and the other stem cell-specific cellular procedures, which is a crucial factor that results in tumor recurrence and metastasis [10]. CXCR4 is the most common chemokine receptor which will be overexpressed in various cancers and exert a critical part in tumorigenesis [11]. Tumor recurrence and metastasis are closely related to the overexpression of CXCR4. Studies have shown that patients with breast cancer who have higher expression of stemness and metabolic-related genes in plasma exosomes have a poorer prognosis compared to patients with normal or lower expression of these genes. More importantly, CXCR4-positive exosomes derived from CXCR4 positive breast cancer cells can promote the expression of stem-related genes in breast cancer cells through the paracrine pathway and promote breast cancer cell proliferation and invasion in vivo and vitro. Also, recipient cells treated with exosomes from CXCR4 positive cells showed increasing abilities of self-renewal and phenotypic plasticity preservation [12]. Similarly, Wnt pathway plays an important role in the stemness maintenance of CSCs, and abnormal activation of the Wnt pathway is involved in the renewal and differentiation of CSCs [13]. Gerald G. Wulf et al. have proved that that exosomes derived from congenic side population of diffuse large

B-cell lymphomas (SP cells) carry a large amount of Wnt3a, which can act on non-SP cells and activate the Wnt pathway, facilitating the conversion of non-SP cells to SP cells [14]. DKK family is a specific inhibitor of the Wnt/ $\beta$ -catenin signaling pathway. CC Chen et al. found that exosomes of acute myeloid leukemia (AML) cells attenuate of hematopoietic stem cells' stemness through activating Wnt pathway to impair the osteogenic potential of bone marrow mesenchymal stem cells (MSC). And animal models treated with DKK1 inhibitor survived more days after transplantation of AML cells [15]. Interestingly, Xiaowu Li et al. have identified that exosomes derived from pancreatic ductal adenocarcinoma (PDAC) carried lncRNA-Sox2ot (which acts as a ceRNA of miR-200 family) and can be transported to recipient PDAC to promote EMT and stem cell properties [16]. These studies above suggest that the biologically active substances carried by tumor-derived exosomes are recycled by cancer stem cells to promote the overexpression of cancer stem cell stem genes and promote tumor proliferation and metastasis.

#### *TCexos in tumor proliferation*

Not only do the exosomes from tumor cells mediate the stemness related genes to promote proliferation, but also can regulate proliferation directly. Syndecan-1 is a four cell-surface heparan sulfate proteoglycans (syndecan-1 through-4) and is primarily expressed on lung epithelial cells [17]. Syndecan-1 is able to regulate cell proliferation, migration, survival and adhesion. Peter Chen et al. found that Syndecan-1 regulates the miRNA profile in exosomes released by A549 cell lines to promote tumor proliferation by mediate ErbB and p53 signaling pathway [18]. Similarly, in Rui Zhang's research, they found that exosomal MALAT-1 was highly expressed in non-small cell lung cancer (NSCLC) patients and MALAT-1 could regulate cell cycle regulating proteins (CDK4, Cyclin D1 and Cyclin D2) to accelerate proliferation, migration and invasion [19].

#### *TCexo participate in the regulation of tumor cell migration*

Metastasis is the major challenge in the treatment of tumors and current researches are mainly focused on exploring the mechanism of the escape of metastatic cells [20]. Exosomes

