Biochimica et Biophysica Acta 1858 (2016) 1139–1151

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbamem

Review

Exosomes and other extracellular vesicles in neural cells and neurodegenerative diseases

Anna M. Janas [a,b], Karolina Sapoń [c], Teresa Janas [c], Michael H.B. Stowell [d,e], Tadeusz Janas [c,d,*]

[a] Center for Motor Neuron Biology and Disease, Columbia University, New York, NY 10032, USA
[b] Department of Pathology and Cell Biology, Columbia University, New York, NY 10032, USA
[c] Department of Biotechnology and Molecular Biology, University of Opole, Kominka 6, 45-032 Opole, Poland
[d] Department of MCD Biology, University of Colorado, Boulder, CO 80309, USA
[e] Mechanical Engineering, University of Colorado, Boulder, CO 80309, USA

ARTICLE INFO

Article history:
Received 5 November 2015
Received in revised form 19 January 2016
Accepted 9 February 2016
Available online 10 February 2016

Keywords:
Exosomes
Multivesicular bodies
Neural cells
Neurodegenerative diseases
Synaptic vesicles

ABSTRACT

The function of human nervous system is critically dependent on proper interneuronal communication. Exosomes and other extracellular vesicles are emerging as a novel form of information exchange within the nervous system. Intraluminal vesicles within multivesicular bodies (MVBs) can be transported in neural cells anterogradely or retrogradely in order to be released into the extracellular space as exosomes. RNA loading into exosomes can be either via an interaction between RNA and the raft-like region of the MVB limiting membrane, or via an interaction between an RNA-binding protein–RNA complex with this raft-like region. Outflow of exosomes from neural cells and inflow of exosomes into neural cells presumably take place on a continuous basis. Exosomes can play both neuro-protective and neuro-toxic roles. In this review, we characterize the role of exosomes and microvesicles in normal nervous system function, and summarize evidence for defective signaling of these vesicles in disease pathogenesis of some neurodegenerative diseases.

Contents

Abbreviations: Aβ, amyloid β peptide; ALS, amyotrophic lateral sclerosis; APP, amyloid precursor protein; ARF6, ADP-ribosylation factor-6; AZ, active zone; CME, clathrin-mediated endocytosis; dMVB, multivesicular body involved in the degradation pathway; EE, early endosome; ER, endoplasmic reticulum; ESCRT, Endosomal Sorting Complex Required for Transport; EV, extracellular vesicle; hnRNP, heterogeneous nuclear ribonucleoprotein; ILVs, intraluminal vesicles; LE, late endosome; LEVc, large endocytic vacuole; mLE, maturing late endosome; MSC, mesenchymal stem cell; MVB, multivesicular body; NMJ, neuromuscular junction; NPC, neural progenitor cell; PNS, peripheral nervous system; PrP^{C}, properly folded prion protein; PrP^{Sc}, misfolded prion protein; PS, phosphatidylserine; RBP, RNA-binding protein; RE, recycling endosome; RhoA, Ras homolog gene family, member A; SE, sorting endosome; SMA, Spinal Muscular Atrophy; SMN, Survival Motor Neuron; sMVB, multivesicular body involved in the secretion pathway; SV, synaptic vesicle; TDP-43, transactive response DNA-binding protein 43 kDa; TEM, tetraspanin-enriched microdomain; TGN, trans-Golgi network; TIM-4, T-cell immunoglobulin mucin protein 4; TNT, tunneling nanotube; UEV, ultrafast endocytosis vesicle.

* Corresponding author at: Department of Biotechnology and Molecular Biology, University of Opole, 45-032 Opole, Poland.
E-mail address: tadeuszj@uni.opole.pl (T. Janas).

http://dx.doi.org/10.1016/j.bbamem.2016.02.011
0005-2736/

1. Multivesicular bodies in neural cells: anterograde vs. retrograde transport

Exosomes are small extracellular nano-size vesicles (50–100 nm in diameter) that are presumed to primarily originate from multivesicular bodies (MVBs). MVBs are intracellular endosomal organelles typically with a diameter of 250–1000 nm and containing at least two and up to dozens of intraluminal vesicles (ILVs) within the membrane-enclosed lumen [1]. Upon fusion of MVBs with the plasma membrane ILVs are released into the extracellular space as exosomes. Exosomes are secreted by multiple cell types, including neuronal cells [2], and are characterized by specific sets of lipids, proteins and RNAs. ILVs can be formed via lipid-induced inward budding from the MVB limiting membrane that can involve its raft-like region associated with protein/RNA sorting in exosomes [3,4]. Cellular RNAs continuously interact with the cytoplasmic surface of MVBs, and RNA affinity to the raft-like region on MVB surface can select these RNAs for incorporation into ILVs [4]. The functions of exosomes in the nervous system are currently under active investigation. There is evidence to support their role in intercellular communication, cellular clearance of biomolecular waste, and cell migration by extracellular delivery of chemoattractants [5].

