Review

Circulating extracellular vesicles: friends and foes in neurodegeneration

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Abstract

Extracellular vesicles have been identified as pivotal mediators of intercellular communication with critical roles in physiological and pathological conditions. Via this route, several molecules (e.g., nucleic acids, proteins, metabolites) can be transferred to proximal and distant targets to convey specific information. Extracellular vesicle-associated cargo molecules have been proposed as markers of several disease conditions for their potential of tracking down the generating cell. Indeed, circulating extracellular vesicles may represent biomarkers of dysfunctional cellular quality control systems especially in conditions characterized by the accrual of intracellular misfolded proteins. Furthermore, the identification of extracellular vesicles as tools for the delivery of nucleic acids or other cargo molecules to diseased tissues makes these circulating shuttles possible targets for therapeutic development. The increasing interest in the study of extracellular vesicles as biomarkers resides mainly in the fact that the identification of peripheral levels of extracellular vesicle-associated proteins might reflect molecular events occurring in hardly accessible tissues, such as the brain, thereby serving as a "brain liquid biopsy". The exploitation of extracellular vesicles for diagnostic and therapeutic purposed might offer unprecedented opportunities to develop personalized approaches. Here, we discuss the bright and dark sides of extracellular vesicles in the setting of two main neurodegenerative diseases (i.e., Parkinson's and Alzheimer's diseases). A special focus will be placed on the possibility of using extracellular vesicles as biomarkers for the two conditions to enable disease tracking and treatment monitoring.

Key Words: Alzheimer's disease; amyloid protein; exosomes; misfolded proteins; mitochondrial-derived vesicles; neuroinflammation; Parkinson's disease; quality control; Tau protein; α-synuclein

Introduction

Since their initial identification as a route for the removal of harmful cellular waste, the number of studies investigating extracellular vesicles (EVs) has sharply increased. These membranous shuttles have been recognized as pivotal mediators of inter-cellular communication with critical roles in physiological and pathological conditions (Pan and Johnstone, 1983; Rashed et al., 2017). Via this route, molecular cargoes of different origins (i.e., nucleic acids, proteins, and metabolites) can be transferred to proximal cells or over long distance to convey specific information (Valadi et al., 2007; Edgar, 2016).

EVs isolated from biofluids (e.g., plasma, serum, urine, saliva) consists of a highly heterogeneous population of vesicles with regard to size, function, and biogenesis (Willms et al., 2016). This heterogeneity is reflected by the multiple terms that are used to describe EV subtypes. EV is the general term that refers to a population of vesicles differing for physical and biochemical characteristics and/or sources. EVs can be classified into exosomes and ectosomes (Royo et al., 2020). Ectosomes were initially identified as shedding vesicles from the plasma membrane of stimulated neutrophils (Stein and Luzio, 1991) and now include all EVs generated from the outward budding of the plasma membrane and a diameter of 100–500 nm. These EVs are generally referred to as shedding vesicles, microvesicles, exosome-like vesicles, nanoparticles, microparticles, and oncosomes. According to the minimal information for studies of EVs guidelines (Théry et al., 2018), EVs that originate from the endosomal compartment are defined as exosomes regardless of the generating cells. Exosomes were originally considered a type of vesicles released from the plasma membrane during the maturation of reticulocytes (Johnstone et al., 1987) and are currently identified as EVs with a diameter of 50–150 nm of endosomal origin. Exosomes are generated by the inward budding of discrete domains of the membrane of early endosomes as intraluminal vesicles (ILVs) that subsequently evolve into multivesicular bodies (MVBs) (Raposo and Stoorvogel, 2013; Cocucci and Meldolesi, 2015). MVBs are usually degraded into lysosomes. However, under certain circumstances and

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probably depending on cargo information, MVBs can be re-directed towards the plasma membrane and undergo exocytic fusion followed by release of their ILVs (i.e., exosomes) into the extracellular space (Raposo and Stoorvogel, 2013; Cocucci and Meldolesi, 2015) (**Figure 1**).

EVs can also shuttle nucleic acids such as RNA (Valadi et al., 2007), a finding that laid the groundwork for investigating EV-associated nucleic acids as markers of diseases for their potential of track down the originating cell. In addition, circulating EVs have been proposed as biomarkers of dysfunctional cellular and mitochondrial quality control systems (Marzetti et al., 2020; Picca et al., 2020a) in conditions characterized by the accrual of intracellular misfolded proteins (Picca et al., 2020b, c). Indeed, under mild stressors, cells are able to generate mitochondrial derived vesicles (MDVs) of ~100 nm in diameter by coordinating the activity of the mitophagy proteins phosphatase and tensin homolog-induced kinase 1 and Parkin and the endocytic pathway (Soubannier et al., 2012). Via MDV release, cells enact a housekeeping mechanism that complements mitophagy and recycles damaged, but not yet depolarized mitochondria (Soubannier et al., 2012).

Finally, the identification of EVs as tools for the delivery of nucleic acids or other cargoes to diseased tissues makes these circulating cellular boxes possible targets for therapeutic development (Picca et al., 2020b).