## Function of tumor cells' exosomes and tumor stromal cells' exosomes

**Table 1.** Concise summary of diagnostic and prognostic markers in tumor exosomes

Cancer type	Diagnostic and prognostic markers in exosomes from tumor cells
Non-small-cell lung carcinoma	14-3-3ζ, Tim-3, Galectin-9, miR-181a-5p, miR-21-5p, miR-106a-5p, miR-93-5p, miR-106a-5p, miR-20a-5p, miR-93-5p
Esophageal carcinoma	miR-21, miR-1246, miR-106a, miR-18a, miR-20b, miR-486-5p, miR-584, miR-93-5p
Prostatic carcinoma	PTEN, Survivin, miR107, miR130b, miR181a2, miR141, miR301a, miR326, miR3313p, miR375, miR432, miR5743p,
Hepatic carcinoma	miR-21, miR-18a, miR-221, miR-222 and miR-224, miR-665, miR-101, miR-106b, miR-195
Pancreatic carcinoma	EGFR, miR-17-5p, miR-21
Gastric carcinoma	GRN, miR10b-5p, miR132-3p, miR185-5p, miR195-5p, miR-20a-3p, miR296-5p
Colorectal carcinoma	let-7a, miR-1229, miR-1246, miR-150, miR-21, miR-223, miR-23a
Breast carcinoma	PS, miR-106a-3p, miR-106a-5p, miR-20b-5p, miR-92a-2-5p
Acute myeloid leukemia	TGF-β1, let-7a, miR-99b, miR-146a, miR-155, miR-191, miR-1246

are transporters of proteins and nucleic acids, and some of the miRNAs they carry may be important triggers for many metabolic pathways. Therefore, exosomes may be one of the important ways to promote tumor metastasis. Studies have shown that TCexos can induce host tissues that they select to transform into a state suitable for metastasis. These exosomes transport miRNAs into tumor stromal cells and these miRNAs regulate the expression of genes encoding metalloproteinases, caveolins, adhesion factors, chemokine ligands, and cyclins in tumor stromal cells. CCNG2 is closely related to the cell cycle and is a tumor suppressor gene. The expression of CCNG2 is decreased in thyroid cancer, oral cancer and breast cancer. Li et al. found that miR-1246 is highly expressed in exosomes derived from the MDA-MB-231 cell line and can be taken up by HMLE cells and promote the invasion of HMLE cells. CCNG2 is a target gene of miR-1246, miR-1246 can promote the migration, drug resistance and proliferation of HMLE by inhibiting the expression of CCNG2 [21]. Disturbance of glucose metabolism is a hallmark symptom in cancer patients. Researchers found that breast cancer cells can secrete high levels of miR-122 vesicles in the pre-metabolic microenvironment to inhibit glucose uptake in non-tumor cells. High levels of miR-122 in the circulation can remodel the system's energy metabolism by inhibiting the expression of pyruvate kinase and carbohydrate transporter 1 to promote tumor cell proliferation and metastasis [22]. In addition, MAPKs signal transduction pathway also plays a crucial role in the proliferation and differentiation of tumor cells. It has been found that exosomes derived from human gastric cancer cell line SGC-7901 express high levels of CD97, and high levels of CD97 may promote proliferation and metastasis of tumors by activating MAPKs

signaling pathways. Moreover, we found that there was a significant difference in miRNA expression in exosomes highly expressing CD97 and miRNA in exosomes low expressing CD97, suggesting that CD97 may affect MAPKs signal transduction pathway by affecting miRNA expression [23]. The above studies indicate that TCexos can selectively enrich some specific miRNAs, and the target genes of these miRNAs are important tumor suppressor genes or metabolism-related genes. TCexos mediate tumor cell migration by transporting these miRNAs. Most of these microRNAs have been proved to be important bioactive molecules in tumor exosomes and regulate important signaling pathways through the exosome pathway to promote the development of the tumor itself. Some known carcinogenic microRNAs such as miR-1246, miR-340, miR-320, etc. are highly expressed in tumor exosomes, and some of them have been clinically used as diagnostic and prognostic markers for screening and predicting tumors as (Table 1) [24-34].

### *TCexos participate in the regulation of drug resistance in tumor cells*

Drug resistance is one of the urgent problems to be solved in the treatment of cancer. Drug resistance includes endogenous drug resistance, acquired drug resistance and primary drug resistance. Endogenous resistance is often associated with overexpression of ABC transporters of tumor cells [35]. Acquired resistance refers to the reprogramming of the genome of a tumor cell after receiving radiotherapy and chemotherapy to obtain resistance to the drug [36], while primary drug resistance is caused by a series of signaling pathways affecting tumor cells through regulation of tumor microenvironment [37]. The acquisition

