Clinica Chimica Acta 497 (2019) 27–34

Contents lists available at ScienceDirect

Clinica Chimica Acta

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

Review

Extracellular vesicles and their diagnostic potential in amyotrophic lateral sclerosis

Jeremy Roy[a], Daniel Saucier[b,c], Colleen O'Connell[d], Pier Jr Morin[e,*]

[a] Atlantic Cancer Research Institute, Pavillon Hôtel-Dieu, 35 Providence Street, Moncton, New Brunswick E1C 8X3, Canada
[b] Faculty of Medicine and Health Sciences, Université de Sherbrooke, 2500 de l'Université Boulevard, Sherbrooke, Québec J1K 2R1, Canada
[c] Centre de formation médicale du Nouveau-Brunswick, 100 Des Aboiteaux Street, Moncton, New Brunswick E1A 7R1, Canada
[d] Stan Cassidy Centre for Rehabilitation, 800 Priestman Street, Fredericton, New Brunswick E3B 0C7, Canada
[e] Department of Chemistry and Biochemistry, Université de Moncton, 18 Antonine-Maillet Avenue, Moncton, New Brunswick E1A 3E9, Canada

ARTICLE INFO

Keywords:
Extracellular vesicles
Exosomes
Diagnostic tool
Liquid biopsy
Neurodegenerative diseases
Amyotrophic lateral sclerosis

ABSTRACT

Extracellular vesicles, small reservoirs that carry various biomolecules, have gained significant interest from the clinical field in recent years based on the diagnostic, therapeutic and prognostic possibilities they offer. While information abound regarding the clinical potential of such vesicles in diverse conditions, the information demonstrating their likely importance in amyotrophic lateral sclerosis (ALS) is more limited. This review will thus provide a brief introduction to extracellular vesicles, highlight their diagnostic significance in various diseases with a focus on ALS and explore additional applications of extracellular vesicles in the medical field. Overall, this work sheds further light on the clinical importance of extracellular vesicles in diagnostic applications as well as supports the need to better characterize their roles and signatures in patients diagnosed with ALS.

1. Introduction

Extracellular vesicles have gathered significant attention in recent years notably due to the various clinical applications they have been associated with. From simple cell-derived reservoirs containing a heterogeneous mixture of biomolecules, extracellular vesicles are now being investigated for applications as diverse as disease diagnosis or novel means to monitor therapy response. With a particular interest in highlighting their potential in amyotrophic lateral sclerosis (ALS), this review will first introduce extracellular vesicles and their contents before presenting select studies that have demonstrated the diagnostic potential of extracellular vesicles in numerous conditions. Finally, we present growing evidence of the clinical usefulness of extracellular vesicles in multiple models of ALS as well as discuss additional clinical applications associated with these molecular reservoirs.

2. Extracellular vesicles: an overview

2.1. Extracellular vesicles (exosomes and ectosomes)

Members of the International Society of Extracellular Vesicles (ISEV) have collectively endorsed the generic term extracellular vesicles (EVs) as all particles naturally released from the cell. EVs can be further subdivided into exosomes and ectosomes (microparticles and microvesicles) based on their biogenesis. Exosomes are defined as those derived from endosomal pathways and multivesicular bodies, whereas ectosomes are defined as those derived from the plasma membrane [1,2]. As highlighted in a recent ISEV position paper [3], there is currently no consensus on defining specific markers for the EV subtypes. As such, authors are now recommended to consider use of operational terms such as physical characteristics (size, density), biochemical composition or descriptions of conditions or cell of origin when appropriate [3]. For the purpose of this review, it is important to note that the original published nomenclature utilized in the literature is used when referring to the role of respective EVs and their cargo in the diagnostic potential of ALS. In general, exosomes are small (30–150 nm) EVs with a flotation density of 1.10–1.18 g/ml. They have been isolated from many biological fluids using a variety of methods such as ultracentrifugation and ultrafiltration [4,5]. Their biochemical composition and associated cargo, including DNA, mRNA, miRNA and proteins, have been extensively reported and are available in online databases such as ExoCarta [6], Vesiclepedia [7], and exRNA Atlas [8]. In contrast, ectosomes are large (0.1–1.0 μm) EVs with a range of flotation densities. They have also been isolated from similar biological fluids. The non-invasive and increasingly straightforward means via which these reservoirs can be isolated make them attractive targets for the

