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Review

Exosomes: Key mediators of metastasis and pre-metastatic niche formation

Richard J. Lobb[a,1], Luize G. Lima[a,1], Andreas Möller[a,b,*]

[a] Tumour Microenvironment Laboratory, QIMR Berghofer Medical Research Institute, 300 Herston Road, Herston, QLD 4006, Australia
[b] School of Medicine, University of Queensland, Brisbane, QLD 4072, Australia

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ABSTRACT

While tumour cells are classically known to communicate via direct cell-to-cell contact and the secretion of soluble protein-based factors such as cytokines and growth factors, alternative novel mechanisms that promote tumour progression have recently emerged. Now, new critical components of the secretome thought to be involved in tumour progression are exosomes, small vesicles of endocytic origin that carry a variety of bioactive molecules, including proteins, lipids, RNA, as well as DNA molecules. Cancer cell-derived exosomes have been shown to participate in crucial steps of metastatic spread of a primary tumour, ranging from oncogenic reprogramming of malignant cells to formation of pre-metastatic niches. These effects are achieved through the mediation of intercellular cross-talk and subsequent modification of both local and distant microenvironments in an autocrine and paracrine fashion. Here, we summarise the recent findings that implicate this non-canonical signalling within the tumour as a critical driver of metastatic disease progression, and discuss how understanding the molecular mechanisms involved in exosome-mediated metastasis is of great value for the development of new therapeutic strategies to prevent cancer progression.

Contents

Abbreviation: BM, bone marrow; BMDCs, bone marrow-derived cells; EVs, extracellular vesicles; FasL, fas ligand; FGF2, fibroblast growth factor 2; GM-CSF, granulocyte macrophage colony-stimulating factor; HGF, hepatocyte growth factor; HIF-1, hypoxia-inducible factor 1; HUVECs, human umbilical vein endothelial cells; IBA-1, ionized calcium-binding adapter molecule 1; IL-6, interleukin 6; MDSCs, myeloid-derived suppressor cells; MMP, matrix metalloproteinase; MVBs, multivesicular bodies; PGE2, prostaglandin E2; PKM, pyruvate kinase; PlGF, placental growth factor; PTEN, Phosphatase and tensin homolog; TGF-β, transforming growth factor beta; TLR, toll like receptor; TNF-α, tumour necrosis factor alpha; TRAIL, TNF-related apoptosis-inducing ligand; VEGF, vascular endothelial growth factor; VEGFR-1, vascular endothelial growth factor receptor 1; VLA-4, very late antigen 4; ZO-1, zonula occludens.

* Corresponding author at: 300 Herston Road, Herston, QLD, 4006, Australia.
E-mail address: andreas.moller@qimrberghofer.edu.au (A. Möller).
[1] These authors contributed equally to this work.

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1. Introduction

Despite significant advancements in therapies, a large proportion of cancer patients will ultimately pass away due to metastatic disease progression. It is therefore a key goal of cancer research efforts to further our understanding of metastatic disease progression and its dynamics. Based on recent research findings, it is clear that metastatic disease is not a random process. That is, the seeding of cancer cells at secondary organs does occur in an organ-specific manner, depending on the cancer type, verifying the so called "seed and soil" hypothesis, which was originally proposed over 100 years ago by Stephen Paget [1,2]. This concept of metastatic growth specificity has since been validated experimentally and clinically [3], and decisively shown that even when cancer cells can be found in the vasculature of multiple organs, only selective sites consistently develop metastatic tumour deposits [4]. It is now widely accepted that the spread of cancer cells to secondary organs is indeed promoted by the prior formation of a specialised environment at distant sites, termed the pre-metastatic niche.

Originally, pre-metastatic niche formation was shown to consist of bone marrow-derived hematopoietic progenitor cells (BMDCs), which accumulate at pre-metastatic sites in organs different to the site of the primary tumour and before the arrival of any cancer cells [5]. These BMDCs expressed VLA-4, and were recruited by tumour-derived secreted factors, which resulted in the accumulation of the VLA-4 ligand fibronectin at pre-metastatic organs [5]. Since then, numerous studies have established that variable tumour-secreted factors are responsible for establishing a permissive secondary organ through the modulation of a number of stromal cell-types [6]. However, these studies have largely focused on canonical intercellular communication based on classical cytokines, chemokines and growth factors; yet, it is becoming evident non-canonical signalling pathways are also involved in pre-metastatic niche formation [7].

