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Review

Extracellular vesicles, new actors in the search for biomarkers of dementias

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ABSTRACT

Increased life expectancy impacts directly on the number of older people worldwide with the associated increase in neurodegenerative diseases. Besides their social implications, the different forms of dementia, including Alzheimer's disease, Parkinson's disease, dementia with Lewy bodies or frontotemporal dementia, show clinical and pathological overlaps; this hinders their specific and differential diagnosis. To date, biomarkers for each of these types of dementia have been investigated in the cerebrospinal fluid or blood. More recently, the field of biomarker search found a new opportunity to improve diagnosis in extracellular vesicles (EVs). EVs are released by cells including those of the central nervous system and these can be isolated from cerebrospinal fluid and blood. This review summarizes the current knowledge related to the search for dementia biomarkers in the field of EVs including studies of specific EV content, mainly proteins such as α-synuclein or tau and RNA species.

1. Introduction

Life expectancy has significantly increased during the last decades, so that around 900 million people are aged over 60 years (Global burden of Disease Study Collaborators, 2015), raising the possibility of developing aging-related chronic diseases (Prince et al., 2016). In this aging context, neurodegenerative diseases (NDDs) and dementia-related disorders are one of the most critical public health problems in our society. The term dementia generally refers to a group of pathological situations presenting symptoms characterized by the loss of memory and other intellectual abilities such as decision making, problem solving, creative and critical thinking, and later also activities of daily living (Harada et al., 2013; Martin, 1999; Prizer and Zimmerman, 2018). The most studied dementia-related diseases include NDDs like Alzheimer's disease (AD), Parkinson's disease (PD), dementia with Lewy bodies (DLB), and frontotemporal dementia (FTD) (http://www.alzcare.org/dementia). With the aim of disentangling the clinical and pathological overlaps between these diseases, efforts have been focused on the search of specific biomarkers for each of the disorders (Ahmed et al., 2014; Biomarkers Definitions Working Group, 2001). Therefore, this review focuses on liquid biopsy biomarkers, specifically on extracellular vesicles (EVs) as biomarker source for the differential diagnosis of dementia-related disorders.

2. Biomarkers for dementia-related disorders

AD accounts for more than 60% of all dementia cases and neuropathologically, it is characterized by the presence of neurofibrillary tangles and senile plaques (Martin, 1999; Winblad et al., 2016). The beta amyloid (Aβ) peptide is the primary constituent of neuritic plaques deposited extracellularly, whereas intraneuronal neurofibrillary tangles are mainly composed of hyperphosphorylated tau (P-tau) (Ross and Poirier, 2004). In AD-biomarker research, there is an almost complete consensus reporting Aβ forms or P-tau levels as measurable biomarkers in the cerebrospinal fluid (CSF) (Blennow, 2017; Bousiges et al., 2016). Besides Aβ and tau, other proteins have also been proposed as possible biomarkers in CSF-proteomic studies in AD (Nayak et al., 2015; Perrin et al., 2011). When referred to blood biomarkers, different studies using plasma have

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been published as summarized in the recent review of Zetterberg (Zetterberg, 2017).

PD is the second most common NDD after AD (Mhyre et al., 2012) and in advanced stages of the disease, at least 50% of patients develop dementia, called PD with dementia (PDD) (Hanagasi et al., 2017). DLB is the second most common type of dementia worldwide accounting for 20%–30% of the cases (Jellinger, 2018), and together with PD, it belongs to the group of Lewy body diseases. Their pathological hallmark is large intraneuronal inclusions called Lewy bodies (LBs) and Lewy neurites. These are mainly composed of α-synuclein (α-syn) and distributed throughout the brain (Ingelsson, 2016; Martin, 1999). Furthermore, LB pathology can be concomitant with AD characteristic Aβ and P-tau pathology, reported as crucial factors for the development of dementia in PD (Colom-Cadena et al., 2017; Ubhi et al., 2010). Thus, especially CSF α-syn is being investigated as a Lewy body disease–specific biomarker, although controversial and diverse results have been reported (Malek et al., 2014). Several studies have described decreased CSF α-syn in patients with PD compared to healthy individuals (Hong et al., 2010; Tokuda et al., 2006), whereas others found higher levels in PD than in controls (Park et al., 2011). For DLB, the Aβ-42/40 ratio was defined as higher than that in AD but lower than that in patients with PDD (Llorens et al., 2016a,b; Nutu et al., 2013). Recently, Chiasserini et al. (2017) proposed the combination of different neurodegeneration-related proteins as possible biomarkers to differentiate between AD, PD, PDD, and DLB. In blood, consensus is almost found regarding increased α-syn levels in PD compared to controls (Lin et al., 2017), although decreased expression has also been reported (Li et al., 2007). So far, consistent results on blood-based biomarkers for DLB have not been reported in the literature (El-Agnaf et al., 2006; Laske et al., 2011).