of tumor drug resistance is closely related to the change of the tumor microenvironment. Exosomes are an important part of the tumor microenvironment. Therefore, TCexos may be involved in the formation of endogenous drug resistance in tumors. Studies have shown that drug-resistant tumor cells can increase the drug resistance of drug-sensitive tumor cells by secreting exosomes which are rich in drug efflux pump proteins and transporting them into drug-sensitive tumor cells. Similarly, Juliana et al. found that miR-155 in breast cancer stem cells and drug-resistant cell exosomes was significantly higher than drug-sensitive tumor cells. By co-culturing cancer stem cells and drug-cell-derived exosomes with drug-sensitive cells, drug-sensitive breast cancer cells also express high levels of miR-155. And its EMT-related genes such as BMI1, SLUG, SNAIL, SOX9, EZH2 expression increased and miR-155 target genes such as TGF- $\beta$ , FOXO-3a, C/EBP- $\beta$  expression decreased. Further studies showed that drug-sensitive cells transfected with miR-155 increased resistance to antitumor drugs by more than 50% [38]. This reveals that resistant tumor cells transfect miR-155 into non-drug resistant cells through exosomal pathways, increasing drug resistance of tumor cells in non-drug resistant cells. Second-generation sequencing analysis and qPCR validation confirmed miR-100, miR-17, miR-222, miR-342p, and miR-451 in drug-resistant cell exosomes and in non-drug resistant cells treated with drug-resistant exosomes. miR-21 was significantly elevated, and further studies confirmed that the target gene PTEN of miR-222 is more highly expressed in drug-sensitive cells than drug-resistant cells, and PTEN expression is decreased when drug-sensitive cells are treated with drug-resistant cell exosomes [39]. Not just miRNAs, lncRNAs are also enriched in certain tumor exosomes. Related studies have shown that in exosomes of renal cell carcinoma-resistant cells, delivery of lncARSR as a miR-34 and miR-449 sponge to sunitinib-sensitive tumor cells enhances their resistance [40]. These studies indicate that exosomes derived from drug resistant tumor cells can mediate drug resistance either by directly expelling the drug out of the cell, or by transporting nucleic acid, protein, and other molecules to activate a series of molecular pathways.

### TCexos' roles in tumor stromal cells

#### *TCexos regulate tumor-associated macrophages*

Tumor-associated macrophages (TAMs) have been considered to have a very important role in determining the prognosis of tumors in recent years [41]. TAM density is closely related to the survival rate of tumor patients. In most solid tumors, peripheral monocytes are mobilized and recruited around tumor cells and differentiate into macrophages to become TAM [42]. A large number of studies have shown that tumor cells promote the reprogramming of macrophages through the exosomal pathway, forming a unique TAM population. Harris et al. showed that P53-mutant colon cancer cells can transport miR-1246 to peripheral macrophages via the exosomal pathway, causing M0, M2 macrophages to secrete large amounts of VEGF, IL-10, CCL2 and TGF- $\beta$ . In addition, IL-8 and TNF- $\alpha$  levels are significantly reduced to induce an anti-inflammatory microenvironment, recruit immunosuppressive Tregs and promote tumor progression [43]. Mimori et al. also found that plasma exosomes in patients with colon cancer contain a marvelous amount of miR-203, and that miR-203 can promote the differentiation of monocytes into M2 macrophages and promote the development of tumors. In contrast, metastasis of colon cancer is negatively correlated with miR-203 content. This may be due to the fact that the target cells of plasma exosomes are mainly monocytes and the main target cells of tumor exosomes are tumor stromal cells, so miR-203 can inhibit the occurrence of EMT [44]. Martina Seiffert et al. found that exosomes of chronic lymphocytic leukemia cells contain a large amount of Y RNA HY4. These exosomes carrying HY4 can be recycled by monocyte and activate the TLR pathway in monocyte to secrete a large amount of CCL2, CCL4 and IL-6 and high expression of PD-L1 to promote the development of CLL [45]. David Lyden et al. showed that in the pancreatic cancer model, Kupffer cells selectively uptake the macrophage migration inhibitory factor MIF and release a large amount of TGF- $\beta$ , which promotes hepatic stellate cells to secrete a marvelous amount of fibronectin. The deposition of fibronectin in the liver will recruit bone marrow-derived macrophages and neu-

