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A brief review of exosomes and their roles in cancer

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ABSTRACT

Exosomes are small membrane vesicles of endocytic origin, which can contain DNA fragments, mRNAs, microRNAs and proteins. Exosomes transport these cargos from a donor cell to target cells, where they can play important roles. So the role of exosomes in cancer development has become the focus of much research. Here, we discuss different mechanisms associated with biogenesis, function and application of exosomes. We highlight the functional relevance of exosomes in cancer and their applications as novel cancer biomarkers and therapeutic approach. Recently, a large number of studies have reported that exosomes influence major tumor-related pathways, such as hypoxia-driven epithelial to mesenchymal transition, angiogenesis, and metastasis. So, understanding the molecular mechanism of their action would open a new avenue to cancer diagnosis and treatment.

Contents

1. Introduction

Malignant tumors have a complex composition containing both tumor cells and the stroma around them. Cell-cell communication and the microenvironment are main factors for tumor growth. Recent evidences suggest that exosomes have a pivotal role in cell-cell communication in cancer development (Kahlert and Kalluri, 2013). Exosomes are small extracellular vesicles (EVs) with a size of 30–100 nm (Trams et al., 1981) that are secreted from most human cell types. In addition, most of the tumor cells secrete these small vesicles which give the possibility to detect them in different fluids of the human body, including plasma, serum, urine, saliva, breast milk and amniotic fluid (Keller et al., 2006). Previously, exosomes were considered as "garbage bag" specified for depleting wasteful metabolic products of the cells. Preceding studies have discovered multiple different functions for these vesicles. Nowadays, they are considered as bio-vesicles, which formulate cell-cell communications through packaging and transferring the bio-molecules such as proteins, mRNAs and miRNAs throughout the body (Valadi et

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al., 2007). Corresponding to their original cells, exosomes have different physiological or pathological functions. (Azmi et al., 2013; Fais, 2014; Kahlert and Kalluri, 2013; Keller et al., 2006; Tickner et al., 2014). Regarding to beneficial advantages of exosomes in cancer diagnosis and their newly-suggested application, these nano-vesicles prepared a new interesting area of research around the world. In current paper we review some of the recent studies and overviews the biogenesis, function and application of exosomes in cancer biology.

2. Exosome biogenesis

Unlike to the larger microvesicles which directly bulged out from the plasma membrane, exosomes originate from endosomal parts of the cell. In the first step, they derive from late-vesicles during the ceramide-dependent initiation phase and encompass intracellular biomolecules such as proteins or RNAs (Trajkovic et al., 2008). Here the role of ceramide is to help vesicles contents escape from lysosomal digestion in favor of release as exosomes (Trajkovic et al., 2008). In the next step, these multivesicular bodies (MVBs) become incorporated into the plasma membrane and release the exosomes into the extracellular matrix (Fevrier and Raposo, 2004). Cell-derived exosomes not only carry the tissue-specific biomolecules, but they also carry common proteins that are known as exosome markers such as tetraspanins family (CD63, CD9, CD81 and CD82), members of ESCRT complex (TSG101 and Alix) and heat shock proteins (HSP60, HSP70 and HSP90) (Kahlert and Kalluri, 2013). The two-layered membrane of exosomes protects their content against degradation events (Taylor and Gercel-Taylor, 2013).

3. Cell-specific exosome uptake

Several mechanisms have been suggested for EV-uptaking by the cells: Clathrin-dependent endocytosis, phagocytosis, macro-pinocytosis and cell membrane fusion. A set of protein-protein and protein-lipid interaction play role in each mechanism (Mulcahy et al., 2014). Although some studies declared that stained EVs could target all cell types, it was found that EV-uptaking is a cell type_specific process which happens when the cell surface receptors are completely matched to the protein compounds of EV (Mulcahy et al., 2014). EV-uptaking has occurred in a non-random procedure by the intervention of trans-membrane proteins (Feng et al., 2010). Recent studies showed that tetraspanin–integrin complex conducts EVs to bind to target cells (Rana et al., 2012).

4. Exosomes and cancer

Though some studies considered the exosomes as cell garbage bags, it has been found that the exosomes derived from tumor cells are been able to transfer information between cells by binding to the target cells *via* specific surface proteins and discharging their load on them and modulate cells' genetic expression. Exosomes exhibit specific cell-type dependent content include proteins (Camussi et al., 2010) and RNAs (Lotvall and Valadi, 2007) and so different functions have been related to exosomes. They could be involved in cell-to-cell information transfer (Lee et al., 2012), induction of hypoxia (Kucharzewska et al., 2013; Park et al., 2010), formation of pre-metastatic niche (Costa-Silva et al., 2015; Peinado et al., 2012) and developing metastasis (Kahlert and Kalluri, 2013). In the following sections we briefly discuss these items.

