Exosomes and Brain Metastases

Subjects: Biochemistry & Molecular Biology
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Brain metastases (BM) are a frequent complication in patients with advanced stages of cancer, associated with impairment of the neurological function, quality of life, prognosis, and survival. BM treatment consists of a combination of the available cancer therapies, such as surgery, radiotherapy, chemotherapy, immunotherapy and targeted therapies. Even so, cancer patients with BM are still linked to poor prognosis, with overall survival being reported as 12 months or less. Intercellular communication has a pivotal role in the development of metastases, therefore, it has been extensively studied not only to better understand the metastization process, but also to further develop new therapeutic strategies. Exosomes have emerged as key players in intercellular communication being potential therapeutic targets, drug delivery systems (DDS) or biomarkers.

Keywords: exosomes ; tumor microenvironment ; pre-metastatic niche

1. Introduction

Cancer is amongst the leading causes of death worldwide, causing nearly 10 million deaths in 2020, while metastases are the primary cause of cancer-related death [1]. Brain metastases (BM), in particular, are a frequent complication in patients with advanced cancer, with critical impact on neurological function, quality of life, prognosis and survival [2][3]. The types of cancer most frequently associated to brain metastases are lung, breast and skin (melanoma) [3][4] with lung and breast cancers being the two most frequently diagnosed cancers in the world [1]. The increase in BM incidence can be in part explained by improvement of systemic cancer treatment, which increases patients' life span. In addition, better imaging technology allows earlier cancer detection. However, BM treatment is complex, and may include one or a combination of available therapies that include surgery, radiotherapy, chemotherapy, immunotherapy and targeted therapies [3][4][5]. Nonetheless, the prognosis for cancer patients with BM remains poor, with the majority of the results from clinical trials showing patients' overall survival below 12 months [5].

One of the major obstacles to develop an effective BM treatment relies on the impermeable nature of the blood–brain barrier (BBB), which confers the brain a sanctuary status, where metastatic cancer cells can settle and proliferate as they are protected from most anticancer drugs [4][6]. In this context, the BBB is nowadays one of the most extensively studied biological barriers for which there is a need to understand its complex physiology and develop new strategies to effectively deliver anticancer drugs to the brain [7]. Exosomes, nano-sized extracellular vesicles with a natural ability to cross the BBB, have been simultaneously described as a strategy used by cancer cells to promote the metastization process and as a promising drug delivery system (DDS) for BM targeting. In this Review, we will focus the role of exosomes in BM formation and discuss their impact on metastatic cancer treatment.

2. Exosomes and Their Role in Cancer and Brain Metastases

2.1. Exosomes' Biogenesis and Composition

Exosomes are nano-sized (30–150 nm) extracellular vesicles (EVs) formed by a lipid bilayer surrounding an organelle-deprived cytosol with several biomolecules, such as proteins, glycans, lipids, RNA and DNA [8][9]. These vesicles are naturally found in various body fluids, such as blood plasma and urine, and they are produced by most (if not all) cells [10]. Exosomes' biogenesis starts with the invagination of the endosomal limiting membranes resulting in intraluminal vesicles (ILVs) inside the endosome, forming the so-called multivesicular body (MVB) [9][11]. This MVB will then fuse with the cell membrane, releasing the ILVs which are now referred to as exosomes [9]. Therefore, contrary to other types of EVs that result from direct plasma membrane budding, exosomes come from the endocytic pathway [9]. In addition to the site of the biogenesis, another feature that distinguishes exosomes from other types of EVs is the size. EVs produced by the cell from direct budding of the plasma membrane are considered to be larger than exosomes (100–1000 nm) [11][12]. Exosomes' production is a complex process which involves several different protein machineries, namely: (1) endosomal sorting complexes required for transport (ESCRT) to regulate ILV formation; (2) tetraspanins, transmembrane proteins

