Seminars in Cell & Developmental Biology xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Seminars in Cell & Developmental Biology

journal homepage: www.elsevier.com/locate/semcdb

Review

Microparticles in cancer: A review of recent developments and the potential for clinical application

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ARTICLE INFO

Article history:
Available online xxx

Keywords:
Biomarker
Cancer
Microparticle inhibitors
Microparticles
Multidrug resistance
P-glycoprotein

ABSTRACT

Once thought of as inert remnants of cellular processes, the significance of membrane vesicles is now expanding as their capacity to package and transfer bioactive molecules during intercellular communication is established. This ability to serve as vectors in the trafficking of cellular cargo is of mounting interest in the context of cancer, particularly in the dissemination of deleterious cancer traits from donor cells to recipient cells. Although microparticles (MPs) contribute to the pathogenesis of cancer, their unique characteristics can also be exploited in the context of cancer management. The detection of MPs in body fluids has the potential to provide an effective means for the diagnosis, prognosis and surveillance of cancer patients. The use of these readily accessible systemic biomarkers has the potential to circumvent the need for invasive biopsy procedures. In addition, the autologous nature of MPs may allow them to be used as novel drug delivery carriers. Consequently, the modulation of MP vesiculation to treat disease, the detection of MPs in disease monitoring, and the application of MPs as therapeutic delivery vehicles present prospective clinical interventions in the treatment of cancer.

Contents

1. Introduction

Microparticles (MPs) are part of a general classification of extracellular vesicles termed microvesicles (MVs), which includes a population of membrane vesicles that are heterogeneous in shape, ranging in size from 0.1 to 1 μm and isolated from biological fluids or conditioned culture media [1]. Other extracellular vesicles include apoptotic bodies and exosomes, which differ on the basis of their size and origin. The irregularly shaped apoptotic bodies are released from cells undergoing apoptosis and fragmentation and range from 1 to 5 μm in size, whereas, exosomes (30–100 nm) are released by the fusion of multivesicular bodies with the cell

Abbreviations: MMPs, matrix metalloproteinases; MSC, mesenchymal stem cells; MPs, microparticles; miRNA, microRNA; MVs, microvesicles; MDR, multidrug resistance; NSCLC, non-small cell lung carcinoma; P-gp, P-glycoprotein; PYK2, proline-rich tyrosine kinase 2.

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http://dx.doi.org/10.1016/j.semcdb.2015.03.009
1084-9521/