FTD accounts for 10%–15% of all dementia cases, being the third most common dementia (Onyike and Diehl-Schmid, 2013). Compared to other dementias, a high proportion of FTD cases develops due to genetic factors (Meeter et al., 2017). Nevertheless, aggregated misfolded proteins, such as tau and TDP-43, are also found. Hence, CSF-tau levels have also been proposed as a biomarker distinguishing it from AD. Nonetheless, due to disease heterogeneity, different conclusions are presented as a result of numerous studies (Llorens et al., 2016a,b; Meeter et al., 2017; Riemenschneider et al., 2002; Skillbäck et al., 2017).

Although considered proteinopathies, not only proteins have been recognized as promising neurodegeneration biomarkers but also RNAs and especially microRNAs (miRNAs). For dementia-related disorders, deregulation of several miRNAs has been described throughout the last few years (Karnati et al., 2015); of these, hsa-miR-15a and the hsa-miRNA-34 family are deregulated in AD (Grasso et al., 2014), and hsa-miR-141 and hsa-miR-193a-3p in PD (Dong et al., 2016).

3. Extracellular vesicles

EV research is an emerging field with increasing production of published data. The term EVs includes exosomes (EXs), microvesicles (MVs), and ectosomes released from different cell types and found in several body fluids (Carreras-Planella et al., 2017; Gámez-Valero et al., 2015; Raposo and Stoorvogel, 2013). Although EVs and specifically EXs were initially considered a cellular garbage disposal mechanism, EVs are nowadays widely accepted as principal players in intercellular communication and also in the pathobiology of several diseases. Furthermore, they are considered suitable for drug delivery and as reservoirs of biomarkers (Carreras-Planella et al., 2017; Kalluri and LeBleu, 2016; Lässer et al., 2011; Mateescu et al., 2017). EVs are enriched in membrane/transport-fusion proteins and in a subset of characteristic proteins from the cell of origin (Kalra et al., 2012; Pan and Johnstone, 1983). Moreover, EVs contain also a rich repertoire of genetic material, including both RNA and DNA (Kalluri and LeBleu., 2016; Lässer et al., 2011). Accordingly, the study of the EV content from a specific source may provide information about the cells and tissue of origin and their physiological state.

Nevertheless, as a still growing field, many processes of vesicular biology and physiology have not been fully identified, and standard methodologies and procedures have yet to be agreed among the scientific community. Since EVs were described (Pan and Johnstone, 1983), ultracentrifugation has been the “gold standard” EV-isolation method used regardless the origin of the sample (Rood et al., 2010). Additional methodologies have been proposed for a rapid, cleaner, and a more efficient EV isolation, such as several commercial kits or the recently described size-exclusion chromatography (Gámez-Valero et al., 2016; Helwa et al., 2017; Rood et al., 2010; Taylor and Shah, 2015). After isolation, characterization of the isolated vesicles before subsequent applications is important. Thus, flow cytometry, nanoparticle tracking analysis or dynamic light scattering, and cryo-electron microscopy or atomic force microscopy are used to study their concentration, morphology, and size distribution. Additional techniques, such as Western blot analyses, would also confirm the presence of the main EV markers (i.e., Alix or CD63) (Carpintero-Fernández et al., 2017). Given a lack of consensus in EV techniques, comparative studies are carried out to determine the best approach that guarantees the purity of EVs, the determination of EV-associated markers, functionality, ease, and feasibility of the procedure. As revealed in the first report of the EV-TRACK Consortium, it has to be taken into account that most of the EV-related publications do not contain enough information and details about the applied methodologies for replication of experiments (EV-TRACK Consortium et al., 2017), precluding optimal comparison.

