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Citation: J Med Discov (2019); 4(4):jmd19028; DOI:10.24262/jmd.4.4.19028

Review

Exosomes: a messenger of melanoma progression and metastasis

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Melanoma is the most dangerous type of skin cancer. For metastasis to occur melanoma cells must communicate with their local/distant environment to initiate tumor growth and spread. Exosomes have emerged as a novel mediator of intercellular communication. Recent evidence has indicated that EXs released from metastatic melanoma cells could reprogram bone marrow-derived cells for distant metastases, probably by inducing endothelial cell angiogenesis. In addition, the genetic factors engulfed by exosomes can be transferred to recipient immune cells, where they exert a lot of functions for melanoma escape from immune system control and tumor progression. The therapeutic potential of exosomes has been demonstrated in the clinical setting. These studies advocate that targeting exosomes may provide a new therapeutic avenue for treating and monitoring the disease progression of melanoma. However, more investigations are required to test the hypothesis of exosomes can be effectively used in diagnostic and therapeutic implication for melanoma patients.

Keywords: melanoma, exosomes, mechanisms

How to cite: Wang Y, Exosomes: a messenger of melanoma progression and metastasis. J Med Discov (2019); 4(4):jmd19028; DOI:10.24262/jmd.4.4.19028; Received August 20th, 2019, Revised October 21st, 2019, Accepted November 05th, 2019, Published November 15th, 2019.

Introduction

Malignant melanoma is the most dangerous form of skin cancer, which accounts for more than 80% of all skin cancer-related deaths. Its incidence has been increasing in the United States and all around the world. Melanoma arises from the malignant transformation of normal melanocytes, which are originally derived from the embryonic neural crest and responsible for production of skin pigment melanin. Exosomes (EXs) are small membrane vesicles (30-120 nm) that derived from the luminal membranes of multivesicular bodies and released into extracellular environment by fusion with cell membrane [1]. EXs have been suggested to mediate local and systemic cell-to-cell communication through the transfer of molecules such as proteins, mRNAs and microRNAs (miRs) between cells. Recent evidence has proposed that EXs released from cancer cells can act as regulators of cancer progression. EXs are small enough to penetrate into and interact with tissues, and have been shown to promote increased migration and proliferation of tumors. Exosomes have also been shown to affect unique stages of tumor progression, including angiogenesis, escape from immune surveillance, extracellular matrix degradation, and metastasis. For example, malignant breast cancer cells-derived EXs promoted the invasion of non-malignant breast epithelial cells [2, 3]. Melanoma cells-derived EXs containing high level of oncoprotein MET educated and mobilized bone marrow derived cells for lung and bone metastasis support [4]. The metastatic potential of cancer cells is a term given to cancers to classify the level of phenotypic changes that are linked to increased metastatic behaviors. For example, a high metastatic potential correlates with high rates of migration and motility. However, a comparison between EXs released from melanoma cells having different metastatic levels hasn't been addressed before. A study has demonstrated an immunoaffinity based methodology for capturing exosomes derived from melanoma patient's plasma [5]. Melanoma derived exosomes could be captured using antibody 763.74, specific for a peptide epitope of the tumor antigen, chondroitin sulphate peptidoglycan 4 (CSPG4), uniquely expressed on melanoma cells. Antigens associated with melanoma such as gp100, VLA4 and TYRP2 were carried by melanoma exosomes, but were not detectable by normal cells produced exosomes.

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Exosomes influence melanoma progression

Genetic, epigenetic and environmental information in contribution to uncontrolled cell proliferation and survival, were involved in the transformation of normal melanocytes into malignant melanoma. Exosomes play a role in the pathogenesis and metastasis of melanoma by protecting cancer cells against immune surveillance and by regulating pro-survival and intracellular signaling via transfer of proteins, cell surface molecules such as human leukocyte antigens, tumor-associated antigens, co-stimulatory molecules and cytokine factors from their parental cells to distant tissues [6]. Melanoma cells released exosomes carrying high level of miRNA-222 which can be transferred to the recipient cells, resulting in the activation of the pro-survival PI3K/AKT pathway required for enhancing melanoma cell proliferation [7, 8]. Emerge of exosomes also actively participate in tumor colonization of distant tissues, by activating the epithelial-mesenchymal transition (EMT) and inducing pre-metastatic niche formation [9].