trophils, which together constitute the microenvironment before the metastasis of pancreatic cancer cells, creating a favorable condition for the liver metastasis of pancreatic cancer [46]. In addition, Long Zhang et al. found that TCexos can transfer activated epidermal growth factor receptor (EGFR) to host macrophages and inhibit IFN $\gamma$ 1 synthesis via triggering IRF3 ubiquitination by activating MEKK2 phosphorylation, which inhibits host cell endogenous anti-virus immune function and leads to imbalance of immune system in tumor patients [47]. The above results represent that TAM is regulated by TCexos, and TAM not only affects the proliferation of the tumor itself and the immune function of the host, but also acts on distant organs to promote tumor metastasis to distant organs. Therefore, TAM can be a new target for the prevention of tumor proliferation and migration, and more profound research can be conducted on this issue.

### *TCexos regulate tumor-associated fibroblasts*

Fibroblasts around the tumor cells, which are the major components of cancer stroma, are called cancer-associated fibroblasts (CAFs). CAFs are perpetually influenced by tumor cells and will not revert to a normal phenotype or undergoes apoptosis and elimination like normal fibroblasts [48]. In the tumor microenvironment, the interaction between the tumor stroma and the substances secreted by the tumor is closely related to the metastasis of the tumor [49]. However, how tumor cells regulate the CAFs has not yet been clarified. Mengchao Wu et al. found that, in the liver cancer microenvironment, highly metastatic HCC cells are more likely to transform normal fibroblasts into tumor-associated fibroblasts (CAFs) than low metastatic cells. HCC exosomes targetedly suppressed B4GALT3 by transporting miR-1247-3p into fibroblasts, converting normal fibroblasts to CAF through activation of the  $\beta$ 1-integrin-NF- $\kappa$ B pathway. Then, CAFs secrete IL-6, IL-8 and other pro-inflammatory factors to promote the development of cancer [50]. Wenrong Xu et al. also confirmed that gastric cancer cell exosomes promote the differentiation of mesenchymal stem cells (MSCs) into CAF by activating Smad pathway by transporting TGF- $\beta$  into MSCs [51]. However, Selaru et al. found that although hepatoma-associated fibroblasts also promote the development of hepatocellular carcinoma through the exosomal pathway, exo-

some component may be transformed into a new way to treat tumors. Selaru treated liver cancer cells with hepatic stellate cell LX-2 derived exosomes transfected with miR-335-5p and found that the invasiveness of hepatocarcinoma cells was reduced in vitro experiments, while it can inhibit the proliferation of hepatoma cells and promote the apoptosis of hepatoma cells [52]. In addition, Atsushi research found that the interaction between pancreatic cancer cell PCCs and pancreatic stellate cell PSCs upregulates TGF- $\beta$  and TNF- $\alpha$  in PCCs exosomes to induce overexpression of ACTA2 and fibrosis-related genes in PSCs, resulting in fibrosis of the pancreas and deterioration of the pancreatic cancer [53]. All of the above studies suggest that TCexos not only can transform normal fibroblasts into CAFs, but also can differentiate MSCs into CAFs, implying that CAFs may be an essential component in tumor microenvironment.

### *TCexos regulate tumor vascular associated endothelial cells*

Angiogenesis is a hallmark of cancer and enables tumor growth and metastasis [54]. The hypoxic environment is another important feature of tumor environment, especially when the disease progresses, the oxygen supply and oxygen consumption of the tumor cells are extremely unbalanced, and the tumor cells in the hypoxic environment are more invasive [55]. Studies have confirmed that hypoxia promotes the exosome secretion of tumor cells. Under extremely hypoxic conditions (0.1% O $_2$ ), tumor cell exosome secretion can increase by 90%. Park JE studies suggest that in glioblastoma, exosomes promote angiogenesis by activating the heparin-binding EGF signaling pathway regulated by protease-activated receptor 2 in endothelial cells [56]. Similarly, exosomes secreted by malignant glioma cells carry a large amount of hypoxia-regulated mRNAs and proteins (metalloproteinases, IL-8, platelet growth factor, caveolin, etc.). These exosomes can be taken up by endothelial cells and promote angiogenesis [57, 58]. In the multiple myeloma model, MM cells secrete large amounts of miR-135b-rich exosomes under hypoxic conditions. MiR-135b can promote the proliferation and vascularization of vascular endothelial cells by activating the HIF-1H pathway [59]. Gu et al. also found that nasopharyngeal carcinoma-derived exosomes, rich in PFKFB3, can pro-