Herein, we discuss the bright and dark sides of EVs in the setting of two main neurodegenerative diseases, i.e., Parkinson's disease (PD) and Alzheimer's disease (AD), with a special focus on their potential as biomarkers for the two conditions.

Search Strategy and Selection Criteria

Studies cited in this review published from 2000 to 2020 were searched on the PubMed database using the following keywords: "extracellular vesicles", "neurodegeneration", "Alzheimer", Parkinson".

The Role of Extracellular Vesicles in Neurodegeneration

AD and PD are the two most common neurodegenerative disorders characterized by the accrual of misfolded proteins within the central nervous system and their spreading across neurons and glial cells.

AD is characterized by deposition of amyloid beta (Aβ) aggregates in the form of extracellular amyloid plaques and accumulation of intracellular neurofibrillary tangles. These histological traits are associated with vascular and parenchymal amyloid deposits, synapse and neuronal loss, mainly at the level of the neocortex and the hippocampus, accompanied by neuroinflammation and reactive astrogliosis (Josephs et al., 2020). Aβ aggregates originate from the proteolytic cleavage of the C-terminus of the amyloid precursor protein (APP) by β- and γ-secretase, while neurofibrillary tangles consist mainly of hyperphosphorylated and misfolded Tau protein (Masters et al., 2015). These biochemical abnormalities negatively impact synaptic homeostasis and lead to fragile synaptic terminals, ultimately contributing to neurodegeneration. Albeit mostly sporadic, familial forms of AD holding mutations in APP or presenilin genes, the catalytic subunit of γ-secretase, have also been reported (De Strooper et al., 2012).

PD is characterized by a progressive loss of dopaminergic neurons of the substantia nigra pars compacta (Alexander, 2004). The accrual of misfolded α-synuclein (α-syn) in these neurons is among the pathogenic mechanisms of neurodegeneration in PD (Mehra et al., 2019).

The systemic spreading of aberrant/misfolded proteins involved in AD and PD has attracted increasing attention for the potential of shedding light on the pathogenic mechanisms of these diseases and their response to treatments. Of note, while the spreading of Tau and α-syn pathology shows a predictable and peculiar pattern (Braak et al., 2003, 2006), amyloid plaque deposition follows a less predictable pattern. This might be the result of a differential inter-cellular protein transmission that, in the first case, involves a prion-like diffusion through which pathologic aggregates may be transferred to recipient neurons and induce misfolding of their endogenous counterparts (Ma et al., 2019; Uemura et al., 2020). Among the shuttling routes of these disease-related proteins, EVs are plausible candidates and their involvement in the two conditions is discussed in the next sections.

AD

The initial step of the APP cleavage sets the fate of its proteolytic processing towards a non-amyloidogenic or amyloidogenic pathway (Zheng and Koo, 2011). APP is synthesized within the endoplasmic reticulum and is then transported to the Golgi apparatus, from which it is delivered to early endosomes or the plasma membrane. Here, APP is cleaved by the α-secretase and enters a non-amyloidogenic pathway (Haass et al., 2012). The result of this first proteolytic step is the production of a soluble APPα and an α-C-terminal fragment (α-CTF or C83). Alternatively, endosomes can internalize APP and produce soluble APPβ and β-CTF (C99) fragments via the amyloidogenic cleavage of APP catalyzed by β-secretase. An active γ-secretase complex located mainly at the plasma membrane and within the endosomal/lysosomal compartments may complement the activity of α- and β-secretases at these sites (Haass et al., 2012). The newborn early endosome can recycle material to the plasma membrane, feed a retrograde transport to the trans Golgi network, or mature into late endosomes/MVBs. MVBs fuse with either lysosomes for degradation or the plasma membrane for ILV secretion as exosomes (Meldolesi, 2018; **Figure 2**).

Alterations of APP trafficking have been described in AD pathogenesis. Indeed, the endosomal sorting complexes required for transport (ESCRT) pathway guides the sorting of APP into ILVs (Morel et al., 2013; Edgar et al., 2015). The inhibition of ESCRT may lead to the accumulation of APP and the formation of enlarged endosomes that secrete higher levels of Aβ (Morel et al., 2013). ESCRT inhibition can also reduce the lysosomal delivery of APP, thereby resulting in intracellular accrual of Aβ in spite of decreased Aβ secretion (Edgar et al., 2015). A relationship between the accumulation of intracellular Aβ and a longer time of residence within the endosomal compartment eventually favoring an amyloidogenic processing has also been hypothesized (Edgar et al., 2015). A sustained EV secretion and high levels of EV-associated Aβ have been observed in presenilin 1-mutated H4 glioblastoma cells with dysfunctional lysosomes (Eitan et al., 2016). Conversely, a reduction in the levels of secreted Aβ-associated EVs has been found in neuroblastoma N2a cells expressing the Swedish mutant form of APP (APPSwe) (Rajendran et al., 2006). High levels of APP and β-CTF, instead, were detected in EVs isolated from APPSwe-expressing neuroblastoma N2a, HEK293, and neuroblastoma SH-SY5Y cells (Rajendran et al., 2006; Cone et al., 2020). In this context, EVs may serve as a shuttle system for the intercellular transport of APP. In recipient cells, APP is processed by γ-secretase and is delivered via EVs as APP or CTFs (Laulagnier et al., 2018). High levels of APP, APP-CTFs, and Aβ have also been identified within EVs isolated from the brain of Tg2576 mice, a mouse model for AD characterized by overexpression of mutated APP (Perez-Gonzalez et al., 2012). Notably, brain-derived EVs from Tg2576 mice contains γ-secretase complex

