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Review

A comprehensive overview of exosomes as drug delivery vehicles — Endogenous nanocarriers for targeted cancer therapy

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ABSTRACT

Exosomes denote a class of secreted nanoparticles defined by size, surface protein and lipid composition, and the ability to carry RNA and proteins. They are important mediators of intercellular communication and regulators of the cellular niche, and their altered characteristics in many diseases, such as cancer, suggest them to be important both for diagnostic and therapeutic purposes, prompting the idea of using exosomes as drug delivery vehicles, especially for gene therapy. This review covers the current status of evidence presented in the field of exosome-based drug delivery systems. Components for successful exosome-based drug delivery, such as choice of donor cell, therapeutic cargo, use of targeting peptide, loading method and administration route are highlighted and discussed with a general focus pertaining to the results obtained in models of different cancer types. In addition, completed and on-going clinical trials are described, evaluating exosome-based therapies for the treatment of different cancer types. Due to their endogenous origin, exosome-based drug delivery systems may have advantages in the treatment of cancer, but their design needs further refinement to justify their usage on the clinical scale.

Contents

Abbreviations: AAV, adeno-associated virus; Aex, ascites-derived exosomes; BACE1, beta secretase 1; BAP-TM, biotin acceptor peptide-transmembrane domain; CAM, cell adhesion molecule; CD, cluster of differentiation; CD, cytosine deaminase; Dex, dendritic cell-derived exosomes; EGFP, enhanced green fluorescent protein; EGFR, epidermal growth factor receptor; ESCRT, endosomal sorting complex required for transport; GAPDH, glyceraldehyde triphosphate dehydrogenase; GBM, glioblastoma multiforme; GTP, guanosine triphosphatase; HCV, hepatitis C virus; HEK-293, human embryonic kidney cell line 293; HeLa, Henrietta Lax; IDH1, isocitrate dehydrogenase 1; LAMP, lysosomal-associated membrane protein; LFA-1, lymphocyte function-associated antigen 1; LPS, lipopolysaccharide; MHC, major histocompatibility complex; miRNA, microRNA; MRI, magnetic resonance imaging; mRNA, messenger RNA; MSC, mesenchymal stem cell; MVB, multivesicular body; PDGFR, platelet-derived growth factor receptor; RAB, Ras-related protein; RNA, ribonucleic acid; RVG, rabies viral glycoprotein; shRNA, short hairpin RNA; SPION, superparamagnetic iron oxide nanoparticle; STAT, signal transducer and activator of transcription; UPRT, uracil phosphoribosyltransferase

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1. Introduction

Exosomes denote a family of nanoparticles with a diameter in the range of 30–120 nm that are secreted by most cell types of the body [1,2]. They can be isolated from several types of extracellular fluids including blood, urine, amniotic fluid, saliva, and cerebrospinal fluid [2–4]. Exosomes were first described by Trams et al. and later substantiated by Johnstone et al., who observed high levels of transferrin binding onto small particles (exosomes), while the same binding activity was lost on parent cells [5–8]. These data suggested that exosomes were used by the cells as a major route of excretion, which would allow them to dispose any unused or harmful RNA and proteins, in case no appropriate lysosomal degradation systems were available [6–8]. Exosomes are now regarded as a distinct cellular entity specifically capable of carrying cargos like RNA, proteins, lipids etc. to be shared between cells [2,9].