Exosomes influence melanoma angiogenesis and invasiveness

For long-distance metastasis to occur, the formation of new blood vessels (angiogenesis) is required. In addition, the tumor requires sufficient blood supply to supply oxygen and nutrients for expansion of tumor mass. It is well recognized that endothelial cells (ECs) are crucial for cancer growth since it generates a suitable vascular microenvironment for tumor expansion and dissemination, to allow cancer cells to invade proximal and distant tissues. The immuno-modulating agents and pro-angiogenic molecules carried by exosomes, such as interleukin (IL)-6, vascular endothelial growth factor (VEGF) and particularly matrix metalloproteinases (MMPs) play important role in this process. Previous studies have demonstrated that melanoma cells support tumor growth and metastasis by releasing secreted factors such as VEGF for tumor angiogenesis or matrix metalloproteinase 2 (MMP2) for induction of immunosuppression [10, 11]. A previous study has also demonstrated that glioblastoma-derived EXs enhanced EC migration and angiogenesis via delivering angiogenic miR-296 and inhibiting the degradation of VEGF receptor-2 (VEGFR-2) in ECs [12]. In addition, searching for miR targets by Targetscan confirmed that miR-200c binds to the 3'-UTR region of VEGFR-2. In addition, degradation of extracellular matrix (ECM) is the first step in the invasion and metastasis of cancer cells. Exosomes carried MMP can activate downstream integrins, epidermal growth factor and Notch receptors for remolding ECM [13, 14]. Exosome derived from melanoma contains high levels of proteases such as uPAR, ADAMs and HAdase, which mediate the digestion of cellular skeleton proteins such like type I and IV collagens, laminins and fibronectin [15].

Exosomes influence melanoma immune microenvironment

Exosome mediated direct or indirect immune escape is another mechanism of melanoma progression. Exosomes can directly deliver inhibitory or apoptotic signals from melanoma to affect distant normal immune cells such as T cell or nature killer cells, or expand the negative regulators of immune system, such as regulatory T-cells (Treg) and myeloid-derived suppressor cells (MDSCs), to supporting tumor cell escape from immune surveillance [16, 17]. MDSCs accumulate in the secondary organs, blood and tumor tissues to provide supporting stromal and immune evasion. For example, a previous study reported that highly metastatic mouse melanoma cell line (B16-F10) derived exosomes contained PTPN11 mRNA and protein for which dose dependently suppressed T cell proliferation, whereas benign melanoma cell line (B16-F0) derived exosomes have negligible effect on T cell proliferation. Mechanism study releaved that the PTPN11 protein was elevated in T cells. Collectively, the results suggest that exosomes deliver a complex biological payload that upregulates PTPN11 to suppress CD8+ T lymphocyte function [18]. It is important to note that the miRNA and protein cargos carried by melanoma exosomes can be changed under different growth conditions. For example, miRNA expression profile was different in melanoma exosomes released under hypoxia stimuli as compared with normoxic condition, pathway analysis pointed at several cellular processes contributing to melanoma proliferation, drug resistance, and modification of the tumor

microenvironment, including immunosuppression [19].

Clinical implication of exosomes in melanoma

Clinical monitoring of exosomes in melanoma progression and prevention of metastasis used reported. A study tested the exosomes derived from the sera of patients with melanoma, and found that tumor-derived exosomes contain melanoma signature proteins such like TYRP2, VLA4, HSP70, MET and Rab27a. The concentration of TYRP2 and MET in exosomes was increased, which were found to be a predictor of disease progression. Melanoma patients with a higher protein content in exosomes had a poor prognosis, when compared to patients who had a low protein concentration in exosomes [20]. Similarly, the amounts of CAV-1, S100B, and MIA (melanoma inhibitory activity) were higher from the sera of melanoma patients, than in healthy controls. A negative correlation between high levels of CAV-1+ exosome and clinical outcome was demonstrated, suggesting the potential prognostic role of exosome in melanoma [21, 22].

Conclusions

Melanoma derived exosomes play a wide range of biological functions, primarily via cell to cell cross-talk and delivery of effectors or signaling molecules that regulate different cellular processes. They can contribute to cancer development, angiogenesis and metastasis, as well as immune suppression. Clinical strategy use of melanoma represents a promising biomarker for disease progression and prognosis.

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