which enable vesicle formation by promoting membrane curvature; (3) Rab GTPase proteins for endosomal trafficking control and (4) several enzymes, such as sphingomyelinase, to produce ceramides and promote vesicle formation [9][11][12]. Interestingly, some of these protein networks and complexes are also involved in the formation of other types of EVs and, therefore, despite having distinctive sites for biogenesis and sizes, exosomes and other EVs share common protein machinery [9][12]. Importantly, the need for such a complex protein machinery for exosome formation implies that this is a heavily regulated process involving the secretion of specific substrates, which suggest a critical function for these vesicles, as discussed in the next section. Another piece of evidence of the specificity and selectivity of exosomes' biogenesis is the heterogeneity of the exosomes' population with different subpopulations exhibiting different molecular compositions and organ distribution, and suggesting different roles [13]. Recent studies suggest the classification of the subpopulations of exosomes as follows: Exo-Large (90–120 nm), Exo-Small (60–80 nm) and membrane-less exomeres (<50 nm) [13].

Exosomes' lipidic composition shares similarities to that of membrane lipid rafts, and it includes ceramides, sphingolipids, cholesterol and glycerophospholipids [10][14]. The protein content of exosomes is very broad as it can contain cytosolic or nuclear proteins, transport-involved or adhesion-related and also membrane-bound proteins [10]. Some examples of this wide variety of proteins include heat shock protein (HSP70, HSP90), tetraspanins (CD9, CD63, CD81 and CD82), epithelial cell adhesion molecule (EpCAM) and proteins involved in exosomes biogenesis (ESCRT complex, ALIX, TSG101) [15]. For more specific details on exosomes composition, a manually curated web database containing information about exosomal proteins, RNAs and lipids is available at www.exocarta.org (accessed on 04 October 2021) [16].

2.2. Exosomes' Roles in Metastatic Cancer

Exosomes were initially thought to be a mechanism through which cells could eliminate unnecessary proteins [17][18]. However, the past decades were marked by a notable development in the study of exosomes and it is now demonstrated that these EVs play a critical role in intercellular communication, which is of paramount importance in the context of tumor progression and metastases [8][9][19][20][21].

Even though the mechanisms by which exosomes are taken up by recipient cells is not fully understood, several studies bring evidence of a non-random process which is dependent on transmembrane proteins [22][23]. For example, a study by Kuroda et al. recently identified possible receptors for the uptake of exosomes derived from SK-Mel-28 melanoma cells in human brain capillary endothelial cells (hCMEC/D3) [22]. This study revealed that the uptake of SK-Mel-28-derived exosomes by hCMEC/D3 cells occurs via macropinocytosis and receptor-mediated pathways, with major contribution of the presence of CD46 in hCMEC/D3 [22]. This selective uptake by recipient cells together with the heavily regulated loading process briefly described in the previous section, supports the specific and critical function of these vesicles in intercellular communication.

Recent reports have demonstrated that the successful development of brain metastases rely on a complex intercellular communication occurring between metastatic cancer cells and brain stroma cells, which involves secreted proteins or small vesicles, namely exosomes [24][25]. The existence of various mechanisms by which exosomes are capable of positively or negatively influencing brain colonization by cancer cells is evidence of an immense complex intercellular communication network, which can be considered as a target for new therapeutic approaches or as an inspiration for new drug delivery strategies. In the next sections, we will review some roles of exosomes in tumor progression with focus on intercellular communication within the tumor microenvironment (TME) and in pre-metastatic niche (PMN).

2.2.1. The Tumor Microenvironment (TME): A Dynamic Neighborhood

The TME and its intrinsic complex intercellular communication network, established between stromal and cancer cells, highlights the magnitude of the challenge in understanding and treating cancer. The TME constantly changes during cancer progression as a response to evolving tumors and their oncogenic signals [26]. Therefore, when addressing the formation of metastases, it is necessary to consider the influence of the TME, as its dynamic character allows tumor cells to modulate their own niche. This topic has been reviewed in detail by Quail and Joyce [26].

