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Exosomes in Tumor Angiogenesis

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ABSTRACT

Intercellular communication in tumor micro environment is critical for tumor development and progression. Typically, communication between cells includes direct cell-to-cell contact, or soluble communication signals. Recently, exosomes represent a novel mechanism that mediates paracrine effect and long-distance communication has been emerged. It has been demonstrated that exosomes released by tumors carry multiple biological messages to endothelial cells to regulate angiogenesis. Here, we present an overview of tumor-derived exosomes and their role in tumor angiogenesis.

Key words: Intercellular communication; Exosomes; Tumor angiogenesis

INTRODUCTION

Angiogenesis is vital for solid tumor growth and metastasis. Without blood vessel, tumors cannot get oxygen and other essential nutrients they need in order to grow beyond a certain size (generally 1-2 mm^3) [1]. A complicated intercellular communications take part in the regulation of angiogenesis. The soluble communication signals, such as pro-angiogenic factors vascular endothelial growth factor **(VEGF)**, fibroblast growth factor **(FGF)** and angiopoietin-2 **(Ang-2)** [2], are involve in the early stage of angiogenesis. They promote endothelial cell proliferation,

migration and invasion from pre-existing vessels that stimulate vascular destabilization and angiogenic sprouting [2]. In contrast, both the soluble communication signals and cell-to-cell contact communication involved in the late stage of angiogenesis [3]. For soluble communication signals, Tie cells in the newly formed endothelial cell tubes release PDGF-BB that targets pericytes to promote the recruitment of pericytes to the surrounding region of the endothelial lumen [4], while angiopoietin-1 **(Ang-1)** secreted by pericytes phosphorylates the Tie-2 receptor that selectively expressed in endothelial cells to promote vascular stabilization [5]. For cell-to-cell contact effects, pericyte-endothelial interactions including peg-socket junction complex and adhesion plaques [6]. Except for the soluble communication signals and cell-to-cell contact communications, exosomes represent as an novel approach for communication between various cell types and has been demonstrated to be involved in tumor angiogenesis [7,8].

Exosomes are small extracellular vesicles **(EVs)** with 50-200 nm in size that are formed by a ceramide-mediated inward budding of multivesicular endosomes **(MVE)** and secreted after fusing with the plasma membrane [9,10]. Exosomes contain microRNAs **(miRNAs)**, mRNA and proteins that differ in imprint of the parent cells [11,12], which can reach distant tissues and be uptake by recipient cells and then interact with the recipient cells to influence multiple cell physiology. Upon travel to the target cells, exosomes enter the cells via receptor-mediated endocytic processes [13,14], or through membrane fusion events [15-17]. Hence, exosomes are served as important signaling entities to transfer biological massages between two distant cells.

In this chapter, we provide a review of exosomes produced by tumor cells, endothelial cells, pericytes, platelets and other cell types and their underlying mechanism of regulating tumor angiogenesis.

TUMOR CELL-DERIVED EXOSOMES AND ANGIOGENESIS

Accumulative evidiences have revealed that tumor cell-derived exosomes modulate the process of angiogensis [18-20]. Colorectal cancer cell-derived exosomes that are enriched cell cycle-related mRNAs promoted the proliferation of endothelial cells [21]. Exosomes containing active EGFR secreted by human tumor cells such as A549 and A451 could be delivered to endothelial cells and promote angiogenesis *in vitro* [22]. Recently, the recognition of cancer cell-derived exosomes affect different process of angiogenesis by modulating soluble factor production has been expanded. Exosomes containing VEGF and MMP-2 secreted by melanoma cells such as SkMel28, A2058, A375 and HTB63 triggered the process of angiogenesis [23]. Hypoxic multiple myeloma cells-derived exosomes, which harbored with miR-135b, accelerated angiogenesis via targetingHIF-1α [24]. HepG2 secreted exosomes loaded with vasorin, and then transfered to human umbilical vein endothelial cells **(HUVECs)** to promote the migration of HUVECs [25]. Exosomes containing miR-105 secreted by breast cancer cells such as MCF-7 and MDA-MB-231 were transfered to endothelia cells, then destroyed the tight junctions and the integrity of the endothelial cells, thereby changing the permeability of endothelial monolayers

[26]. Besides, it is also reported that 786-0 renal cancer cell-derived exosomes promoted tubular structure formation of HUVECs via up-regulation of VEGF [27]. Exosomes released from chronic myelogenous leukemia **(CML)** cells caused the increase of the endothelial cell motility and reorganization of the tube formation of HUVECs cultured on Matrigel [28].

