Exosomes and Glioblastoma

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Definition

Brain tumours are a serious concern among both physicians and patients. The most feared brain tumour is glioblastoma (GBM) due to its heterogeneous histology, substantial invasive capacity, and rapid postsurgical recurrence. Even in cases of early management consisting of surgery, chemo-, and radiotherapy, the prognosis is still poor, with an extremely short survival period. Consequently, researchers are trying to better understand the underlying pathways involved in GBM development in order to establish a more personalised approach. The latest focus is on molecular characterisation of the tumour, including analysis of extracellular vesicles (EVs), nanostructures derived from both normal and pathological cells that have an important role in intercellular communication due to the various molecules they carry. There are two types of EV based on their biogenesis, but exosomes are of particular interest in GBM. Recent studies have demonstrated that GBM cells release numerous exosomes whose cargo provides them the capacity to facilitate tumour cell invasion and migration, to stimulate malignant transformation of previously normal cells, to increase immune tolerance towards the tumour, to induce resistance to chemotherapy, and to enhance the GBM vascular supply. As exosomes are specific to their parental cells, their isolation would allow a deeper perspective on GBM pathogenesis. A new era of molecular manipulation has emerged, and exosomes are rapidly proving their value not only as diagnostic and prognostic markers, but also as tools in therapies specifically targeting GBM cells. Nonetheless, further research will be required before exosomes could be used in clinical practice. This review aims to describe the structural and functional characteristics of exosomes and their involvement in GBM development, diagnosis, prognosis and treatment.

1. Introduction

Brain tumours are one of the most aggressive cancer types. Among the different types of brain tumour, glioblastoma (GBM) has the worst prognosis. Despite early diagnosis and treatment, even the most optimistic studies have reported a survival period of only up to 18 months after diagnosis [1]. GBM is characterised by impressive heterogeneity, invasive capacity, and a high proliferation rate. Consequently, surgical resection is difficult and tumour recurrence is inevitable [2].

2. History and Development

Recently, several studies have demonstrated the importance of extracellular vesicles—and particularly exosomes—in the development of brain tumours such as GBM. Exosomes are involved in shaping favourable microenvironments for local tumour growth by transporting various molecules that assure indispensable vascular supply through angiogenesis and increase immune tolerance towards tumour cells. Furthermore, exosomes enhance tumour proliferation and dissemination by transferring pro-migratory factors from cancer cells to normal recipient cells, thus inducing malignancy in normal cells [3].

The variety of molecules contained within extracellular vesicles (EVs) and the different interactions between their cargo and recipient cells broaden the investigative possibilities related to intercellular communication. The vast majority of proteins carried by exosomes are common among all cell types. However, a small proportion is specific to parental cells, and these proteins facilitate EV isolation and quantification [4]. EVs are of particular interest in cancer research since an immense number of EVs are secreted by cancer cells and serve major roles in tumour dissemination. This context could be used to the advantage of researchers since EVs could be transformed into vehicles to transport therapeutic molecules [3]. Additionally, ongoing studies are using EVs as cancer biomarkers with the goal of detecting potential recurrences earlier. Furthermore, researchers are attempting to design new treatments targeting the molecules contained in EVs [3]. This review aims to summarise the most relevant information on the roles of exosomes in GBM development, diagnosis, prognosis and treatment.

3. Exosome Biogenesis

EVs are nanostructures secreted by most human cells. Their role in intercellular communication makes them important components in both normal and pathological biological processes [5]. Their aqueous core and lipid bilayer allow the transport of a wide variety of molecules (e.g., lipids, proteins, coding and non-coding RNA and DNA fragments) from cells of origin to nearby or distant cells through autocrine or paracrine mechanisms [3,5].