ILV-containing MVBs can be transported in neuronal cells in order to fuse with the plasma membrane of the cell body, the plasma membrane of dendrites, the axonal plasma membrane, or the presynaptic membrane. Neuronal MVBs in the peripheral nervous system (PNS) and central nervous system (CNS) are 50 times more abundant in cell bodies and dendrites than in axons [1]. Electron microscopy of the adult rat hippocampal neurons revealed the presence of MVBs in dendrites, appearing as large vacuoles delimited by a single membrane and containing varying numbers of 50–80 nm membrane vesicles [6]. MVBs were detected in dendritic shafts and inside a limited number of spines (small dendritic protrusions that express glutamate receptors and appose the active zone of synapsing axons). Movements of MVBs to synapses of hippocampal neurons were shown to be tightly linked to synaptic plasticity. For instance, recruitment of MVBs into or near spines in cultured neurons was correlated with long-term potentiation presumably by insertion in the postsynaptic compartment of glutamate receptor subunits [7]. In addition to cortical neurons, MVBs have been described at the ultrastructural level at the *Drosophila* larval neuromuscular junction (NMJ) in the synaptic bouton (presynaptic terminal) apposing the presynaptic membrane [8].

Fig. 1 shows the biogenesis and trafficking of MVBs in neurons. The primary endocytic vesicles deliver their contents and their membrane to early endosomes (EEs) in the peripheral cytoplasm [9]. EEs are recognized as the main sorting station in the endocytic pathway and they generate recycling tubules and vesicles targeted to distinct organelles, including the plasma membrane and the trans-Golgi network (TGN) [9]. Housekeeping receptors and other proteins can be recycled back to the plasma membrane via the recycling endosomes (REs) derived from EEs [10]. During the maturation of late endosomes (LEs), lumen is acidified by vacuolar proton pumps (V-ATPases). Trafficking between endosomes and the TGN is a continuous process and it is responsible for the delivery of lysosomal components and removal of endosomal components during endosome maturation [9]. The maturing late endosome (mLE) in the cell body, can be (1) anterogradely transported along the axon, (2) converted into an MVB involved in the degradation pathway (dMVB) resulting in a fusion with a lysosome, or (3) converted into an MVB involved in the secretion pathway (sMVB) resulting in a fusion with plasma membrane at the cell body or the dendrite and a release of ILVs as exosomes into the extracellular space. The p75 neurotrophin receptor defines a subpopulation of MVBs that does not mature to lysosomes and is available for exosomal release by neuronal cells [11]. The sMVBs are enriched in ceramides while dMVBs are enriched in bismonoacylglycerophoshate (BMP, LBPA) [4].

Since MVBs are present in both axons and presynaptic terminals [1,6,8,12], and there is currently no evidence that MVBs are transported anterogradely within axons [1], we postulate that a mLE enters the axon from the neuron cell body, and during its anterograde transport this mLE converts into a sMVB. A diverse array of proteins, lipids and RNAs are transported anterogradely in the REs or LEs to distal synapses; LEs can be transported bi-directionally in fast axonal transport and approximately half of LEs in the axon have bidirectional motility [13]. Kinesins drive anterograde transport outward from the cell body, and dynein drives retrograde transport back from distal axon. However, most cargos have both motor types bound simultaneously [13], For example, axonal accumulation of the cell adhesion molecule L1/neuron–glia cell adhesion molecule (NgCAM) occurs via nondegradative somatodendritic endosomes and subsequent anterograde axonal transport, which is consistent with transcytosis [14].

MVBs can move retrogradely from apical regions (axon terminals or dendritic spines) to the cell body along axons or dendrites in order to fuse with the cell body lysosome in the degradation pathway [1]. Thus MVBs can participate in several distinct bidirectional trafficking pathways in neural cells: intrasomal (somato-somatic), axo-somatic (between axon and the cell body), somato-dendritic (between cell body and dendrite), axo-dendritic (a transcytotic pathway between dendrites and axon), and interdendritic [1].

MVBs present in axon terminals or dendritic spines have both intracellular and intercellular functions which involve signaling and sorting/recycling, e.g. regulation of receptor surface expression, exosome release, neurosecretion via degradation and/or processing of neurosecretory materials, signal termination, clearance of toxins and unnecessary proteins via degradation, or export to the extracellular space or neighboring cells [1,15].

2. Extracellular vesicles (EVs) released from neural cells: exosomes vs. microvesicles

Exosomes are a class of EVs (50–100 nm in diameter) that originate from the endosome and are released from cells when MVBs containing