Interestingly, as cancer cell-derived exosomes' role in angiogenesis has been explored, accumulative researches focus on the possibility that cancer cell-derived exosomes might be useful therapeutic tools for regulating angiogenesis. Bethany N found that breast cancer cells MCF-7 and MDA-MB-231stimulated the tube formation of endothelia cells via secreting exosomes involving microRNAs (let-7a, miR-23b, miR-27a/b, miR-21, let-7 and miR-320b). And treatment with docosahexaenoic acid **(DHA)** inhibited the tube formation through altering breast cancer exosome secretion and microRNA contents [29]. Exosomes released by chronic myeloid leukemia cells K562 promoted the tube formation of endothelial cells. After imatinib and dasatinib treatment, the secretion of the exosomes and the number of tube formation were reduced [30]. Besides, the generation of *in vitro*-engineered exosomes has attracted much attention. It has been realized to import some exosomes into the target cells to modify the cells' phenotype. For example, after incubated the U373 cells with exosomes released by their EGFRvIII transformed counterparts **(U373vIII)**, U373 cells also expressed the EGFRvIII [17,31]. Now, a novel device strategy has been proposed, which allowing rapid and selective retention capture of certain exosomes from patients' entire circulatory system through an affinity plasmapheresis platform. And this device removes certain exosomes and would not induce drug toxicity or interaction risks compare with pharmacological approaches [32]. Taken together, these studies support the idea that tumor cell-derived exosomes may be an attractive therapeutic option for the treatment of angiogenesis, but more work is still needed to identify its utility as a therapeutic candidate.

The factors related to the secretion of tumor cell-derived exosomes is complicated. Oxygen deficit may be one of the most important factors. Cancer cells will secret exosomes to promote angiogenesis in order to ensure the oxygen and nutrient supply, when they meet with hypoxia condition. It was reported that hypoxia facilitated the release of the exosomes by three breast cancer cells such as MCF-7, MDA-MB-231 and SKBR3, and this process was regulated by the HIF oxygen sensing pathway [33]. Exosomes released from brain tumor glioblastoma multiforme **(GBM)** grown at hypoxic condition had a potent effect on the tube formation and microvascular sprouting than that at normoxic conditions [34]. Similarly, under hypoxia condition, tumor cells A431 produced more exosomes to facilitate tumor angiogenesis and metastasis compared with normal condition [31]. Besides, the difference of tumor malignant degree may also contributes to the secretion of exosomes. Exosomes derived from high-grade ovarian cancer had a prominent impact on the cell viability and tube formation of HUVECs compared with unlikely high-grade ovarian cancer [35]. Moreover, heparanase, an enzyme often over-espression in the aggressive tumors, impacts the secretion, composition, and function of tumor cell-derived exosomes. Heparanase-high expressing cells stimulated the invasion of endothelial cells significantly compared with heparanase-low expressing cells [36].

TUMOR STROMAL CELLS-DERIVED EXOSOMES AND TUMOR ANGIOGENESIS

Tumor stromal cells are a kind of connective tissue cells in tumor, and provide parenchymal cells with support and nutrition. Tumor stroma basically consists of fibroblasts [37], inflammatory cells [38], endothelial cells [39], pericytes [40], immune cells [41] as well as platelets [42].

Endothelial cells play one of the most important roles during angiogenesis. After stimulated by several angiogenic factors, endothelial cells secrete exosomes, either loaded with proangiogenic factors or antiangiogenic factors, to modulate signaling pathways [43]. Endothelial cell-derived exosomes protected cultured endothelial cells from apoptosis through diminishing level of caspase-3 [44]. Endothelial cells-derived exosomes which equipped with MMP-2 and MMP-9 promoted the degradation of matrix, the migration of HUVECs and the tube formation [45]. Moreover, miR-214 released from endothelial cells enhanced angiogenesis *in vitro* and *in vivo*, and this effect was associated with the changes in the expression of ataxia telangiectasia mutated in neighboring target cells [46]. But, a contradictory evidence was observed that miR-145 secreted by endothelial cells and transferred to the neighboring tumor cells inhibited the tube formation *in vitro* [47]. In summary, endothelial cell-derived exosomes is vital in the process of angiogenesis but when and how endothelia cell-derived exosomes initiate or inhibit angiogenesis needed further studies.