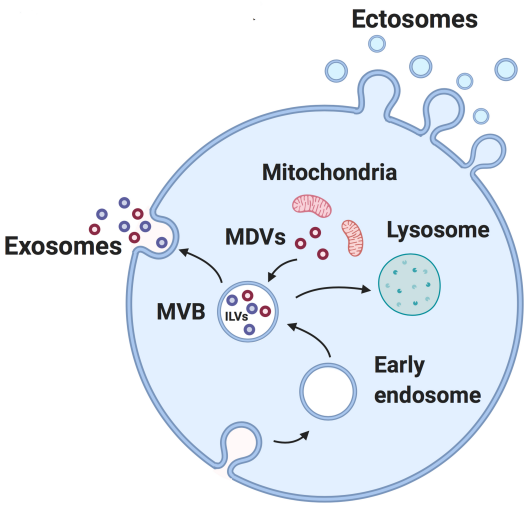

Figure 1 | Genesis and release of extracellular vesicles.
Ectosomes originate from the outward budding of the plasma membrane of all cells and extrude intracellular components, including nucleic acids, proteins, and metabolites. Exosomes, instead, incorporate cargo molecules that are processed along the endosomal pathway before their ultimate release into the extracellular space. The generation of exosomes involves a multi-step process: (1) the inward budding of the plasma membrane originates an early endosome that forms intraluminal vesicles (ILVs); (2) the endosome evolves into a multivesicular body (MVB); (3) the MVB fuses with the plasma membrane and releases ILVs into the extracellular space where they are identified as exosomes; (4) following an alternative route, MVBs can fuse with or mature into lysosomes for ILV degradation. The release of mitochondrial-derived vesicles (MDVs) of endosomal origin has also been documented as a step of mitochondrial quality check. Figure was drawn using the web-based tool BioRender (Toronto, Canada).

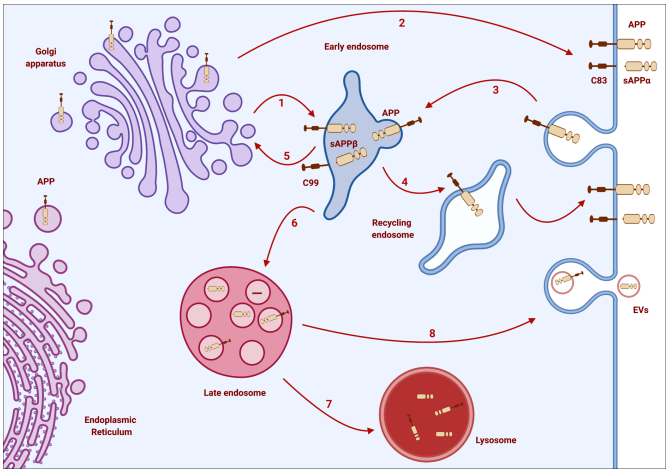

Figure 2 | Schematic representation of amyloid precursor protein processing.
Following its synthesis within the endoplasmic reticulum and its transport through the Golgi apparatus, amyloid precursor protein (APP) can be sorted into (1) early endosomes or (2) towards the plasma membrane. At the plasma membrane, APP is processed by a non-amyloidogenic pathway to produce soluble APPα (sAPPα) and an α-C-terminal fragment (α-CTF or C83). APP internalized and transported to early endosomes (3) is cleaved in the amyloidogenic pathway to generate sAPPβ and β-CTF (C99). The cleavage of APP at the level of plasma membrane and endosomes is completed by a γ-secretase complex. From early endosomes, APP protein can be (4) recycled to the plasma membrane or (5) transported to the Golgi apparatus or (6) late endosomes/multivesicular bodies (MVBs). From here, APP can undergo lysosomal degradation (7) or be secreted after the fusion of MVBs with the plasma membrane followed by the release of intraluminal vesicles as extracellular vesicless (EVs) (8). Figure was drawn using the web-based tool BioRender (Toronto, Canada).

which indicates that APP processing may occur within EVs (Perez-Gonzalez et al., 2012). This extracellular proteolytic mechanism of APP has been confirmed by a subsequent study showing APP cleavage in brain-derived EVs incubated *in vitro* in the absence of other neuronal cells (Pérez-González et al., 2020). Moreover, APP, APP-CTFs, Aβ, and several other secretases have been retrieved in EVs isolated from APP-expressing Chinese hamster ovary (Sharples et al., 2008).

