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Review

The role of exosomes in cancer metastasis

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ABSTRACT

Exosomes are small membrane vesicles with a size ranging from 40 to 100 nm. They can serve as functional mediators in cell interaction leading to cancer metastasis. Metastasis is a complex multistep process of cancer cell invasion, survival in blood vessels, attachment to and colonization of the host organ. Exosomes influence every step of this cascade and can be targeted by oncological treatment. This review highlights the role of exosomes in the various steps of the metastatic cascade and how exosome dependent pathways can be targeted as therapeutic approach or used for liquid biopsies.

Contents

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1. Introduction

Most studies of the pathogenesis of metastasis focus on genetic or phenotypic changes of the cancer cell itself, however, there is growing evidence that cancer cells communicate with each other and the surrounding stroma leading to metastasis [1].

Metastasis is a multistep process including invasion of the tumor cell through the basal membrane and into blood vessels, survival in the blood circulation, attachment to the blood vessels, extravasation and at last colonization and growth in the host organ [2]. Cells can communicate with various types of extracellular membrane vesicles. These include exosomes, proteasomes, apoptotic blebs and microvesicles [3]. Since exosomes can promote a variety of intratumoral biological processes, it seems likely that they can also influence metastatic properties of malignant tumors. The following review focuses on the role of exosomes in this multistep metastatic process.

2. Biogenesis and morphology of exosomes

2.1. Morphology

Trams and co-authors first described exosomes in 1981 as microvesicles containing 5'-nucleotidase activity which are released by neoplastic cell lines [4]. A few years later their endocytic origin was proven [5]. Exosomes can be identified by a few characteristics. They have a size between 40 and 100 nm and are secreted after fusion of multivesicular endosomes with the cell surface or by direct budding from the plasma membrane [6]. They are round or have a cup shaped morphology and have a density between 1.13 and 1.19 g/ml [3]. Exosomes can be identified by their unique protein and lipid composition and double lipid layer due to their origin in the fusion of late endocytic compartments with the plasma membrane [7].

2.2. Biogenesis

Exosomes ori ginate in a reverse budding event, causing the vesicles to carry cytosol and expose the extracellular domain of surface receptors [8]. They constitutively fuse with the plasma membrane either after Ca^{++}-dependent activation or after activation of Rab-GTPases [9]. Rab25 regulates exosome binding to and tethering with the plasma membrane and Rab27b exosome release [10,11] (Fig. 1). The increased secretion of exosomes by cancer cells is induced by overexpression of Rab3D (a small GTPase, [12]. Release of exosomes can also be induced by diverse signalling pathways including the activation of the Wnt pathway, which is especially important in deregulated exosome secretion in cancer cells [13]. The acidic microenvironment around tumors stimulates the release of exosomes and enhances their cell fusion capabilities [14]. The uptake of exosomes is accomplished via endocytosis, receptor-ligand interaction or by direct fusion and dependent on microenvironmental pH [14,15] (Fig. 2).

2.3. Exosomal content

Exosomes contain cytosolic proteins or proteins of the plasma/endosome membrane while proteins of the nucleus, mitochondria, endoplasmatic reticulum or golgi-appartus are absent [16]. The sorting of proteins into exosomes is an area of current research and is at least in part dependent on protein ubiquitylation and the ESCRT (endosomal sorting complex required for transport machinery) [3,17,18] (Fig. 1). The ESCRT form small necks that occur at the plasma membrane during exosome formation. They contain filaments, flat spirals, tubes and conical funnels that are thought to direct membrane remodeling. Their assembly and disassembly is ATP-dependent [19].

Exosomes contain a high amount of transport proteins like tubulin, actin and actin-binding molecules [16] as well as several proteins associated with specific functions of secreting cells [8]. Nearly all exosomes carry MHC class I- molecules [20] and heat shock protein (HSP), especially HSP 70 and HSP 90 [8,16]. HSP 70 and HSP 90 are involved in antigen presentation and can bind antigenic peptides to MHC class I-molecules [8]. Exosomes carry high concentrations of tetraspanins – including CD9, CD63, CD81 and CD82–that are rarely present in other microvesicles and are involved in antigen presentation and adhesion through interaction with other transmembrane proteins. CD9 and CD82 inhibit migration and invasion of tumor cells in vitro and in vivo by interaction with integrins [21]. To date more than 41 860 different proteins have been reported as cargo of exosomes and are listed in online databases like Exocarta (http://www.exocarta.org) and Visclepedia (http://www.microvesicles.org).

In addition to proteins, exosomes contain lipids, particularly raft-lipids like ceramides, sphingolipids, cholesterol and glycerophospholipids as well as micro-RNA, mRNA and DNA enabling cells to exchange genetic information [22].

Mi-RNAs are small non-coding RNAs that bind within the 3′-UTR (3′-untranslated region) of mRNAs leading to destabilisation and fragmentation of these RNAs and consequently to reduced expression of the encoded protein [23,24]. That miRNA is the major RNA component of exosomes and was first discovered at the University of Gotteburg by the scientific group around Prof. J. Lotvall in 2007 [25,26]. This mode of transportation makes the miRNA resistant of degradation through extracellular ribonculeases [27]. The miRNA transported in TDEs (tumor derived exosomes) reflects the dysregulated miRNA profile of the cancer cells and can be transported to different cell types or to the pre-metastatic niche enabling wide spread influence on the gene expression of target cells [28]. Despite solely transporting miRNA, exosomes are able to process pre-miRNAs to mature-miRNAs, allowing direct interaction with

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