3.1. EVs in the central nervous system

EVs are released from neurons, oligodendrocytes, and other CNS cells, playing an important role in the synaptic physiology and being relevant effectors in the neuron-neuron, neuron-glia communication, and axon damage regeneration (Court et al., 2011; Lachenal et al., 2011). Since Haqqani et al. (2013) first described EVs from the blood-brain barrier, researchers have studied their role and their capacity to cross the blood-brain barrier in both directions (García-Romero et al., 2017). In the case of dementia-related diseases, EVs from brain cells could be found in the CSF reflecting the pathological changes taking place in the affected brain. Moreover, the search of brain-derived EVs in the bloodstream has increased in the last years being hypothetically considered a peripheral noninvasive source of biomarkers for NDDs. For this purpose, Fiandaca et al. (2015) described an immunochemical approach for the specific enrichment of brain-derived vesicles using L1-cell adhesion molecule (L1CAM) or neural cell adhesion molecule (Goetzl et al., 2015; Kapogiannis et al., 2015). Nevertheless, some doubts about the specificity of the methodology can arise as L1CAM and neural cell adhesion molecule are not brain-specific proteins, but they have also been described as important glycoproteins in epithelial cells of the renal system (Allory et al., 2008; Marković-Lipkovski et al., 2015). In any case, this cerebral-EV enrichment approach represents a new point of view regarding isolation of CNS-EVs.

3.2. EV proteomics as dementia biomarkers

Because the CSF is in direct contact with cerebral tissue, CSF biomarkers have been widely studied in dementia-related research.

In 2012, Street et al demonstrated that EVs are also present in the CSF (Street et al., 2012). The largest and most complex proteomic study on CSF-EVs was performed in 2014 and reported a total of 760 proteins, from which 50% were present in the EV pellet and also in the remaining supernatant; 489 of them were exclusively present in vesicles. Neurodegeneration-related proteins, such as tau, α-syn, or Aβ peptides were also found in this vesicular fraction (Chiasserini et al., 2014). Not only neuron-to-neuron transmission of tau pathology has been proven to occur via EVs in vitro and in vivo (Polanco et al., 2016; Saman et al., 2014), but the role of EV-tau as a biomarker for AD progression was also early assessed. Mild (stage 3) and advanced (stage 5) patients with AD were recruited to analyze their CSF-EV-tau content, and an increase of total and AT270 P-tau levels in both pathological groups compared to controls was found (Saman et al., 2012). Interestingly, P-tau was increased in the exosomal (but not total CSF) fraction of mild AD cases, and it decreased with disease severity. On the other hand, stage 5 AD showed a decrease of P-tau in EXs, but an increase in the total CSF fraction (Saman et al., 2012). Recently, another study has reported the proteomic profile of CSF-EV in AD by targeted proteomic assay. Neuroinflammation markers, such as YKL-40 or cystatin-C, both increased in AD compared to non-AD, and tau and Aβ levels were assessed (Paterson et al., 2016). Moreover, the combination of overexpressed malate dehydrogenase, APOE, and YKL-40 in AD compared to non-AD showed a high area under the curve (0.88) differentiating both cohorts (Paterson et al., 2016). Inversely, EV proteins such as Alix or Hsp70 have been reported to accumulate in amyloid plaques of AD brains as well (Musunuri et al., 2016; Rajendran et al., 2006). Last year, increased Aβ42 and low tau content in EVs from AD-CSF were described and analyzed; authors reported their toxic effect to primary neurons, which was not observed when using EVs from healthy controls (Eitan et al., 2016). Also in the CSF, EV-packaged α-syn has been explored as a biomarker for LB disorders. Grey et al. demonstrated that low amounts of α-syn–enriched EXs are enough to induce and catalyze the formation of α-syn fibrils (Grey et al., 2015). Previously, in 2012, Danzer et al. reported that not only PD-EV but also DLB-CSF derived EVs, induce oligomerization of soluble α-syn in recipient cells, a finding that was recently confirmed by Ngolab et al. (2017), (Danzer et al., 2012; Ngolab et al., 2017). Last year, α-syn levels in CSF-derived EXs were compared between PD, DLB, and controls. Interestingly, PD-CSF contained more vesicles and a higher concentration of α-syn compared to DLB and control groups, showing high sensitivity and specificity for the discrimination between the three groups (Stuendl et al., 2016). In addition, in patients with AD, CSF enrichment in myeloid MVs has been reported in comparison to controls. Correspondingly, AD-CSF contained a higher concentration of vesicles than mild cognitive impairment (MCI), and both had higher MV levels than healthy individuals (Agosta et al., 2014). Of note, patients with MCI who converted to AD reached AD-levels of MVs in their CSF after a time (Agosta et al., 2014). Nevertheless, there are no clear guidelines about the isolation and recovering of these vesicles. Despite these observations regarding EV concentration, in most of the studies, no difference was reported in the amount of EVs between patients and controls. However, Eitan et al described an increased EV concentration only when the lysosomal pathway is affected (Eitan et al., 2016).

