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Review

Small extracellular vesicles as tumor biomarkers for glioblastoma

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ABSTRACT

Small extracellular organelles such as exosomes and microvesicles are currently being studied as a novel way to track tumor progression, pseudoprogression, and treatment monitoring. Their role in intercellular communication shows potential in the treatment of even the most formidable cancers. Glioblastoma (GBM) is the most common malignancy of the brain and has no known cure. A large emphasis has been placed on trying to improve the prognosis of this aggressive primary brain tumor. It has recently been discovered that small extracellular vesicles, mainly exosomes and microvesicles, play a role in the cell signaling process that leads to uncontrollable cell growth indicative of a tumor state. Here we describe the role of exosomes and microvesicles as a tumor biomarker for tracking the progression of different types of cancer, with an emphasis on GBM.

Contents

1. Introduction

Glioblastoma (GBM), a grade IV astrocytoma, is the most prevalent primary brain tumor and remains difficult to treat, with an average survival rate of just 14–16 months (Jensen et al., 2013; Omuro and DeAngelis, 2013). Although treatment modalities such as surgical resection, radiation, and chemotherapy are commonly applied to patients diagnosed with GBM, residual tumor cells infiltrate into the normal brain surrounding the main tumor mass. These cells inevitably proliferate over time and result in tumor progression and the ultimate demise of the patient (Hou et al., 2006).

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The ability to detect tumor progression in a more sensitive manner is needed for patients with GBM. Currently, patients undergo serial MRI scans of the brain to detect differences in imaging that may suggest progression. Clinicians are faced with the difficult task in determining whether the patient imaging is more consistent with treatment related effects (response to injury) from chemo- and radiotherapy, also known as pseudoprogression, or if the imaging reflects true tumor progression.

Small extracellular vesicles (EVs), namely exosomes and microvesicles, play an important role in cell signaling among numerous cell types (Candelario and Steindler, 2014). Ranging from 30 to 1000 nm in diameter, EVs secreted from healthy cells are capable of transporting various types of RNA including mRNA, microRNA (miRNA), and other noncoding RNAs as well as proteins. These different components allow cells to remove unnecessary metabolites and participate in cell-to-cell signaling, immune regulation, and angiogenesis (Gonda et al., 2013). EVs are also secreted by different types of cancer cells. The presence of RNA and proteins specific to cancer cells in EVs suggests a role for EVs in the interaction between tumors and other cells in the body (Al-Nedawi et al., 2008) as well as serving as a useful tool in the detection of tumor progression and treatment monitoring in GBM patients. Exosomes and microvesicles are the most common EVs that are studied, and are the focus of this review.

2. Exosomes

Exosomes, a particular type of EV, are small (50–90 nm diameter) vesicles of endocytic origin that are released into the extracellular space to allow for cell-to-cell communication (Gonda et al., 2013; Valadi et al., 2007). They were first proposed when researchers encountered viable miRNAs within the blood, which would have otherwise degraded had there not been a protective envelope around them (Vlassov et al., 2012). They are produced when an endosomal membrane folds in upon itself to create a multivesicular body (Fig. 1) (Johnsen et al., 2014; Johnstone, 2006). Exosomes released from endothelial cells and pericytes play an important role in changing the phenotype of the tumor vasculature and can result in the formation and maintenance of the hypoxic environment in which tumors are known to reside in (Kucharzewska et al., 2013). The secretion of certain exosomes by malignant cells can result in the formation of a thick protective fibrous layer surrounding the tumor, known as desmoplastic reaction, which makes targeted drug delivery more difficult (Azmi et al., 2013). Exosomes associated with breast cancer have been observed to release microRNAs (miRNA) which reprogram the transcriptome of the target cell by silencing specific mRNAs; this leads to the transformation of epithelial cells into tumor cells (Fig. 2) (Melo et al., 2014).

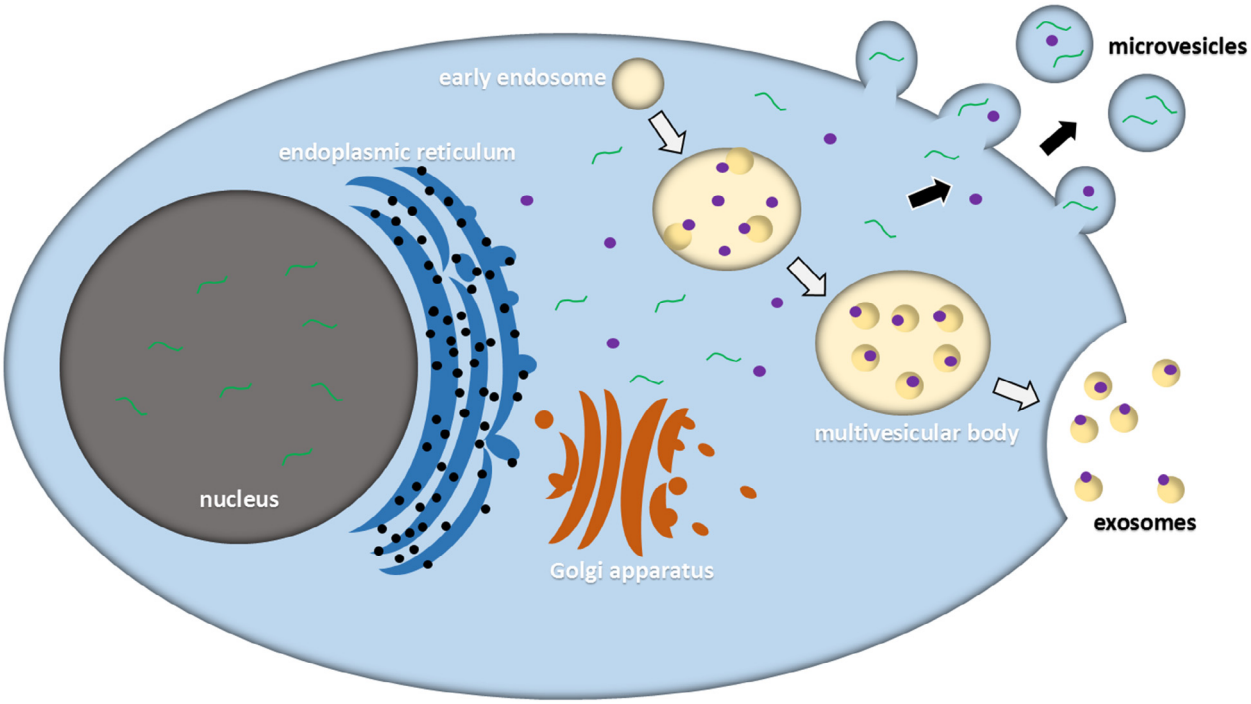

Fig. 1. Formation of exosomes (white arrows) and microvesicles (black arrows) within a eukaryotic cell. Various proteins (purple) direct endsomes (yellow) to fold inward and create exosomes. Mature exosomes are released once the multivesicular body leaves the cell. Microvesicles form when the cellular membrane undergoes direct budding. Depending on the location of microvesicle formation, RNAs (green) and other proteins (purple) may make it inside. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)