EV trafficking may also convey beneficial effects in AD. Indeed, EVs isolated from N2a neuroblastoma cells or cerebrospinal fluid (CSF) of healthy donors have been shown to prevent the synaptic disruption induced by the infusion of Aβ-containing human AD brain extracts in rats (An et al., 2013). Neural EV secretion has also been implicated in inducing conformational changes of Aβ protein and promoting the formation of non-toxic amyloid fibrils that are taken up and degraded more efficiently by the microglia *in vitro* (Yuyama et al., 2012). Notably, the hippocampal administration of EVs isolated from N2a cells (Yuyama et al., 2014) or mouse primary neurons (Yuyama et al., 2015) to APPSweInd mice has been shown to scavenge total Aβ levels and prevent plaque formation. As an alternative mechanism of EV-associated clearance of Aβ, microglial cells treated with statins show an increase in Aβ degradation and the release of insulin-degrading enzyme-associated EVs (Tamboli et al., 2010). Accordingly, APPSwe-expressing N2A cells are characterized by altered insulin-degrading enzyme-containing EV trafficking and impaired extracellular Aβ degradation (Bulloj et al., 2010).

The delivery of EVs generated within damaged cells can also reverse the positive effects conveyed by EVs in AD. While the accrual of toxic aggregates can initially be prevented by EV secretion, the same EVs may also exert negative effects in recipient cells in the long term. Indeed, EV secretion has been indicated as a mechanism through which cells escape from excessive intracellular Tau deposition (Simón et al., 2012; Dujardin et al., 2014). However, data also suggest that plaque deposition occurs with EV-associated Aβ secretion. In particular, a partial colocalization of the EV marker Flotillin-1 with Aβ peptide in senile plaques of Tg2576 mice has been observed (Kokubo et al., 2005). Furthermore, an enrichment in Alix and Flotillin-1 proteins has been identified in amyloid plaques of AD patients compared with age-matched controls (Rajendran et al., 2006). Moreover, an uptake of isolated EVs containing Tau and Aβ oligomers has been observed in neuronal cultures (Asai et al., 2015; Sardar Sinha et al., 2018). Once acquired by the cells, these cargoes are released by EVs to elicit their cytotoxic effect or migrate to further recipient cells (Sardar Sinha et al., 2018). In fact, target cells besides regulating the uptake of EVs can also re-secret them, ultimately boosting their spreading ability (Polanco et al., 2018). In this regard, blockade of EV secretion in neuronal cultures has shown to decrease Aβ oligomers toxicity (Sardar Sinha et al., 2018). Finally, human CSF- and astrocyte-derived EVs isolated from AD patients were also found to mediate neuronal toxicity *in vitro* (Joshi et al., 2014; Nogueras-Ortiz et al., 2020) through the activation of necroptosis (Goetzl et al., 2018b; Nogueras-Ortiz et al., 2020). Moreover, Tau pathology may be propagated by Tau-containing EVs. Indeed, Tau aggregation has been observed *in vitro* after incubation with EVs isolated from N2a cells expressing aggregation-prone Tau (Wang et al., 2017b), the brain of Tau transgenic rTg4510 mice (Polanco et al., 2016) or cerebrovascular fluid (CSF) derived from AD patients (Wang et al., 2017b; Crotti et al., 2019). Beneficial effects of inhibiting EV secretion in AD have also been reported. Indeed, the systemic administration of GW4869, an inhibitor of neutral sphingomyelinase 2 has been shown to halt EV secretion and slow Tau propagation and amyloid plaques load (Asai et al., 2015). Accordingly, the depletion of microglia induces a decrease in the levels of EV-derived Tau and suppresses the propagation of Tau pathology (Asai et al., 2015; Crotti et al., 2019).

PD

Similar to AD, dysfunctional EV signaling has been proposed as a pathogenic mechanism in PD. Several reports indicate that, after interaction with the ESCRT pathway, a portion of secreted α-syn is released in association with EVs (Lee et al., 2005; Emmanouilidou et al., 2010; Jang et al., 2010). Moreover, the aggregation of α-syn *in vitro* is accelerated by EVs via the promotion of a catalytic environment favoring α-syn nucleation (Marie et al., 2015). This phenomenon has been observed especially within EVs isolated from the CSF of patients with PD and dementia with Lewy bodies (Stuendl et al., 2016). It also has been observed that the uptake of α-syn-containing EVs by neurons *in vitro* (Danzer et al., 2012; Marie et al., 2015) and that of EV-associated oligomeric α-syn is more efficient that the uptake of EVs devoid of α-syn (Danzer et al., 2012; Gustafsson et al., 2018). Several studies have reported that EVs isolated from α-syn-expressing cells or obtained from the CSF of dementia with Lewy bodies patients are able to induce α-syn spreading towards interconnected brain regions when injected into wild-type mice (Minakaki et al., 2018) and to promote an endogenous α-syn aggregation when delivered to recipient neurons *in vitro* (Guo et al., 2020). Similar data were obtained upon intrastriatal injection of plasma-derived EVs obtained from PD patients (Han et al., 2019).