1.1. Biogenesis of the exosome

Inside the cell, exosomes are initially produced by a process of invagination into endosomal membranes to create multivesicular bodies (MVBs) (Fig. 1) [10]. This distinguishes the exosomes from the shedding microvesicle that forms via direct budding of the cell membrane [2,7]. The formation of MVBs in exosome genesis suggests some similarities with the MVBs formed during lysosome formation, since lysosomal surface proteins, such as LAMP and CD63, are present in the exosomal membrane [10–12]. The formation of exosomes and sorting of cargo into them entails a collection of proteins, the so-called endosomal sorting complex required for transport (ESCRT), which is also crucial for lysosome formation [13,14]. The ESCRT machinery encompasses four major protein complexes, ESCRT-0–ESCRT-III. Together with a number of accessory proteins, the ESCRT machinery is known to favor endosomal sorting of ubiquitinylated proteins for secretion in nanoparticles such as exosomes [13]. Distinct from that of lysosome formation, exosome formation in some cell types can also be dependent on lipid raft-like domains on the endosome membrane rich in the sphingolipid, ceramide [15].

Secretion of exosomes is achieved by fusion of the MVB and the cell membrane (Fig. 1), which is thought to be dependent on several Rab GTPase proteins including RAB27A, RAB27B, RAB11 and RAB35 [16,17]. This secretion can be inhibited experimentally by treatment with the ceramide biosynthesis inhibitor, GW4869 [15,18]. Exosome release is increased in highly proliferative cells (such as mesenchymal stem cells (MSCs)), and the large exosome formation capability of these cells can be experimentally induced without mediating any physiological changes to the resulting exosomes by transfection with the MYC gene [19,20]. Interestingly, detachment of cultured breast cancer cells from various substrates rapidly increases the release of exosomes, with significant effects on attachment and spreading; cellular processes, which could clinically favor metastasizing cancer [21].

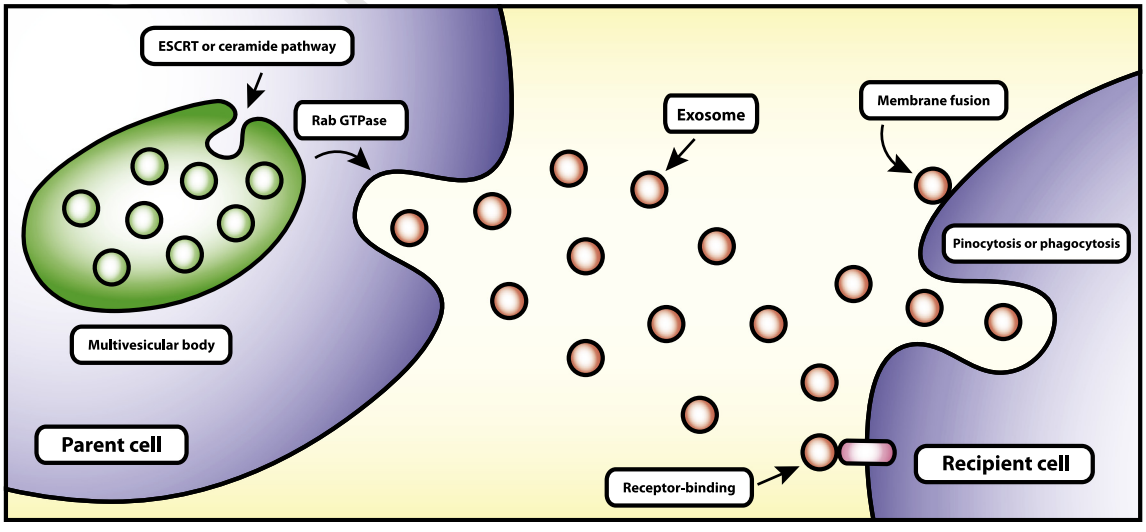

Fig. 1. Biogenesis of exosomes. The formation of exosomes starts by inward budding of the endosomal membrane to create multivesicular bodies (MVBs) in the cell cytoplasm. This process is dependent on either the endosomal sorting complex required for transport (ESCRT) machinery or the sphingolipid ceramide. Rab GTPase-dependent fusion of the MVBs with the parent cell membrane releases the produced exosomes to the extracellular space, where they can interact with recipient cells. The delivery of the exosomal cargo to the recipient cell can occur by ligand–receptor interaction, pinocytosis/phagocytosis or fusion with the cell membrane.

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