Pericytes are a kind of mural cells embedded in the basement membrane of capillaries [6], which play a dual role in vascular progression. When pericytes take part in the formation of new vessels, they show proangiogenic effect, but when they participate in vessels maturation and stability, they exert anti-angiogenic effect [48-53]. These dual effects on vascular progression are mainly via cell-cell contact communications, paracrine manners as well as exosomes. The latest research showed that pericytes treated with $CoCl_2$ were stimulated to a proangiogenic state by activating HIF pathway, and resulted in faster wound healing, greater endothelia cells tube formation and greater vascular density in spinal cord tissue [54]. Furthermore, pericyte-derived exosomes also took part in the angiogenesis progression by chemical inhibition of ceramide-dependent exosome secretion and endocytosis-dependent membrane vesicle cycling [54].

Platelets are also increasingly being recognized for affecting tumor progression. Emerging evdiences suggest that activated platelet-derived exosomes regulate the process of angiogesis. They may have pro- and anti-angiogenic effect during the process of angiogensis, depending on their composition [1,18]. Platelet-derived exosomes enhance the monocyte adhesion to HUVEC in a time- and dose-dependent manner and then increased the expression of angiogenesis factors in endothelia cells [55]. Exosomes derived from activated platelets transferred the platelet-derived integrin CD41to the lung cancer cells, then resulted in the activation of MAPK p42/44 and AKT and the up-regulation of the mRNA for cyclin D2 and MT1-MMP.In addition, exosomes could also increase the mRNA levels of angiogenic factors like MMP-9, VEGF, IL-8 and HGF, thus accelerate

angiogenesis and tumor progression or metastasis in lung cancer [56]. In contrary, it was also comfirmed that platelet-derived exosomes induced endothelial cells caspase-3 activation and apoptosis by the generation of superoxide, NO and peroxynitrite [57]. These studies suggest that the role of activated platelet-derived exosomes in angiogenesis is complicated and the underlying mechanism of its dual effects on angiogenesis needed future research.

OTHER CELLS-DERIVED EXOSOMES AND TUMOR ANGIOGENESIS

Mesenchymal stem cells **(MSCs)** potentially differentiate into multiple cell types, which migrate to microenvironment and exert complex effects on tumor progression. MSCs-derived exosomes may have pro- and anti-angiogenesis effect during the process of angiogensis, depending on their contents [58-60]. miR-125 a enclosed in exosomes secreted by human adipose-derived MSCs **(adMSC-Exo)** was transferred to endothelial cells and took part in angiogenesis *in vitro* and *in vivo* by suppressing the angiogenic inhibitor delta-like 4 **(DLL4)** [61]. Similar study also pointed out that MSCs-derived exosomes were loaded with transcription factors involved in proangiogenic pathways, such as Hepatocyte Growth Factor **(HGF)** that can stimulate proliferation and migration of endothelial and vascular smooth muscle cells [62]. Three novel miRNA (miR-222, miR-21, and let-7) released from MSCs have been shown to modulate angiogenesis *in vitro* [63]. Additionally, the further study reported that MSCs-exosomes induced an increment of VEGF and CXCR4 mRNA and protein in cancer cells and made a proangiogenic program via activation of ERK1/2 pathway to stimulate tumor growth and angiogenesis [64]. However, it was also showed that MSCs-derived exosomes were enriched in miR-16, a miRNA known to target VEGF, and exerted partially anti-angiogenic effect in a dose-dependent manner [65,66]. Although the pro- or anti-angiogenic effect of MSCs-derived exosomes is unkown, their involvement in tumor angiogenesis has attracted wide attention and they may be a novel therapeutic approach for angiogenesis.

Myeloid-derived suppressor cells **(MDSCs)** are present in the tumor microenvironment, and they are a heterogenic and immunosuppressive subset of cells that trigger tumor angiogenesis and progression. The role of MDSCs-derived exosomes has not been clearly understood. A recent study showed that doxorubicin **(DOX)** treatment of 4T1 breast tumor cells bearing mice led to the induction of IL-13R^{+}miR-126a^{+} MDSCs, and the exosomes miR-126a from DOX induced-MDSCs enhanced endothelial cells tube formation *in vitro* and increase the number of EC-containing (CD31^{+} and α-SMA^{+}) blood vessel *in vivo*[67].

CONCLUSION

The current researches indicate that tumor-derived exosomes play an important role in tumor angiogenesis, and targeting exosomes may be an ideal therapeutic strategy to inhibit tumor angiogenesis.

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