Not all α-syn oligomers promote aggregate formation and toxicity to the same extent (Tsika et al., 2010). The intrastriatal administration of EV-associated α-syn isolated from transgenic A53T mouse brain into wild-type mouse brain does not induce PD (Karampetsou et al., 2020). This was observed in the face of preserved ability of promoting assembly of recombinant α-syn preformed fibrils (PFFs) into higher-order multimers *in vitro* (Karampetsou et al., 2020). The detrimental effects of α-syn PFFs uptake by primary cortical cultures *in vitro* and the inability to induce α-syn accumulation after intrastriatal injection in wild-type mice were attributed to the neutralization effect exerted by pre-incubation of α-syn PFFs with these EVs (Karampetsou et al., 2020). The observation that mutated forms of α-syn are more associated with EVs has led to speculate that pathogenic α-syn species may be preferentially sorted into EVs (Gustafsson et al., 2018). Indeed, misfolded and oligomeric α-syn, the more toxic forms of α-syn, are preferentially released within EVs compared with native and highly aggregated α-syn (Jang et al., 2010; Poehler et al., 2014).

Among the pathogenetic mechanisms of PD, exposure to environmental stressors (e.g., rotenone and manganese) is a well-documented pathway (Andruska and Racette, 2015). EVs have been identified as relevant shuttles also under these circumstances. Indeed, the secretion of EVs containing α-syn oligomers is enhanced in α-syn-expressing murine dopaminergic neuronal cells following manganese exposure (Harischandra et al., 2019). The propagation of α-syn pathology and the development of parkinsonian motor deficits have also been verified in wild-type mice following intrastriatal injection of these EVs (Harischandra et al., 2019). Similarly, exposure to rotenone increases the generation and release of α-syn-containing EVs from wild-type primary neurons (Pan-Montojo et al., 2012).

Dysfunctional endolysosomal and autophagic pathways have also been documented in PD. Treatment of neuroblastoma SH-SY5Y cell lines with bafilomycin A1, a blocker of lysosomal fusion with the autophagosome, enhances the secretion of EV containing α-syn (Jang et al., 2010; Danzer et al., 2012; Poehler et al., 2014) and promotes the uptake of these EVs by recipient cells (Alvarez-Erviti et al., 2011). Similarly, an increase in α-syn release by EVs has been observed upon blockade of macroautophagy via silencing of the autophagy-related gene 5 with beneficial effect towards the prevention of intracellular accumulation of α-syn in lund human mesencephalic cells (Fussi et al., 2018). Finally, mutations in the lysosomal enzyme glucocerebrosidase (GCase) and the consequent impairment in its activity have been strongly associated with PD (Sidransky et al., 2009; Gegg et al., 2012; Rocha et al., 2015). The pharmacological inhibition of GCase by conduritol-B epoxide increases the overall secretion of EVs and levels of EV containing oligomeric α-syn in the brain of A53T α-syn transgenic mice (Papadopoulos et al., 2018). Of note, the ratio between plasma levels of EV α-syn and total α-syn has been shown to be inversely correlated with GCase enzymatic activity in patients with PD (Cerri et al., 2018). As such, a link between the GCase activity and the release of EVs has been hypothesized.

A snapshot of positive and negative actions conveyed by EVs in AD and PD is depicted in **Figure 3**.

Extracellular Vesicles as Potential Biomarkers for Alzheimer's Disease and Parkinson's Disease

The increasing interest in the study of EVs as biomarkers resides mainly in the fact that identification of peripheral levels of EV-associated proteins might reflect molecular events in the brain, thereby representing a brain liquid biopsy (Abdel-Haq, 2020). This approach would allow overcoming the issue of the non-accessibility of neural tissues and holds potential for the development of personalized approaches. In particular, EVs isolated from the CSF or immune-isolated from serum/plasma for the neuronal surface marker L1CAM or NCAM are enriched in neural-derived EVs. This EV subtype enrichment via targeted purification strategies is extremely informative through selecting neuronal EVs eventually carrying specific disease-associated factors (Mustapic et al., 2017). Indeed, protein levels and the profile of mediators isolated from the CFS and immune-isolated EVs from the blood show a similar pattern and the same ability to identify people with AD (Jia et al., 2019).

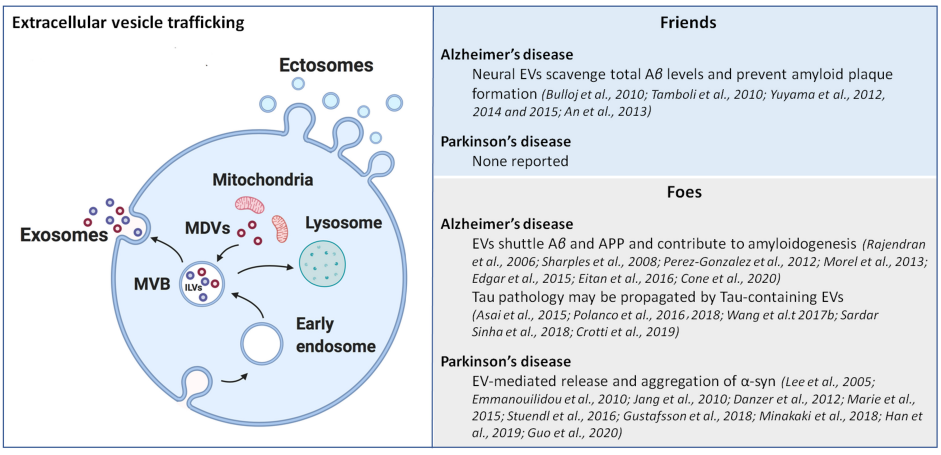

Figure 3 | Positive and negative actions of extracellular vesicles in Alzheimer's and Parkinson's diseases.

