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Review

Diagnostic and therapeutic potentials of exosomes in CNS diseases

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ABSTRACT

A newly discovered cell-to-cell communication system involves small, membrane-enveloped nanovesicles, called exosomes. We describe here how these extracellular nanoparticles were discovered and how it became gradually apparent that they play fundamental roles in regulation of physiological functions and pathological processes. Exosomes enable intercellular communication by transporting genetic material, proteins and lipids to cells in their vicinity or at distant sites, and subsequently regulating functions of targeted cells. Relatively recent experiments indicate that exosomes are released also by CNS cells, including cortical and hippocampal neurons, glial cells, astrocytes and oligodendrocytes, and that exosomes have significant impact on pathophysiology of the brain. How it is decided what individual exosomes will carry to their targets is not understood, but it appears that the contents may represent "signature cargos" that are characteristic for various conditions. Exploration of such characteristics could result in discovery of novel diagnostic biomarkers. Exosomes are also promising as a vehicle for therapeutic delivery of micro RNA or other compounds. How to deliver exosomes to selected sites has been a tantalizing question. Recent experiments revealed that at least some exosomes carry antibodies on their surface, suggesting that it may be feasible to deliver exosomes to unique sites based on the recognition of antigens by those antibodies. This discovery implies that rather precise targeting of both natural and engineered exosomes may be feasible. This would reduce distribution volume of therapeutics, and consequently minimize their side effects.

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1. Introduction

Exosomes are key players in intercellular communication that can fundamentally affect various physiological functions at targeted cells. Exosomes are generated inside cells from multivesicular bodies (MVB) and released into extracellular space via exocytosis. These membrane enveloped nanovesicles carry genetic material, proteins and lipids that are employed in regulation of targeted cells and travel in extracellular body fluids that allow them to act on nearby cells, as well as on distant targets. Here we highlight some of critical discoveries in exosomal research, describe ongoing efforts and challenges in this rapidly developing field with the emphasis on CNS, and finally, propose how immunological principles could be employed in the design of exosome-based treatment.

2. MVB and the discovery of exosomes

MVB are endosomal organelles that are characterized by internal membrane-enveloped vesicles, which were described for the first time in neurons by Palay and Palade (1955). Originally, these vesicles were regarded to be pre-lysosomal structures involved in protein degradation (Piper and Katzmann, 2007), but more recent evidence indicates that MVB mediate diverse intra- and intercellular trafficking of molecules (Von Bartheld and Altick, 2011).

Nearly three decades after the discovery of intracellular MVB, Trams and co-workers analyzed cell-free supernatants collected from human neuronal neoplastic cell lines. The supernatants were span at the speed of 100,000*g* for 90 min, and the pellets of these supernatants were then studied by electron microscope (Trams et al., 1981), which resulted in the discovery of extracellular membrane-enveloped vesicles ranging in size from 40 to 1000 nm that were visualized by electron microscopy (for comparison, obtaining a pellet of cells from peripheral blood requires a centrifugation force of about 400*g*). The supernatant pellets possessed enzymatic activities, including 5-nucleotidase and ATPase, suggesting that the vesicles could play some physiological roles rather than just be cellular waste products (Trams et al., 1981).

The extracellular vesicles found by these researchers included subsets that are today known as nanovesicles or exosomes (<100 nm), as well as larger ectosomes (also referred to as microvesicles or microparticles) that typically range in the size 0.1–1.2 μm. While exosomes have been shown to be derived from MVB, ectosomes shad from cellular membranes (Fleury et al., 2014; Harding et al., 1984; Heijnen et al., 1998; Heijnen et al., 1999; Peters et al., 1991; Raposo et al., 1996; Thery et al., 2009) and differ in their content, implying that exosomes and ectosomes may have distinct purposes (Lazaro-Ibanez et al., 2014; Revenfeld et al., 2014). In this review we focus primarily on exosomes.

3. Exosomes are functional

The early work of Rose Johnstone and colleagues supported the idea that the extracellular vesicles obtained after ultracentrifugation of cell culture supernatants may be functional. They found that the vesicles from *in vitro* cultured sheep red blood cell precursors, reticulocytes, posses unique enzymatic activities resembling those of reticulocyte cell membrane, and a lipid composition reflecting sphingomyelin content of red blood cell membrane (Johnstone et al., 1987). For a long period, however, it remained unclear what is the purpose of these vesicles, and the general view of these early studies was that they serve as “garbage cans” removing unwanted molecules

After a decade without a follow up, experiments by Raposo and co-workers turned around this concept, as their results indicated that exosomes seem to play an active role in intercellular communication within the immune system (Raposo et al., 1996). The authors reported that cultured B cell lines secrete 60–80 nm vesicles containing complexes of antigens and major histocompatibility complex (MHC) II, which are known to be essential for presentation of antigens to T lymphocyte to induce their activation (Raposo et al., 1996). In follow up studies, Zitvogel and co-workers demonstrated that dendritic cells (professional antigen-presenting cells) also release nanovesicles expressing MHC class I, MHC class II, as well as co-stimulatory molecules that are critical for T cell activation and proliferation (Zitvogel et al., 1998). The investigators then pulsed vesicles from the dendritic cells with tumor derived peptides and administered them to mice bearing tumors. This resulted in stimulation of anti-tumor T lymphocyte responses *in vivo* and improved tumor eradication (Zitvogel et al., 1998), clearly indicating a critical contribution of exosomes to important immune responses *in vivo*.