Over the past decades, emerging evidence suggests that tumor-derived exosomes (TDEs) and exosomes derived from stromal cells of the TME are crucial in modulating tumor growth, angiogenesis, invasion, survival, and metastases formation [27][28]. Virtually, TDEs play critical roles in every step of the metastatic cascade. Overall, this process can be considered as having two different stages: the TME stage, where the TDEs induce the epithelial–mesenchymal transition (EMT) in neoplastic epithelial cells conferring them intravasation and migration ability; the PMN stage, which happens in distal and specific organs that will foster metastases [29]. These two stages are represented in **Figure 1**, which

schematically represents the subject reviewed in this work. The role of exosomes in the PMN will be discussed in the next section. In fact, when trying to describe the role of exosomes in brain metastases formation, the most critical and intriguing step may be the transmigration of the BBB and further brain parenchyma colonization by cancer cells. However, before reaching that stage in the metastatic cascade, tumor cells need to first lose their adhesion to the surrounding stroma and enter the bloodstream [29][30].

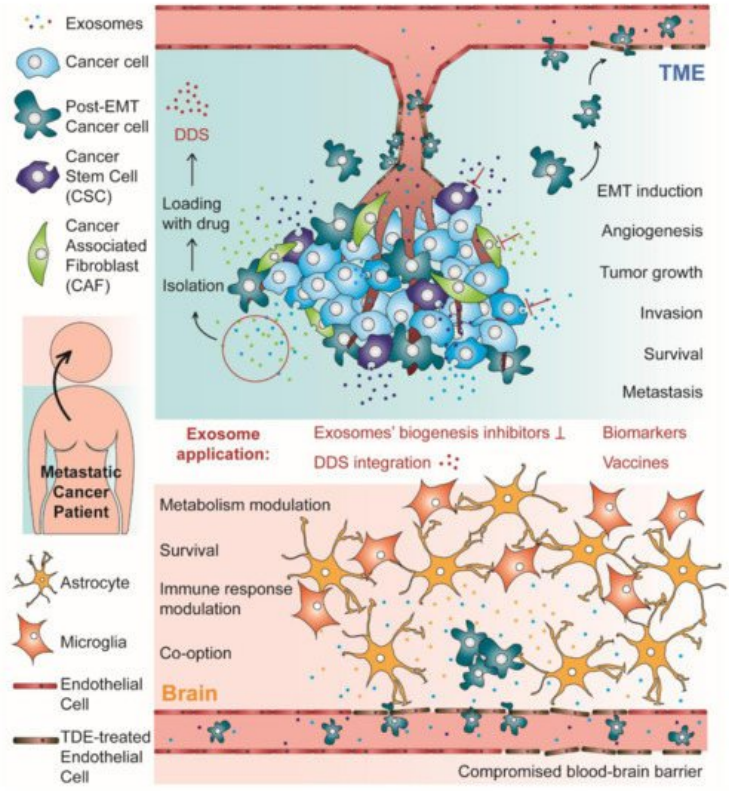

Figure 1. Schematic representation of both stages of the process of metastases formation with tropism to the brain: the tumor microenvironment (TME) and the pre-metastatic niche (PMN)/metastases establishment in the brain. In the TME, tumor derived exosomes (TDEs) are responsible for many critical phenomena, such as epithelial–mesenchymal transition (EMT) and angiogenesis, which supports tumor growth, invasion, survival, and metastases formation. In this stage, the exosomes can also induce endothelial barrier permeation, facilitating the passage of cancer cells to the blood flow. In the brain, exosomes from cancer cells induce many alterations that contribute to PMN establishment, such as blood–brain barrier (BBB) permeation, metabolism and immune response modulation and vascular co-option induction, which supports the brain parenchyma invasion by arriving circulating tumor cells, metastases formation and cancer cells survival. Brain metastases are also supported by the crosstalk between cancer cells and cells from the BBB, such as astrocytes. For their critical role in metastases formation, exosomes can be considered as a promising new target for metastatic cancer therapy, using inhibitors of exosomes' biogenesis. Alternatively, these extracellular vesicles have been investigated as biomarkers for metastatic cancer diagnosis and prognosis, as vehicles in drug delivery systems (DDS) and as cell-free therapeutic tools in anti-tumor vaccination.