Aβ: Amyloid beta; APP: amyloid precursor protein; α-syn: α-synuclein; EVs: extracellular vesicles; ILVs: intraluminal vesicles; MDVs: mitochondrial-derived vesicles; MVB: multivesicular body. Figure was drawn using the web-based tool BioRender (Toronto, Canada).

Effort has also been dedicated to the analysis of EVs in the brain in the attempt of gathering indication on tissue- and disease-specific markers to be searched at the systemic level. Aβ oligomers were identified in EVs isolated from the temporal neocortex, but not in non-neuronal EVs of AD patients (Sardar Sinha et al., 2018). A positive correlation between levels of phosphorylated Tau and $A\beta_{1-42}$ protein in brain tissue homogenates and brain-derived EVs of AD patients has also been found (Muraoka et al., 2020). The identification of Aβ oligomers in circulating EVs from AD patients and its correlation with amyloid plaques deposition in the brain have also been reported and represent a promising finding towards its inclusion among circulating biomarkers for AD (Lim et al., 2019). Together with $A\beta_{1-42}$, tau protein phosphorylated at several sites (i.e., pS262/pS356, pS396/pS404, and pT181) was also identified in neural EVs isolated from the CSF and plasma/serum of AD patients (Saman et al., 2012; Fiandaca et al., 2015; Goetzl et al., 2016b; Wang et al., 2017a; Jia et al., 2019). More relevant, increased circulating levels of pT181 Tau, pS396 Tau, and $A\beta_{1-42}$ were found to characterize people with mild cognitive impairment who converted to AD (Winston et al., 2016). High levels of phosphorylated Tau and $A\beta_{1-42}$ peptides have also been identified in circulating neuronal EVs from young people with Down syndrome (Hamlett et al., 2018). The presence of these mediators within EVs may indicate signs of dementia in this population already during childhood and may therefore be exploited as early biomarkers of AD (Hamlett et al., 2018). However, these findings warrant further investigation as conflicting results have been obtained possibly due to differences in the EV isolating procedures adopted. For the same reason, a rich list of candidate biomarkers identified in neural EVs isolated from serum or plasma has been proposed. These mediators were selected for their ability to discriminate AD patients from controls, support disease staging, and predict disease development from a preclinical stage (Vandendriessche et al., 2020).

An altered insulin signaling, characterized by changes in the phosphorylation status of the insulin receptor substrate-1 eventually triggering insulin resistance associated with AD pathogenesis, has also been found to be reflected in plasma-derived neuronal EVs (Kapogiannis et al., 2015). Of note, levels of some mediators of the insulin signaling pathway carried by these vesicles were able to identify people with sub-clinical cognitive decline and predict longitudinal changes in cognitive performance (Kapogiannis et al., 2019; Eren et al., 2020). Moreover, lower levels of synaptic proteins and transcription factors involved in neuronal protection (e.g., lipoprotein receptor-related protein 6, repressor element 1-silencing transcription factor) and higher levels of several lysosomal proteins have been identified in plasma-derived neuronal EVs of AD patients at different disease stage compared with controls (Goetzl et al., 2015a, b, 2016a, 2018a; Winston et al., 2016). Among these factors, levels of the proteins synaptopodin, synaptophysin, GluA4-containing glutamate, neuroligin 1, and the synaptosomal-associated-protein 25 in plasma-derived neuronal EVs showed a positive correlation with the cognitive performance of AD patients (Goetzl et al., 2016a, 2018a; Agliardi et al., 2019). Finally, an association was found between circulating levels of several EV-associated miRNAs and neuropsychological and neuroimaging findings in patients with AD (Cheng et al., 2015). In particular, lower levels of miR-100-3p, miR-132, miR-193b, and miR-212, and higher levels of miR-23a-3p, miR-223-3p and miR-190a-5p, and miR-384 have been reported in people with AD compared with controls (Liu et al., 2014; Yang et al., 2018; Cha et al., 2019; Serpente et al., 2020).

Several studies have also provided indications of the potential held by EV-associated factors as biomarkers of PD. The characterization of EVs purified from the serum of people with early-stage PD identified distinct profiles relative to healthy controls (Tomlinson et al., 2015). Discriminative cargo molecules included the vacuolar protein sorting-associated protein 13D, peroxiredoxin-2, S100A8, cytochrome b-245 heavy chain, and syntenin 1 (Tomlinson et al., 2015). Moreover, the analysis of immune-isolated neuronal EVs showed an association of specific proteins with PD severity (Jiang et al., 2019). In particular, clusterin, complement C1r subcomponent, afamin, apolipoprotein D, gelsolin, and pigmented epithelium derived factor were all upregulated in mild and severe cases of PD. Instead, the human neuroblastoma cDNA clone CS0DD006YL02, complement C1q subcomponent, myosin-reactive immunoglobulin, Ig kappa chain, and Ig mu chain were down-regulated (Jiang et al., 2019). Finally, urinary EVs from PD patients showed an enrichment in endolysosomal proteins with synaptosomal-associated-protein 23 and calbindin being the two most abundant proteins in PD (Wang et al., 2019). Notably, these mediators had a prediction success of 76–86% for PD and a low interindividual variability in two independent cohorts (Wang et al., 2019). Urinary phosphorylated leucine-rich repeat kinase 2 (LRRK2) is a promising biomarkers of PD progression and treatment. Indeed, missense mutations of LRRK2 gene, the most common genetic cause of PD, induce LRRK2 autophosphorylation at serine 1292 (pS1292) sites and brain neurotoxicity by increasing LRRK2 kinase activity (Wang et al., 2017). pS1292-LRRK2 can be taken up by MVBs and subsequently packaged into exosomes for release (Fraser et al., 2013). A higher Ser(P)-1292 LRRK2 to total LRKK2 ratio has been found in urinary EVs of PD patients with and without LRKK2 mutations (Fraser et al., 2016; Wang et al., 2019). In patients without LRKK2 mutations, urinary Ser(P)-1292 LRRK2 levels correlated with non-motor PD symptoms (Fraser et al., 2016).