In contrast to PD or AD, only very few studies related to FTD CSF-derived vesicles exist. Nevertheless, a type of FTD (N279K tau mutant FTD) has been related to vesicle impairment with an increase of EX proteins in the patient's cortex. Furthermore, in neuronal stem cells derived from these patients, the accumulation of endosomes and EXs was observed (Wren et al., 2015). Accordingly, a decrease of EX release in progranulin-associated FTD using human fibroblasts was reported (Benussi et al., 2016).

Because CSF collection requires an invasive process, analysis of blood-derived EVs is intensely evaluated. Although many blood-based biomarkers have been proposed for dementia-related diseases, to date, data on EV-proteomic analysis from plasma or serum are limited (Chahine et al., 2014; Guo et al., 2013; Suzuki et al., 2015). Currently, only one study comparing EX concentration between PD, amyotrophic lateral sclerosis, and healthy controls has been published. This study showed similar EX levels and some differences in EX-protein enrichment. A total of 54 proteins distinguished PD from amyotrophic lateral sclerosis; and although no enrichment in α-syn or tau was found, the EV marker syntenin-1 was elevated in PD compared to controls (Tomlinson et al., 2015). In addition, in 2014, Fiandaca et al found that concentrations of tau forms could differentiate FTD from AD with high sensitivity and specificity, using the immunocapture of L1CAM-enriched EVs (Fiandaca et al., 2015). Total tau and T181 P-tau showed higher levels in both pathologies when compared to controls. Moreover, levels of total tau, T181 P-tau, S396 P-tau, and Aβ1-42 were increasing with AD progression from preclinical to advanced AD (Fiandaca et al., 2015). To date, several works have used L1CAM-based EV enrichment to biomarker research in AD, FTD, and PD. Thus, the enrichment of α-syn in PD-derived EVs compared with healthy controls was described (Shi et al., 2014). Moreover, higher levels of EX-tau protein were found in patients with PD than in controls (Shi et al., 2016). In 2015, transcription factors related to neuronal defenses were studied in L1CAM-enriched plasma EXs. Their levels were lower in AD than in control subjects or FTD, which showed similar levels (Goetzl et al., 2015). Although higher levels of neuronal-EVs were found in blood of individuals with MCI compared to advanced AD, EV-tau concentration showed an inverse correlation being overexpressed in advanced AD (Winston et al., 2016). The presence of indirect neurodegeneration effectors such as lysosomal proteins has been reported in L1CAM-enriched vesicles. While cathepsin D or LAMP-1 is overexpressed in AD compared to FTD or controls, HSP70 has a lower concentration in FTD compared to controls or AD (Goetzl et al., 2015). In another work, levels of synaptoglobin and synaptopodin were measured in L1CAM-neuronal–derived EXs, presenting significantly lower expression levels in FTD and AD than in controls and showing AD an even higher decrease than FTD (Goetzl et al., 2016). Last year, these levels were associated with the progression of the disease in another work (Goetzl et al., 2018). Finally, high levels of AD-related proteins (Aβ1-42 and tau) in L1CAM vesicles have also been reported for individuals with Down syndrome (Hamlett et al., 2017). Table 1 summarizes the main proteins described in EVs as dementia biomarkers.

Interestingly, urine-EVs are being studied as a biomarker source for NDDs as well. LRRK2 and DJ-1 proteins are present in urine EXs with some differences in male patients with PD respect to controls (Fraser et al., 2016; Ho et al., 2014; Wang et al., 2017).

