Molecular Aspects of Medicine xxx (2017) 1–14

Contents lists available at ScienceDirect

Molecular Aspects of Medicine

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

Role of extracellular vesicles in glioma progression

Claudia Quezada [a, *], Ángelo Torres [a], Ignacio Niechi [a], Daniel Uribe [a], Susana Contreras-Duarte [b], Fernando Toledo [b, c], Rody San Martín [a], Jaime Gutiérrez [b, d, **], Luis Sobrevia [b, e, f, ***]

[a] Molecular Pathology Laboratory, Institute of Biochemistry and Microbiology, Faculty of Sciences, Universidad Austral de Chile, Valdivia, Chile
[b] Cellular and Molecular Physiology Laboratory (CMPL), Division of Obstetrics and Gynaecology, School of Medicine, Faculty of Medicine, Pontificia Universidad Católica de Chile, Santiago 8330024, Chile
[c] Department of Basic Sciences, Faculty of Sciences, Universidad del Bío-Bío, Chillán 3780000, Chile
[d] Cellular Signaling and Differentiation Laboratory (CSDL), School of Medical Technology, Health Sciences Faculty, Universidad San Sebastián, Santiago 7510157, Chile
[e] Department of Physiology, Faculty of Pharmacy, Universidad de Sevilla, Seville E-41012, Spain
[f] University of Queensland Centre for Clinical Research (UQCCR), Faculty of Medicine and Biomedical Sciences, University of Queensland, Herston, QLD 4029, Queensland, Australia

ARTICLE INFO

Article history:
Received 1 September 2017
Received in revised form
1 December 2017
Accepted 4 December 2017
Available online xxx

Keywords:
Glioma
Glioblastoma
Extracellular vesicles
Exosomes
Microvesicles
Apoptotic bodies
Large oncosomes

ABSTRACT

The role of extracellular vesicles in cancer biology has emerged as a focus of the study of great importance and has been shown to directly influence tumour development in several cancers including brain tumours, such as gliomas. Gliomas are the most aggressive brain tumours, and in the last time, a considerable effort has been made to understand their biology. Studies focus in the signalling pathways involved in the processes of angiogenesis, viability, drug resistance and immune response evasion, as well as gliomas ability to infiltrate healthy tissue, a phenomenon regulated by the migratory and invasive capacity of the cells within a tumour. In this review, we summarize the different types and classifications of extracellular vesicles, their intravesicular content, and their role in the regulation of tumour progression processes in glioma.

1. Introduction

Gliomas are neoplasms of the central nervous system (CNS) located mainly in the brain (Wang and Jiang, 2013). Malignant gliomas have an incidence rate of 5.26 per 100,000 inhabitants and approximately 17,000 new cases are diagnosed per year (Omuro and DeAngelis, 2013). Gliomas are classified into grades from I to IV, depending on their histopathological and genetic characteristics (Louis et al., 2007, 2016). Glioma grade IV, also called glioblastoma (GB) is the most common and aggressive brain tumour with high proliferation and vascularization rates, and potential cell invasive heterogeneity (Omuro and DeAngelis, 2013; Wang and Jiang, 2013; Wen and Kesari, 2008). GB represents ~70% of the total gliomas and the patients diagnosed with GB have a survival rate of only 26% in 12–15 months (Stupp et al., 2005; Wen and Kesari, 2008). Multimodal treatments include tumour resection followed by radiotherapy in combination with chemotherapeutic agents such as temozolomide (TMZ) and anti-angiogenic drugs (Omuro and DeAngelis, 2013; Stupp et al., 2005; Vtorushin et al., 2014). However, patient management is deficient due to early tumour recurrence, which explains the low patient survival rate (Bambury and Morris, 2014; Omuro and DeAngelis, 2013).