EV-associated miRNAs have also been identified in people with PD. In particular, higher levels of miR-24 and miR-195 and a lower abundance of miR-19b were found in serum EVs of people with PD (Cao et al., 2017). Plasma-derived EVs of PD patients, instead, showed higher abundance of miR-331-5p and lower levels of miR-505 (Yao et al., 2018).

The endo-lysosomal system besides delivering portions of plasma membranes to the endosomal compartment for recycling purposes, orchestrates the execution of autophagy as part of cell's quality control processes. Via this pathway, mitochondrial homeostasis is also regulated and emerged as a crucial factor in age-related conditions, including neurodegeneration (Picca et al., 2020b). Indeed, dysfunctional mitochondria produce higher rates of reactive oxygen species that may amplify the damage to organelle's macromolecules and overwhelm antioxidant defenses, ultimately resulting in overt oxidative stress. In the setting of a pro-oxidant environment, aberrant protein folding and accrual (i.e., $A\beta_{1-42}$, huntingtin, Tau, and α-syn) may occur (Picca et al., 2020b). If not appropriately disposed, this cellular waste may negatively impact cellular activities, spread throughout neighboring cells, and be released at the systemic level (Picca et al., 2020b). The extrusion of MDVs as an attempt to cope with dysfunctional mitophagy and operating within the endo-lysosomal pathway for the removal of damaged mitochondria has been proposed as a quality control mechanism in PD (Picca et al., 2020c). In this regard, circulating MDVs may represent promising biomarkers of PD (Matheoud et al., 2016). The characterization of small EVs isolated from the serum of PD patients allowed identifying lower levels of mitochondrial markers, including adenosine triphosphate 5A, NADH:ubiquinone oxidoreductase subunit S3, and succinate dehydrogenase complex iron sulfur subunit B, in the face of enhanced EV secretion compared with non-PD controls (Picca et al., 2020c).

Taken as a whole, these findings hold promise for the implementation of these mediators as biomarkers for disease

tracking over time and in response to treatments.

A list of EV biomarkers discussed for AD and PD is shown in **Table 1**.

Conclusion

The richness of biomolecules packaged within EVs and their potential involvement in intracellular trafficking and quality control processes have placed these shuttles in the spotlight as biomarkers for conditions characterized by cellular quality decline as part of their pathogenetic mechanism. This is the case of AD and PD neurodegeneration. Both systemic and neuronal EVs have contributed unprecedented pieces of information to the whole complex regulatory network of neuronal intracellular trafficking in both conditions. Moreover, ongoing and more focused studies continue to enrich the list of cell-specific derived vesicles which represent even more informative tools of investigation. For instance, EVs produced by astrocytes and immunoprecipitated via the glutamine aspartate transporter have shown great potential for monitoring the effectiveness of specific drugs in AD (Goetzl et al., 2016b).

A major obstacle to the implementation of EVs in clinical practice resides in the sophisticated isolation procedures and the absence of a standardized purification protocol and quality control measures. However, the minimal information for studies of EVs guidelines provide precise indication on how to obtain reliable and reproducible results and to ensure a comprehensive interpretation of biological knowledge on EVs (EV-TRACK) (Théry et al., 2018; Roux et al., 2020). Undoubtedly, the great value of EV-derived biomarkers resides in the fact that their collection can be performed from biofluids, thereby avoiding safe but rather invasive procedures such as CSF collection via lumbar puncture (Duits et al., 2016). Indeed, EVs can cross the blood-brain barrier (Saint-Pol et al., 2020) and be detected at the systemic level whereby their cargoes are sheltered from degradation (Hampel et al., 2018; Zetterberg and Burnham, 2019).

