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Extracellular vesicles and intercellular communication within the nervous system

Valentina Zappulli,[1] Kristina Pagh Friis,[2] Zachary Fitzpatrick,[2] Casey A. Maguire,[2] and Xandra O. Breakefield[2,3]

[1]Department of Comparative Biomedicine and Food Science, University of Padova, Legnaro, Italy. [2]Department of Neurology and [3]Center for Molecular Imaging Research, Department of Radiology, Massachusetts General Hospital and NeuroDiscovery Center, Harvard Medical School, Boston, Massachusetts, USA.

Extracellular vesicles (EVs, including exosomes) are implicated in many aspects of nervous system development and function, including regulation of synaptic communication, synaptic strength, and nerve regeneration. They mediate the transfer of packets of information in the form of nonsecreted proteins and DNA/RNA protected within a membrane compartment. EVs are essential for the packaging and transport of many cell-fate proteins during development as well as many neurotoxic misfolded proteins during pathogenesis. This form of communication provides another dimension of cellular crosstalk, with the ability to assemble a "kit" of directional instructions made up of different molecular entities and address it to specific recipient cells. This multidimensional form of communication has special significance in the nervous system. How EVs help to orchestrate the wiring of the brain while allowing for plasticity associated with learning and memory and contribute to regeneration and degeneration are all under investigation. Because they carry specific disease-related RNAs and proteins, practical applications of EVs include potential uses as biomarkers and therapeutics. This Review describes our current understanding of EVs and serves as a springboard for future advances, which may reveal new important mechanisms by which EVs in coordinate brain and body function and dysfunction.

Introduction

Recent research has revealed an expanded range of modes of communication among cells, which includes not only the secretome (organic molecules and inorganic elements), but also vesicular and particulate carriers, which contain proteins, lipids, and nucleic acids that are not soluble or are unstable in the extracellular environment on their own. This new modality is exemplified by extracellular vesicles (EVs), which are produced by virtually all cells, have various means of biogenesis, carry different cargoes, and change dynamically in number and content in response to physiologic and environmental conditions. The classification of these vesicle subtypes is ongoing and includes exosomes (30 to 100 nm in diameter), which are formed from multivesicular bodies; microvesicles (or ectosomes) (100 nm to 1 μm in diameter), which bud from the cell surface; oncosomes (ranging from 1 μm to >2 μm in diameter), which are large protrusions released from cancer cells through budding; and apoptotic blebs (ranging from 1 μm to >2 μm in diameter), which are generated by dying cells (1–4). Throughout this Review the different types of vesicles will be referred to as EVs.

EVs are released from virtually all cell types in the brain, including neural stem/progenitor cells (5, 6), neurons (7–9), astrocytes (9–13), oligodendrocytes (13–15), and microglia (16, 17) as well as Schwann cells and neurons in the peripheral nervous system (18–20). A schematic overview of potential EV-mediated interactions in the nervous system is provided in Figure 1.

The contents of EVs comprise both molecular entities the cells are trying to divest themselves of as well as information packets intended to alter the phenotypic state of other cells. Each vesicle contains multiple proteins, specialized lipids, and selected nucleic acids, such that their effects on recipient cells are combinatorial. As such, it is difficult to factor out the effects of individual components within the vesicles. Interactions with recipient cells, both near to and far from the cells of origin, can include ligand/receptor signaling at the cell surface, fusion of vesicle and plasma membranes, and uptake via endocytosis. The fate of vesicular contents includes degradation or release into the cytoplasm and then transport into the nucleus or cellular membranes, leading to functional consequences. The exchange of vesicles is active and dynamic in both directions among cells, so as to allow response to and coordination of biologic events.

This Review will focus on new areas of research into the action of EVs in the nervous system, including the implications during neural development, synaptic communication, and nerve regeneration. These functions are all essential for maintaining the health of the nervous system. The second part of this Review focuses on the "dark side" of EVs and how EVs can be used to augment the pathology of various neurological diseases. Finally, we provide an account of research into applying EVs to drug and gene therapeutic strategies, focusing on recent developments in the field.

Role in development

Production of EVs by neural cells during development. The interconnection as well as the maintenance of neuronal circuits depends on a wide variety of interactions between the different cell types in the brain. EVs are an emerging component of these interactions. They appear to have a substantial impact with respect to neural development and genetic variety based on their ability to

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