mote the proliferation, migration, and angiogenesis of vascular endothelial cells [60]. In addition, inhibition of PFKFB expression promotes the apoptosis of CNE cells, suggesting that the exosomes derived from nasopharyngeal carcinoma cells not only maintain the stable development of their own tumor microenvironment, but also promote their own growth. Summing up the above, TCexos can promote tumor angiogenesis by many critical pathways to promote tumor progression.

### *TCexos regulate adipocytes*

Adipose tissue mediates various physiological and pathological processes by secreting factors that control glucose metabolism, inflammatory responses, angiogenesis, blood pressure regulation and reproductive function [61]. The most significant effect of tumors on adipose tissue is the occurrence of cachexia in patients with malignant cancer. Cachexia is one of the most common complications of cancer patients [62]. It manifests as atrophy of skeletal muscle and adipose tissue that cannot be completely reversed by nutritional support treatment [63]. Adipocytes are important constituent cells of the tumor microenvironment, so TCexos may be involved in the metabolism of adipocytes. Gunisha et al. found that pancreatic cancer cell-derived exosomes can promote the lipolysis of adipose tissue. Pancreatic cancer cell exosomes carry a large amount of adrenal medullary hormone (AM). AM binds to AM receptors on adipocytes membrane to activate p38 and ERK1/2 MAPKs pathways, which promote the expression of HSL, ATGL, and MGL to increase lipolysis [64]. On the other hand, Wang et al. showed that tumor exosomes inhibit the formation of adipose by inhibiting the differentiation of pre-adipocyte into adipocytes. The exosomes of A549 cells carry a large amount of TGF- $\beta$ , and TGF- $\beta$  can suppress adipogenesis-related pathways such as JNK, AKT, ERK, and P38 pathways, thereby inhibiting the production of adipose [65]. Patients with malignant tumors often develop cachexia in the late stages of the disease. This not only reduces the quality of life of patients, but also reduces the patient's immunity and the tolerance of anti-tumor therapy, greatly shortening the survival time of cancer patients. Therefore, inhibiting the exosomal pathway may reduce or even reverse tumor cachexia and improve patient prognosis.

### **Tumor stromal cell-derived exosomes (TSCexos) roles in tumor progression**

#### *Tumor-associated macrophage derived exosomes*

TAMs play a key role in the growth of malignant tumors. In most studies, the poor prognosis of tumor patients is positively correlated with the density of TAMs [66]. Different types of macrophages respond differently to different stimuli, and fully polarized M1 macrophages can be activated by bacteria and other anti-inflammatory factors such as lipopolysaccharide, M2 macrophages can be activated by anti-inflammatory factors such as IL-4 [66, 67]. Recent studies have found that TAMs can secrete a large number of exosomes, and the proteins and microRNAs carried by these exosomes can be taken up by cells in the tumor microenvironment. Many studies have found that M2 macrophages play an important role in the development of tumors [68]. TAMs can promote the growth and invasion of breast cancer cells and tumor angiogenesis by secreting a large number of cytokines. Erwei Song et al. found that the miR-223 carried by M2 macrophage-derived exosomes can be taken up by SKBR3 and MDA-MB-231 cells and activate the Mef2c- $\beta$ -catenin pathway, promoting the growth and metastasis of SKBR3 and MDA-MB-231 [69]. M2 macrophages not only promote the invasion of tumor cells, but also increase the resistance of tumor cells to drugs through the exosomal pathway. Lisong Shen et al. found that the miR-21 carried by exosomes from M2 macrophages can be taken up by MFC, MGC-803 cells and activate PI3K/AKT pathway through down-regulation of PTEN, thereby inhibiting the apoptosis of gastric cancer cells to achieve drug resistance [70]. The above studies indicate that after the macrophage differentiates into TAMs, the exosomes have similar functions as exosomes of the tumor cells, indicating that TAMs have undergone functional remodeling and acquired an activated phenotype in the tumor microenvironment, which makes it develop in the direction of tumor growth.