EVs have also been tested in a few clinical trials for their ability to serve as biomarkers in response to a treatment in mildly cognitive impaired and PD patients (Winston et al., 2018; Mustapic et al., 2019). Although in most cases the profile of the EVs-associated mediators was not significantly different

Table 1 | **EV-associated biomarkers in Alzheimer's disease and Parkinson's disease**

Source	Category	Markers	References
Alzheimer's disease			
Brain	Neurotoxic proteins	$A\beta_{1-42}$ an	Sardar Sinha et al., 2018
	Neurotoxic proteins	pTau and $A\beta_{1-42}$	Muraoka et al., 2020
CSF	Neurotoxic proteins	EV pT181Tau/EV tTau ratio	Saman et al., 2012
		EV pT181 Tau/CSF pT181 Tau ratio	
	miRNA	miR-193b	Liu et al., 2014
Plasma	Survival factors	LRP6, HSF1, and REST	Goetzl et al., 2015a
	Lysosomal proteins	LAMP1, cathepsin D	Goetzl et al., 2015b
	Synaptic proteins	Synaptotagmin, synaptophysin, synaptopodin	Goetzl et al., 2016a
	Synaptic proteins	AMPA4 and NLGN1	Goetzl et al., 2018a
	Neurotoxic proteins	$A\beta_{1-42}$, BACE1, gamma secretase, pS396 Tau, pT181 Tau, sAPPa, sAPPb	Goetzl et al., 2016b
	Neurotoxic proteins	$A\beta_{1-42}$, pS396 Tau, pT181 Tau	Winston et al., 2016; Jia et al., 2019
	Neurotoxic proteins	pT181Tau, pT231	Kapogiannis et al., 2019
	Insulin signaling	IRS-1-pS312, and IRS-1-pTyr	Kapogiannis et al., 2015, 2019
	miRNAs	miR-23a-3p, miR-100-3p, miR-132, miR-212, miR-223-3p, miR-190a-5p	Cha et al., 2019
			Serpente et al., 2020
Plasma/serum	Neurotoxic proteins	pS396 Tau, pT181 Tau, $A\beta_{1-42}$	Fiandaca et al., 2015
Serum	miRNAs	miR-135a, miR-193b, miR-384	Liu et al., 2014; Yang et al., 2018
	Synaptic protein	SNAP 25	Agliardi et al., 2019
Parkinson's disease			
CSF	Neurotoxic proteins	α-syn	Stuendl et al., 2016; Guo et al., 2020
Plasma	Neurotoxic proteins	α-syn	Shi et al., 2014; Cerri et al., 2018; Xia et al., 2019; Zhao et al., 2019
	miRNAs	miR-331-5p, miR-505	Yao et al., 2018
Serum	Neurotoxic protein	α-syn	Han et al., 2019; Jiang et al., 2020
	Other protein factors	Vacuolar protein sorting-associated protein 13D, peroxiredoxin-2, S100A8, cytochrome b-245 heavy chain, syntenin, clusterin, complement C1q and C1r subcomponents, afamin, apolipoprotein D, gelsolin, pigmented epithelium derived factor, myosin-reactive immunoglobulin,	Tomlinson et al., 2015; Jiang et al., 2019; Jiang et al., 2020
	MDVs	ATP5A, NDUFS3, SDHB	Picca et al., 2020c
	miRNAs	miR-24, miR-195, miR-19b	Cao et al., 2017
Urine	Synaptic protein	SNAP23	Wang et al., 2019
	Other proteins	Calbindin, pSer1292 LRKK2	Fraser et al., 2016; Wang et al., 2019

$A\beta_{1-42}$: 42 amino acid form of amyloid β peptide; AMPA4: GluA4-containing glutamate; APP: amyloid precursor protein; α-syn: α-synuclein; ATP5A: adenosine triphosphate 5A; BACE1: β-site APP cleaving enzyme-1; CSF: cerebrospinal fluid; EV: extracellular vesicle; HSF1: heat-shock factor-1; IRS-1: insulin receptor substrate-1; LAMP1: lysosomal-associated membrane protein 1; LRKK2: leucine-rich repeat kinase 2; LRP6: lipoprotein receptor-related protein 6; MDVs: mitochondrial-derived vesicles; miRNA: microRNA; NDUFS3: NADH:ubiquinone oxidoreductase subunit S3; NLGN: neuroligin 1; pTau: phospho Tau; REST: repressor element 1-silencing transcription factor; sAPP: soluble APP; SDHB: succinate dehydrogenase complex iron sulfur subunit B; SNAP: synaptosomal-associated-protein.

in response to the specific treatment nor were changes in EV cargoes detected (Winston et al., 2018; Mustapic et al., 2019), the results obtained still hold promise towards their use as biomarkers to validate a patient's response to a treatment (Athauda et al., 2019).

The research framework of the National Institute on Aging–Alzheimer's Association (NIA–AAA) and the International Working Group recognized the CSF as the only biofluid for a biomarker-based definition of AD (Dubois et al., 2014; Jack et al., 2018). In particular, low levels of $A\beta_{1-42}$ or $A\beta_{1-42}/A\beta_{1-40}$ ratio, elevated p-Tau, and elevated CSF t-Tau define AD and support diagnostic accuracy in case of inconclusive clinical diagnosis (Dubois et al., 2014; Niemantsverdriet et al., 2017; Jack et al., 2018). Conversely, no validated biomarkers are yet available for PD diagnosis.

The steep increase in findings gathered from the investigation of EVs as biomarkers of neurodegenerative diseases indicates that the way ahead for the identification of novel and predictive biomarkers for AD and PD may be approaching in the near future.

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