Recurrence is largely attributed to two processes: resistance to

* Corresponding author. Molecular Pathology Laboratory, Institute of Biochemistry and Microbiology, Faculty of Sciences, Universidad Austral de Chile, Campus Isla Teja, P.O. Box 567, Valdivia 5090000, Chile.
** Corresponding author. Cellular Signaling and Differentiation Laboratory (CSDL), School of Medical Technology, Health Sciences Faculty, Universidad San Sebastián, Santiago 7510157, Chile.
*** Corresponding author. CMPL, Division of Obstetrics and Gynaecology, School of Medicine, Faculty of Medicine, Pontificia Universidad Católica de Chile, Santiago 8330024, Chile.
E-mail addresses: claudiaquezada@uach.cl (C. Quezada), jaime.gutierrez@uss.cl (J. Gutiérrez), lsobrevia@uc.cl (L. Sobrevia).

https://doi.org/10.1016/j.mam.2017.12.003
0098-2997/

chemotherapeutic drugs (Chen et al., 2016) and tumour invasion into healthy tissue (Campos et al., 2016). Chemoresistance is mainly due to overexpression and activation of efflux pumps that extrude drugs out of the cell and has been extensively studied in various types of cancer, including gliomas (Vtorushin et al., 2014). Additionally, tumour infiltration or invasion is mainly due to the activation of signalling pathways that promote cell migration, extracellular matrix remodelling and the expression of matrix metalloproteinases (MMPs) (Bonnans et al., 2014). These cellular processes are regulated by different signalling pathways activated by external and internal factors. Thus, many studies have focused on the regulation of these signalling pathways, aimed to define the origin of the cellular malignancy and to propose potential therapeutic mechanisms.

Over the last decade, the attention has been concentrated on how extracellular vesicles (EVs) mediate cell communication within the tumour microenvironment of various types of cancer, including gliomas (Azmi et al., 2013). EVs may be responsible for the transfer of molecules from one cell to another, such as enzymes, ligands, receptors, DNA, complementary DNAs (cDNAs), mRNAs, microRNAs (miR), among others (Balaj et al., 2011; Pardo et al., 2018; Sáez et al., 2018). Many of these molecules are active when they arrive to the recipient cell, therefore, EVs regulate various processes, many of which are related to cancer progression and resistance to therapy. In this review, we summarize the available information regarding the types of EVs produced in gliomas and their content. Moreover, we also discuss the main effects of these glioma-derived EVs over angiogenesis, cell viability, chemoresistance, immune system regulation, and cell migration and invasion.

2. Types of extracellular vesicles

The concept of EVs has emerged as a consensus definition encompassing all membrane particles carrying a specific cargo and that is released from the cell independent of its biogenesis or composition (Gould and Raposo, 2013). EVs are classified according to different criteria, such as their size, cargo, density, biogenesis, or by their empirical definition (differential centrifugation). The types of EVs are referred as exosomes, microvesicles (MVs) and apoptotic bodies (ABs) (Fig. 1) (Zaborowski et al., 2015). However, a new type of EVs called oncosomes is described in brain tumour cells. Oncosomes are atypically large vesicles whose content seems to contribute to cancer progression (Al-Nedawi et al., 2008). Glioma cells generate and release the four types of EVs. Depending on their cargo, they promote different aspects of glioma malignancy, including cell invasion, proliferation, angiogenesis, and resistance to therapy (Al-Nedawi et al., 2008, 2009a,b; Muller et al., 2016). Recently, another type of EVs called migrasomes have been described in carcinogenic cells (Ma et al., 2015); however, information about migrasomes is scarce.