#### *Tumor-associated fibroblasts derived exosomes*

The tumor-associated fibroblasts (CAFs) is an important component of the tumor microenvironment, and its interaction with tumor cells plays a crucial role in the development of the

tumor. Qinglei Gao et al. found that the content of TGF- $\beta$  in exosomes of ovarian cancer-associated fibroblasts was higher than that of normal ovarian fibroblasts. By co-cultivation, the exosome of CAFs can be taken up by the ovarian cancer cell lines SKOV-3 and CAOV-3, which promotes the occurrence of EMT by activating the Smad pathway, and enhances tumor migration and invasion ability [71]. Corresponding to the above findings, Kefeng Dou found that exosomes from miR-320a-free CAFs can promote the growth and metastasis of liver cancer. Dou making a sequencing analysis of miRNAs carried in exosomes from CAFs and NAFs showed that the miR-320a content in CAFs was significantly lower than that in NAFs. Subsequently, miR-320a was found to be involved in the inhibition of PBX3 to inhibit the MAPK signaling pathway and thus inhibit the growth of hepatoma cells [72]. Mirnezami et al. also found that compared with normal fibroblasts, exosomes from fibroblasts with the highest expression levels of miR-21 and colon cancer cells co-transplanted into mice are more likely to have liver metastases [73]. Fibroblasts act as a natural physical barrier to restrict tumor expansion, when fibroblasts are influenced, tumor cells exhibit increased survival and local expansion, which can lead to metastasis. In addition, the tumor microenvironment including CAFs co-evolves with cancer cells during evasion, drug resistance, angiogenesis, and cancer progression, a penetrating understanding of interactions between CAFs and cancer cells is much crucial for better treatment outcomes and for overcoming treatment resistance. Exosomes pathway in this interaction may play an essential role in this process.

### *Tumor-associated adipocyte derived exosomes*

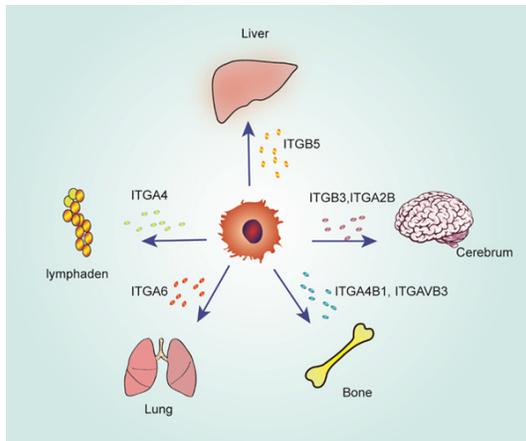
Adipose tissue consists of adipocytes and non-adipocytes (mesenchymal stem cells, macrophages, etc.), and these cells can communicate with other cells by releasing various molecules [74]. Studies have shown that adipocytes can participate in the development and invasion of tumors by secreting pro-inflammatory factors, altering metabolic state of cells, and recruiting immune cells [75, 76]. However, the role of adipocytes-derived exosomes in tumorigenesis is often overlooked. Melanoma cells can promote their own migration and invasion by ingesting exosomes derived from adipocytes around the tumor. This effect is more pronounced in mouse

obesity models [75]. Further research found that tumor-associated adipocyte-derived exosomes can increase the rate of fatty acid oxidation around tumor cells, providing a suitable metabolic environment for the maintenance of stem cells of cancer stem cells. MMP3 is a matrix metalloproteinase, and Shenglin Ma et al. found that 3T3-L1 cell exosomes contain large amounts of MMP3 and can transport MMP3 into lung cancer cell line 3LL cells, activate MMP9 in 3LL cells, and increase the invasiveness of 3LL cells [77]. So far, the study of the effects of tumor-associated adipocyte exosomes on tumors has not been fully explored, but it has been clarified that tumor-associated adipocytes carry large amounts of free fatty acids, which can alter the metabolic state around tumors and promote fatty acid oxidation to accelerate tumor development. In addition, exosome secretion and exosome activity of adipocytes derived from obese cancer patients are higher than those of non-obese patients, which may explain the poor prognosis of obese patients compared with those with normal weight.