More recently, a new mechanism of intercellular communication *via* the secretion of extracellular vesicles (EVs) has been established as an integral part of complex tumour-host interactions [8]. Clinical interest in EVs has heightened due to the fact that continuing evidence supports the notion that EVs represent a new paradigm of intercellular communication [9]. EVs are constitutively secreted by most likely all different cell lineages in the body, and carry diverse molecular contents, including proteins, lipids, RNA (mRNA, miRNA, lncRNA, and other RNA molecules), as well as DNA molecules (dsDNA, ssDNA, mtDNA) [10]. There are a variety of EVs subtypes, and their accurate annotation is currently an ongoing, contentious problem in the field [11]. There are clearly two distinct subtypes of EVs that can be separated effectively through differential centrifugation: microvesicles are the larger subclass (200–1000 nm) and sediment between 10,000 and 20,000*g*, while smaller EVs known as exosomes exhibit a more homogenous size distribution of 30–150 nm, and sediment at 100,000*g* [9,11,12]. Exosomes are constitutively released by a variety of cell lineages, including cancer cells [10]. The biogenesis of exosomes is classically described as originating from the endosomal compartment and are formed as intraluminal vesicles by inward budding of the limiting membrane of late endosomes, forming multivescular bodies (MVBs). The subsequent fusion of MVBs with the plasma membrane allows the release of exosomes into the extracellular environment. This fusion and release into the extracellular milieu, allows cancer cells to utilise exosomes to modify local microenvironments, or systemically modify distant organs to provide favourable microenvironments for the dissemination and outgrowth of metastases [13–15]. These effects are achieved by the bioactive molecular constituents of exosomes mentioned earlier, which are in turn determined by the cell of origin that the exosomes are secreted from [10,13–15]. For this very reason, exosomes have become a valuable target in identifying novel cancer biomarkers that could potentially diagnose cancer, predict patient outcome or response, and understand, and perhaps prevent, cancer progression.

Cancer cell-derived exosomes have been shown to significantly contribute to different aspects of metastatic dissemination of a primary tumour, including invasion of the surrounding tissues, angiogenesis, modulation of immune responses, and formation of the pre-metastatic niche [16]. The roles exosomes have in pre-metastatic niche formation are diverse, and range from metabolic reprogramming, to recruitment of numerous immune and non-immune stromal cells in order to facilitate metastatic outgrowth. The aim of this review is to discuss the particular multi-faceted roles of these extracellular particles that impact both cancer cell spread from primary to secondary organs, resulting in the outgrowth of macroscopic metastatic lesions (Fig. 1), and lastly, provide new insights into how this can be translated to clinical applications.

2. The role of exosomes in the primary tumour microenvironment

2.1. Exosomes and angiogenesis

A common process known to be involved in tumour progression is hypoxia. Hypoxia is the relative reduction in oxygen tension and occurs in all solid tumours larger than 1 cm^3. This results from inadequate blood supply due to the aberrant microcirculation found in most tumours [17,18]. The microcirculation is essential in normal tissues homeostasis, as it is responsible for balancing the supply of nutrients and removal of cellular waste products [19,20]. In the context of a solid tumour, neo-angiogenesis, or the physiological process of new blood vessel growth, is necessary for continued tumour growth in response to hypoxia [19,20]. Typically, solid tumours have been described to induce vascular remodelling through the secretion of soluble factors, such as VEGF and PlGF. However, exosomes are also capable of being key mediators between cancer cells and the surrounding vasculature by eliciting pro-angiogenic responses [21,22]. Hypoxic glioblastoma-derived exosomes are capable of inducing microvasculature sprouting and vascularisation of xenografts models [22]. In response to this angiogenic phenotype, tumours displayed accelerated growth kinetics, demonstrating a role for exosomes during early tumour progression events. Hypoxia content changes in multiple myeloma derived exosomes also induce angiogenesis in recipient endothelial cells [23]. Under hypoxia conditions, multiple myeloma cells increase the secretion of miR-135b contained within exosomes in order to promote an angiogenic response. Endothelial cells that received miR-135b-containing exosomes had significantly increased HIF-1 alpha levels, as miR-135b binds the 3′-UTR of factor-inhibiting hypoxia-inducible factor-1 (FIH-1). This induced a hypoxic response and greatly accelerated angiogenesis [23]. In further support of the role that exosomes play during angiogenesis, $CD105^+$ vesicles from renal carcinoma cells have been shown to induce proliferation of HUVECs *in vitro* and *in vivo* [21]. These