2.1. Exosomes

The exosomes are the smallest EVs presenting a relatively homogeneous size, ranging from 40 to 120 nm in diameter (Rani et al., 2011; Théry et al., 2006). Exosomes originate from the endosomal system from early endosomes, recycling endosomes to reach the state of late endosomes. Early endosomes are formed by invagination of the plasma membrane, after which they fuse with endocytic vesicles to drive their content either to degradation, recycling or secretion (Grant and Donaldson, 2009). Endosomes that are not for degradation or recycling become late endosomes, which after successive invaginations of their membranes, and therefore incorporation of cytosolic material, form intraluminal vesicles (ILVs). Late endosomes containing ILVs are referred as multivesicular bodies (MVBs), which ultimately fuse with the plasma membrane and release their ILVs as exosomes (AndreuAbels and Breakefield, 2016). During ILVs formation, the proteins tetraspanins (mainly CD9 and CD63) group into clusters by protein-protein interactions forming the Tetraspanin Enriched Microdomains (TEMs) microdomain (Andreu and Yáñez-Mó, 2014). CD9 and CD63 allocate in exosomes membrane and are used for their identification and isolation from normal and cancerous cells (Jansen et al., 2009; Shao et al., 2012). Together with the membrane structural changes, the recognition and sorting of cargo into ILVs is another fundamental process for the biogenesis of exosomes described in excellent previous reports (Hurley, 2010; Matsuo et al., 2004; Trajkovic et al., 2008).

2.2. Microvesicles

Microvesicles (MVs) are also known as nanoparticles, membrane particles and matrix vesicles, and correspond to larger EVs, with a diameter ranging from 50 to 1500 nm (Heijnen et al., 1999; Palmisano et al., 2012). Unlike exosomes, information regarding biogenesis and MVs release is less understood. However, MVs are believed to be formed by a mechanism called microvesiculation, which involves the outward budding of the plasma membrane (Al-Nedawi et al., 2009a,b). MVs shedding is induced by alterations in the asymmetric distribution of phospholipids in the plasma membrane, including the repositioning of phosphatidylserine and phosphatidylethanolamine on the extracellular side of the plasma membrane (Larson et al., 2012; Lima et al., 2009). The plasma membrane budding process required for the release of MVs is completed by ADP-ribosylation factor 6 (ARF6), which triggers a signalling cascade involving phospholipase D (PLD), recruitment of extracellular signal-regulated kinase (ERK), phosphorylation of myosin light-chain kinase (MLCK), and activation of the myosin light chain (Akers et al., 2013).

2.3. Apoptotic bodies

Apoptotic bodies (ABs) are EVs presented in a wide range of sizes, with diameters ranging from 50 to 2000 nm (Atkin-Smith et al., 2015; Crescitelli et al., 2013; Thery et al., 2001). This type of vesicles is produced and released by dying cells in a controlled manner to avoid the release of potentially toxic and immunogenic content into the surrounding tissue (Poon et al., 2014). Cells that begins programmed cell death or apoptosis undergoes continuous cellular processes that affect its integrity including ABs release (Elmore, 2007; Kerr et al., 1972; Taylor et al., 2008). Macrophages phagocytose ABs due to phosphatidylserine externalisation (Shiratsuchi et al., 1998). Unlike the budding process during MVs formation, the extracellular relocation of phosphatidylserine in apoptosis is induced by Ca^{2+}-independent scramblases, which are activated by 3- or 7- cleaved caspases (Mariño and Kroemer, 2013). Other changes include the oxidation of membrane components, thus creating binding sites for proteins such as thrombospondin (Friedl et al., 2002) or the complement protein C3b (Takizawa et al., 1996), both of which are recognised by membrane receptors on macrophages (Savill, 1997). In fact, Annexin V, thrombospondin, and C3b are three widely used ABs markers (Akers et al., 2013).

2.4. Oncosomes and large oncosomes

The term oncosome was first used to describe EVs with size range between 100 and 500 nm that were released by glioma cells (Al-Nedawi et al., 2008). This type of EVs promoted malignant transformation through the transference of oncogenic cargo to

Please cite this article in press as: Quezada, C., et al., Role of extracellular vesicles in glioma progression, Molecular Aspects of Medicine (2017), https://doi.org/10.1016/j.mam.2017.12.003