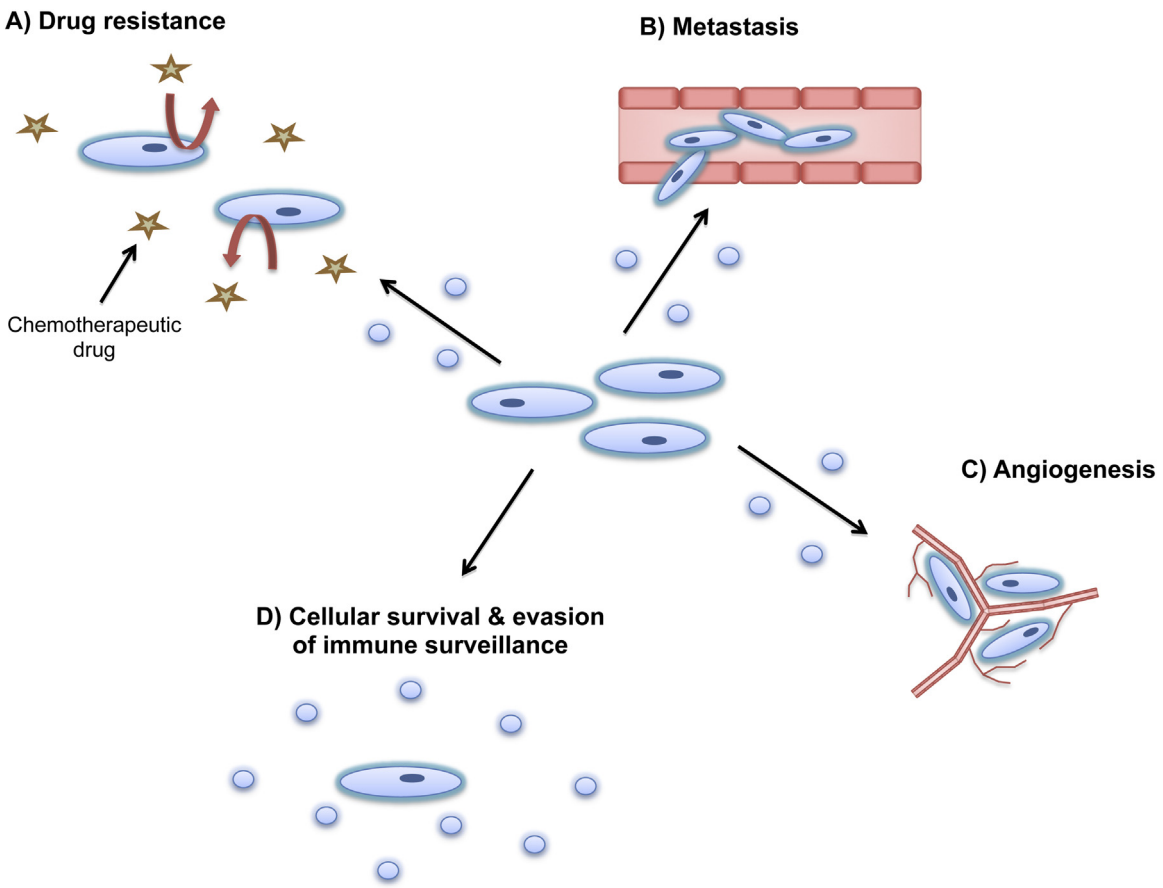

Fig. 1. The role of MPs in cancer progression. MPs facilitate (A) the development of drug resistance through the transfer of functional drug resistance proteins such as P-gp and MRP-1, (B) the enhancement of metastatic potential enabled by the acquisition of proteases, miRNAs and protein tyrosine kinases, (C) promotion of angiogenesis by the dissemination of components such as sphingomyelin and VEGF, and (D) cellular survival and evasion of immune surveillance via the expression of components such as caspase 3, latent membrane protein (LMP-1) and Fas ligand.

membrane [1]. MPs, which are the focus of this review, are released from the surface of cells by the process of outward membrane budding through a loss of calcium-dependent membrane phospholipid asymmetry and cytoskeletal rearrangement [2]. MPs are therefore composed of fragments of the parent cell, which comprise the plasma membrane proteins and cytoplasmic and nucleic constituents of the parent cell. Once MPs bud from the parent cell, they are released into the systemic circulation, where they can effectively deliver their cargo long-range to recipient cells. In this way, MPs serve as systemic vehicles in mediating intercellular communication. MPs have been found to carry various bioactive molecules, proteins and nucleic acids including mRNA and microRNA (miRNA) [3–6]. Thus they are involved in multiple aspects of cancer progression including the development of drug resistance [5,7–10] and metastases [11–13], tumor angiogenesis (by the dissemination of components such as sphingomyelin and VEGF) [14,15] cellular survival (by the removal of cytosolic caspase 3) [16,17] and evasion of immune surveillance via the expression of components such as latent membrane protein (LMP-1) [18] and Fas ligand [19,20] (Fig. 1). In this review, we will be focusing on recent developments in the role of MPs in cancer and how they can be utilized clinically in cancer management.

2. Microparticles provide a link between drug resistance and metastasis

MPs have been shown to confer and transfer multidrug resistance (MDR) in cancer cells [5,7,10,21]. This we showed was mediated through the intercellular transfer of functional resistance proteins, such as P-glycoprotein (P-gp) and Multidrug resistance protein 1 (MRP-1) Fig. 2 is a confocal image which shows the transfer of P-gp-EGFP fusion protein transferred via MPs to recipient drug sensitive cancer cells. We observe significant co-localization with the membrane intercalating dye PKH-26 following a 4 h co-culture period. This is consistent with our previous reports showing functionality of transferred resistance proteins contributing to the acquisition of MDR in recipient cells [5,7,10]. The MP-mediated acquisition of MDR was also shown to be associated with the promotion of an enhanced metastatic capacity in recipient breast cancer cells [11]. The elucidation of this relationship is significant, as these two deleterious traits were previously considered independent. Although an association between the emergence of the two phenotypes had been alluded to previously [22–24], a definitive link and the mechanism behind this remained unknown. Our laboratory was the first to show that MPs serve as a conduit in mediating this relationship [11].

Recipient breast cancer cells, which were both lowly metastatic and responsive to drug treatment, acquired an enhanced metastatic capacity with the ability to resist drug treatment upon co-culture with MPs derived from highly metastatic, drug-resistant donor cells [11]. MPs derived from breast cancer MDR cells were shown to mediate migration, invasion and drug resistance in recipient breast cancer cells to yield a population that was metastatic and drug resistant (Fig. 3).

The clinical relevance of MPs as the link between metastasis and drug resistance is that progression of either metastatic capacity or

Please cite this article in press as: Gong J, et al. Microparticles in cancer: A review of recent developments and the potential for clinical application. Semin Cell Dev Biol (2015), http://dx.doi.org/10.1016/j.semcdb.2015.03.009