EVs consist of two types of structures: ones that bud outward directly from the plasma membrane (e.g., microvesicles, apoptotic

bodies, and oncosomes) and others that originate in multivesicular endosomes, eventually fusing with the plasma membrane and exit into the extracellular medium (e.g., exosomes) [6]. The dimensions also differ: exosomes are the smallest EVs (30–150 nm), while apoptotic bodies are the largest (up to 1000 nm) [4,6,7]. Microvesicles have intermediate sizes, ranging from 100 to 350 nm [4]. In 2018, the International Society for Extracellular Vesicles established a new nomenclature system based on their dimensions: small (<200 nm) and medium/large (≥200 nm) EVs [3,8].

Nevertheless, numerous techniques have been developed to physically characterise EVs. Perhaps the most popular one is based on electron microscopy due to the high-resolution images that can be achieved. Scanning electron microscopy (SEM) provides 3D surface topography characterisation derived from the interaction between EV atoms and beams of electrons that scan the sample surface [9]. The main drawback is that samples are usually fixed and dehydrated, leading to deformed EV morphology [9].

Transmission electron microscopy (TEM) is superior to SEM due to the higher-resolution images it can obtain. It also allows the molecular characterisation of EVs by immuno-labelling [10]. Cryo-electron microscopy (Cryo-EM) is a technique that analyses samples at approximately −100 °C without fixation and staining procedures, thereby avoiding the potential side effects of these procedures on EV structure while providing a veridical round aspect [9]. Atomic force microscopy (AFM) is a far more complex method that provides information about both EV surface topography (via amplitude modulation) and EV constituents such as proteins (via phase modulation) [11]. Other techniques, namely dynamic light scattering (DLS) and nanoparticle tracking analysis (NTA), derive from the ability to trace the Brownian motion of EVs in suspension and assess their size distribution and concentration [12]. DLS is less accurate when samples contain molecules with different dimensions since larger contaminants mask smaller vesicles, thereby hindering proper size-based characterisation. However, NTA permits the more precise measurement of undersized particles (with diameters as low as 30 nm) as well as EV phenotype description by binding fluorescently labelled antibodies with specific surface antigens [12].

Regardless of their origin and dimensions, EVs are circular vesicles that carry molecules specific to their parent cells and have specific purposes such as tissue repair, immune response modulation, and the transport of infectious agents [3,13,14,15]. Notably, the study of RNA species has become one of the most intense areas of cancer research in recent years. RNA transported by EVs can modify gene expression and lead to cell phenotype alteration, which has great significance in cancer pathogenesis [5]. Non-coding RNA is specifically enclosed in the exosomes; in contrast, microvesicles mainly carry cytosolic components [16]. Furthermore, EVs present surface markers—generally known as tetraspanins (e.g., CD9, CD81, and CD63) [17,18,19]—that permit the recognition of bona fide exosomes and serve a key role in exosome isolation in research laboratories. These markers also influence the capture of EVs by target cells [3].

Once the EVs reach their destination, their cargo is released into recipient cells. Endocytosis is the major mechanism by which EVs are taken up, either by non-specifically directed phagocytosis and macropinocytosis or by specific receptor-ligand interaction. Another important mechanism of EV uptake is fusion with the plasma membrane of recipient cells. Following such a fusion, the vesicles are internalised into the cytoplasm, their protector shield is degraded, and the unbound load is transported to the nucleus or other parts of the cell to trigger specific actions. Additionally, the interaction between EV surface markers and recipient cells' membrane receptors can lead to the activation of intracellular signalling pathways [3,20].

4. Conclusions

EVs, particularly exosomes, are rapidly becoming a new field of interest for researchers worldwide due to their involvement in intercellular communication. Recent studies have emphasised their role in the pathways by which brain tumours—particularly glioblastomas—develop, invade surrounding tissue, become resistant to treatment, and disseminate throughout the body. Moreover, the utilisation of exosomes as diagnostic and prognostic markers in brain tumours has evolved substantially in recent years. Due to their structure and capacity to carry various molecules, they are now being considered as tools to fight GBM aggressiveness through the development of personalised therapies that precisely target the tumour. Notably, further research is required before exosome isolation and subtyping can permit exosome-based GBM diagnosis and treatment.

Keywords

extracellular vesicles;exosomes;glioma;glioblastoma