4.1. Transfering macromolecules to target cells

Exosomes are loaded with proteins, coding and non-coding RNAs, which are different according to their origin. So they can be envisioned as a kind of signaling complex. It has also been well documented that cell extracts may induce epigenetic alternation in co-cultured target cells, although the mechanisms responsible are not fully understood (Lotvall and Valadi, 2007). For example, permeabilized fibroblasts that exposed to extracts from lymphocytic cells began to express various genes typical of lymphocytes. Transfering information *via* exosomes could be one of the reasons for this phenomenon (Valadi et al., 2007). Proteomic investigations of exosomes from diverse cell types has revealed a common set of membrane and cytosolic proteins besides an array of proteins that reflect the originating host cell (Simpson et al., 2009). Recent studies showed that exosomes contain inactive forms of both mRNA and microRNA that can be transferred to another cell and be functional in that new environment. For example Valadi et al., using microarray and microRNA chip analysis identified 1300 mRNAs and 120 microRNAs in bone marrow derived -mast cell exosomes (Valadi et al., 2007). The RNA that can be shuttled between cells *via* exosomes is suggested to be called “exosomal shuttle” RNA (esRNA). These RNAs could affect various cancer related pathways based on genetic alternation that they caused in target cells (Lotvall and Valadi, 2007).

4.2. Induction of hypoxia and tumor growth

Exosomes are one the main carriers which influence the homeostasis in the tumor environment and play roles in the development of neoplasia. EVs derived from tumors could change the phenotype of normal cells by introducing proteins and RNAs into them. Since the hypoxia result in induction of tumor factors, suppression of hypoxia and related factors potentially can be considered as a cancer therapeutic way (Wilson and Hay, 2011). Studies have shown that hypoxia causes the secretion of exosomes in glioma (Kucharzewska et al., 2013) and breast cancer (King et al., 2012). Park et al., showed that the cell which undergo hypoxia, secret exosomes containing A431, Alix and Tetraspanins proteins which proceed angiogenesis and metastasis events (Park et al., 2010). Also in a recent study Li et al., reported that hypoxic microenvironment of oral squamous cell carcinoma (OSCC) cells may stimulate tumor cells to generate miR-21–rich exosomes that are delivered to normoxic cells to promote prometastatic behaviors (Li et al., 2016). In addition, same experiments reported that tumor cells adapt themselves to hypoxia by highly production of exosomes and inducing angiogenesis and metastasis capability (Svensson et al., 2011).

4.3. Formation of pre-metastatic niche and develoing metastasis

The most detrimental aspect of cancer is metastasis event whereby the disease persists against the therapeutic procedures. Primary tumor cells secret chemokines and growth factors and prepare an optimal environment for metastasis (Sceneay et al., 2013). Beside secretion of soluble factors in the form of free molecules, tumor cells produce complex mixture of molecules, encompassed by exosomes. Initial steps in the formation of pre-metastatic niche, such as endothelial permeabilization, proliferation and angiogenesis, are regulated by exosomes (Kharaziha et al., 2012). Recently Costa-Silva et al., showed that Pancreatic ductal adenocarcinomas (PDACs) - derived exosomes induce liver pre-metastatic niche formation in naive mice and consequently increase liver metastatic burden. They found that macrophage migration inhibitory factor (MIF) was highly expressed in PDAC-derived exosomes, and its blockade prevented liver pre-metastatic niche formation and metastasis (Costa-Silva et al., 2015). Also Hoshino et al., demonstrate that exosomes from mouse and human lung, liver and brain-tropic tumor cells fuse preferentially with resident cells at their predicted destination, namely lung fibroblasts and epithelial cells, liver Kupffer cells and brain endothelial cells and prepare the pre-metastatic niche. Interestingly in this study exosome proteomics revealed distinct integrin expression patterns, in which the exosomal integrins $\alpha_6\beta_4$ and $\alpha_6\beta_1$ were associated with lung metastasis, while exosomal integrin $\alpha_v\beta_5$ was linked to liver metastasis (Hoshino et al., 2015). Peinado et al., report that exosomes which have EMT receptors could reprogram lung BMDCs to pre-angiogenic phenotype (Peinado et al., 2012). Grange et al., also isolated several proto-oncogenic factors from kidney cancer