The metastatic cascade is initiated within the TME, with the activation of EMT process in neoplastic epithelial cells [29]. EMT is the reversible process by which a neoplastic epithelial cell undergoes to acquire mesenchymal features, such as migratory and invasive abilities [29]. During this process, the cells undergoing EMT downregulate epithelial markers, such as cytokeratin and E-cadherin, and upregulate mesenchymal markers as N-cadherin and vimentin [31][32]. Interestingly, the cadherin switch inherent to EMT modulates pro- and anti-apoptotic genes, allowing cancer cells to avoid programmed cell death induced by adhesion loss once they acquire a mesenchymal phenotype [32]. Other relevant features of the mesenchymal phenotype is the increase of matrix metalloproteinases (MMPs) and altered protein production which contributes to the breakdown of the basement membrane [33][34]. Overall, the mesenchymal phenotype renders neoplastic cells the ability to alter their shape and motility, detach from the primary tumor site and enter the bloodstream [35]. Additionally, exosomes secreted during hypoxia, which is linked to EMT and high risk of metastases, are enriched in EMT inducers when compared to those produced in a normoxic state [29].

Recent studies have been building evidence of TDEs involvement in EMT. More specifically, TDEs have been described to transfer considerable amounts of EMT inducers to recipient tumor stroma epithelial cells, which then undergo biochemical changes consistent with EMT [29][36][37][38]. The EMT induction promoted by exosomes can happen via several EMT-

related signaling pathways. One of the most studied EMT-inducing signaling pathways is Wnt/β-catenin which is also a common target for exosomes [39][40]. For instance, the transfer of exosomal microRNA (miR)-1260b between lung adenocarcinoma cells leads to downregulation of sFRP1 and Smad4, activating the Wnt/β-catenin pathway [41]. Exosomes derived from cancer associated fibroblasts (CAFs) transferred miR-92a-3p to colorectal cancer cells activating the Wnt/β-catenin pathway and thereby inducing EMT [42]. Furthermore, exosomal miR-92a-3p effect in recipient cells also included apoptosis inhibition and chemotherapy resistance [42], which demonstrates that the crosstalk within the TME dictates tumor progression by modulating several features within the tumor niche. Another line of evidence supporting this TME modulation through exosome-mediated crosstalk is the transfer of miR-155 from breast cancer stem cells (CSCs) and chemoresistant breast cancer cells to sensitive breast cancer cells, leading to marked chemoresistance and inducing EMT [36]. Additionally, a study by Donnaruma and co-workers revealed that several exosomal miRNAs secreted by CAFs were able to induce EMT, facilitate anchorage-independent cell growth and increase the ability to form mammospheres in breast cancer cells [43]. In addition to miRNAs, You and co-workers recently showed that CAFs derived exosomes transferred SNAI1 mRNA to lung cancer cells, inducing EMT via Wnt/β-catenin pathway [44]. Snail1 is a transcription factor which represses the expression of E-cadherin, therefore inducing EMT [44]. In another study, Menck and co-workers described the reciprocal loop between infiltrating macrophages and breast cancer cells. Breast cancer cells secrete exosomes that induce the Wnt ligand Wnt5a in infiltrating macrophages. Macrophages are then responsible to shuttle the Wnt5a to tumor cells, promoting their invasion [45].

Alternatively, exosomes secreted by mesenchymal stem cells (MSCs)-derived adipocytes were able to induce EMT in breast cancer cells via Hippo pathway [46]. Even though in this case the cargo responsible for EMT induction was not identified, other studies showed that activation of the Hippo pathway may result from the transfer of exosomal miRNAs or proteins [47][48][49][50]. Another alternative pathway associated with EMT is the extracellular-regulated protein kinase (ERK) pathway. Exosomes secreted by gastric cancer cells activated the mitogen-activated protein kinase (MAPK)/ERK pathway in recipient cells, leading to tumor proliferation [51].

Collectively, these studies are evidence that the exosome-mediated crosstalk within the TME is crucial for the initiation of metastization process, involving not only TDEs but also exosomes derived from CAFs, macrophages and many other cell types.

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