3.3. EV-miRNA as a biomarker for dementia

Several RNA species (mRNA, miRNAs, and ncRNAs) are found to be stable, protected, and functional in EVs (Kim et al., 2017), and also genomic DNA has been found in EVs (Lázaro-Ibáñez et al., 2014; Thakur et al., 2014). As soluble small-RNAs, EV-miRNAs are considered a promising way for the differential profiling of dementia types in a more accurate way. To date, only a few studies have explored the potential of circulating miRNAs in CSF- and blood-EVs as a diagnostic tool for dementia. The first study on the EX-RNA content in samples of PD and AD patients was accomplished by Gui et al. (2015). Differentially expressed miRNAs were found in the different groups; although 16 miRNAs were upregulated, 11 were downregulated in PD when compared to controls. In

Table 1
Main EV-associated proteins described as possible biomarkers for dementia-related disorders

Disorder	Source	Finding	Ref
		Increased tau MVs in AD and MCI	Agosta et al., 2014
AD	CSF	Increase of total and P-tau compared to controls	Saman et al., 2014
		Higher P-tau in mild than in severe AD	Saman et al., 2014
		Increased YKL-40, cystatin-C, APOE	Paterson et al., 2016
		Higher tau and Aβ than in non-AD	
		Accumulated Alix and HSP70	Rajendran et al., 2006; Musunuri et al., 2016
	Blood	T181 P-tau, S396 P-tau, and Aβ1-42 increasing with severity	Fiandaca et al., 2015
		Downregulated LRP6, HSF1, REST compared to controls	Goetzl et al., 2015
		Higher EV-tau concentration than in MCI or controls	Winston et al., 2016
		Higher cathepsin D and LAMP-1 than in controls or FTD	Goetzl et al., 2015
		Downregulated HSP70 compared to controls	
		Less synaptoglobin and synaptopodin than in controls	Goetzl et al., 2016, Goetzl et al., 2017
Lewy Body disorders (DLB & PD)	CSF	Higher EV concentration in PD than in DLB and controls	Stuendl et al., 2016
		Higher α-syn in PD- than in DLB- and control-EVs	
	Blood	Higher α-syn concentration than in control-EVs	Shi et al., 2014
		Higher EV-tau than in controls	Shi et al., 2016
		Increased syntenin-1 in PD compared to controls	Tomlinson et al., 2015

Key: EV, extracellular vesicle; MV, microvesicle; AD, Alzheimer's disease; MCI, mild cognitive impairment; P-tau, hyperphosphorylated tau; FTD, frontotemporal dementia; PD, Parkinson's disease; DLB, dementia with Lewy bodies; α-syn, α-synuclein.

addition to miRNA expression changes, mRNA transcripts of the amyloid precursor protein, α-syn, tau, neurofilament, or DJ-1/PARK7 also showed differential expression levels compared to controls (Gui et al., 2015). Moreover, recent studies have focused on the differences in miRNA content between the CSF remaining supernatant and the EV-pellet fraction after EV isolation (Riancho et al., 2017; Yagi et al., 2017). In one of them, Riancho et al assessed differences in selected miRNA content in the total CSF and EX fraction of AD compared to controls. In the CSF fraction, underexpression of miRNAs miR-9-5p, miR-598, and miR-134 was observed in AD compared to controls; in contrast, although without reaching statistical significance, EX fractions from patients with AD showed a tendency of increased miRNA expression compared to controls (Riancho et al., 2017). In a further study carried out in AD, MCI, and control serum, a signature of 16 EV-miRNAs was assessed for AD prediction together with other risk factors such as the APOE status (Cheng et al., 2015). In addition, the analysis of EXs from patients with AD revealed the presence of 20 differentially expressed miRNAs in comparison with controls. Most of them, including hsa-miR-101-3p, hsa-miR-20a-5p, or hsa-miR-106b-5p, had been previously related to AD pathology and showed higher expression in patients than in controls (Lugli et al., 2015).

4. Conclusions

In recent years, we have seen a considerable increase in research into EVs and a corresponding deepening of our understanding. As well as their fundamental aspects, their suitability as sources of biomarkers or therapeutic tools is also being explored. It has been proven that neurons and other cells of the CNS are able to produce EVs. Currently, there is a significant interest in the study of the vesicular content from different tissues and fluids for dementia-related NDDs to identify biomarkers that may predict the course of the disease and the prognosis for the patient, as well as establishing a more reliable diagnosis. Despite these efforts, more studies are still needed to meet these objectives and particularly EVs from the CNS obtained from blood need to be further explored as a source of biomarkers. The better understanding of EVs' ability to cross the blood-brain barrier and of the brain-derived EV-specific content may help to uncover the pathogenesis of dementia-related disorders and to improve their diagnosis. Therefore, standardized EV isolation and characterization methods are mandatory and will allow the exploitation of their diagnostic potential and the development of new therapeutic approaches.

Disclosure statement

The authors report no conflicts of interest.

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