### *TCexos mediate communications between distant organs*

Exosomes can reach the body throughout the blood [78]. At present, the research on the effects of tumor exosomes on distant organs mainly focuses on the transport of tumor exosomes to distant organs through the blood and lymph, constructing pre-metastatic microenvironment at distant organs to make distant organs more suitable for tumor migration. It has been well established that exosomes target different organs possibly via the different integrin molecules expressed on the surface (**Figure 3**). David Lyden et al. found that there are significant differences in the expression profiles of integrin of different affinity exosomes. The pneumotropic exosomes carry ITG $\alpha$ 6, the hepatotropic exosomes carry ITG $\beta$ 5, and the cerebral tropic exosomes carry ITG $\beta$ 3, which enable different tumor-derived exosomes to be targeted to different organs targeting of different tumor origin exosomes to different organs [79]. Numerous studies have demonstrated that exosomes of highly malignant tumors such as renal cell carcinoma, osteosarcoma, and melanoma can be detected in lung stromal cells. These exosomes mainly up-regulate fibronectin by acting on lung epithelial cells

## Function of tumor cells' exosomes and tumor stromal cells' exosomes



**Figure 3.** Tumor derived exosomes with different integrin target different organs.

and lung fibroblasts. And the expression of the S100 family promotes the recruitment of neutrophils in the lungs, creating favorable conditions for the lung metastasis of tumors [80]. In short, the most important effect of tumor exosomes on distant organs is to create a pre-metastatic environment at the remote site, which plays an important role in clinically predicting and early preventing tumor metastasis. Only if we explore a suitable way can we interdict these pre-metastatic pathways to prevent neoplasm metastasis. Additionally, besides integrin, it is better for us to pay more attention to other molecules which may play a critical part in exosomes targeting.

### Summary and outlook

Together, accumulating studies have revealed that tumor cells and the surrounding cells communicate frequently via exosome pathway (Figure 2). By tuning numerous pathophysiological processes such as inflammatory reactions, immune surveillance, exosomes have been found to be essential in the development and progression of cancer as an important part of the tumor microenvironment. Besides acting on tumor cells, numerous studies have shown that tumor exosomes can act on fibroblasts, macrophages, adipocytes, and vascular endothelial cells around the tumor, and drive tumor development (Figure 2).

One of the hallmarks of tumor exosomes is that exosomes carry organ-specific targeting moieties, such as different types of integrins (Figure 3) and high levels of oncogenic microR-

NAs (Table 1 and Figure 2). As exosomes are secreted into the blood, future work correlating the exosomal miRNAs with TNM status would provide new insights of liquid biopsy for cancer diagnosis. These microRNAs have been proved to be important bioactive molecules when taken up by recipient cells and regulate important signaling pathways to promote the development of the tumor. However, how these oncogenic microRNAs are enriched and sorted into exosomes still remains an unsolved problem. Blocking the pathway by which oncogenic miRNAs are sorted into the exosomes or therapeutically delivery the antagonisms hold promise for cancer treatment. Tumor derived exosomes also contains other types of RNA such as lncRNA, siRNA, and mRNA, and proteins, which also exert strong functions and worth to be explored.

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**Address correspondence to:** Dr. Guodong Yang, Department of Biochemistry and Molecular Biology, Fourth Military Medical University, 169th Changlexi Road, Xi'an 710032, Shaanxi, China. E-mail: yanggd@fmmu.edu.cn; Dr. Li Liu, Department of Hematology, Tangdu Hospital, Fourth Military Medical University, 569 The Xinsi Road, Xi'an 710038, Shaanxi, China. E-mail: liuli1@med-mail.com.cn

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