* Corresponding author.
E-mail address: pier.morin@umoncton.ca (P.J. Morin).

https://doi.org/10.1016/j.cca.2019.07.012
Received 15 May 2019; Received in revised form 9 July 2019; Accepted 9 July 2019
Available online 10 July 2019
0009-8981/

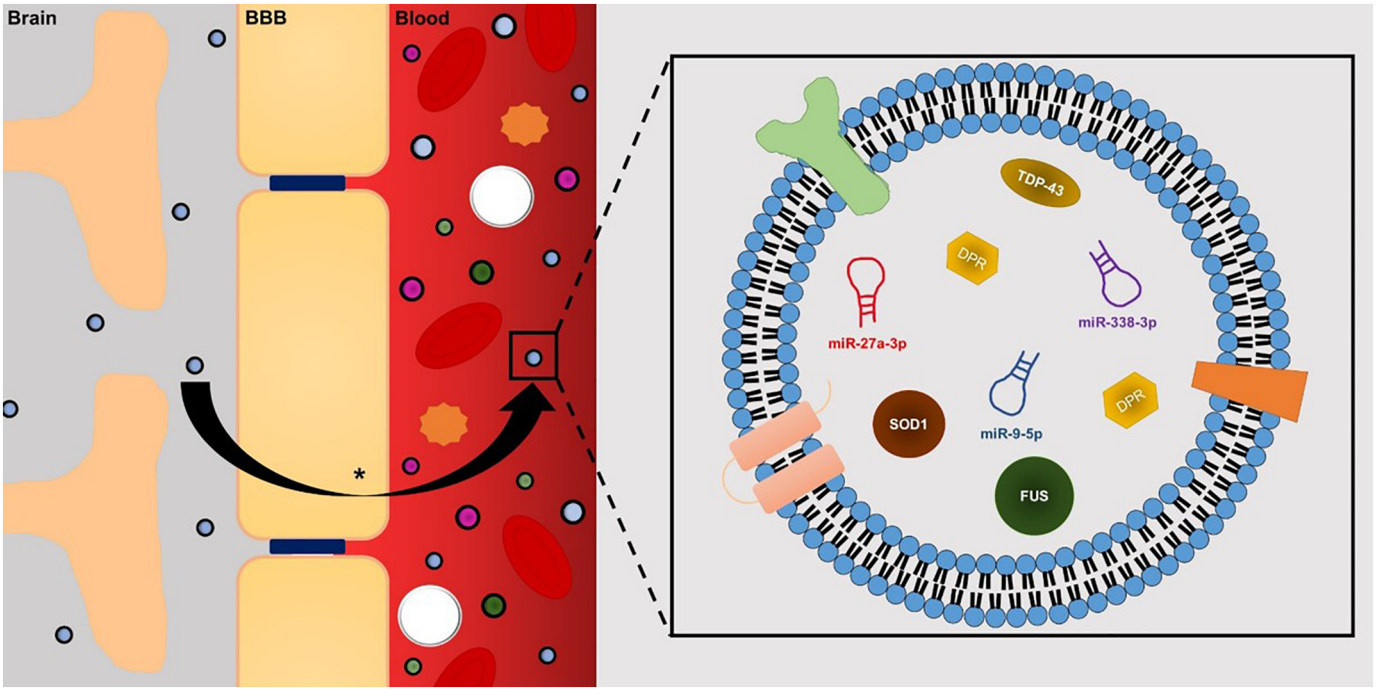

Fig. 1. Extracellular vesicles crossing the blood-brain barrier and relevance for ALS. Schematic representation of extracellular vesicles crossing the blood-brain barrier. Molecular content of such circulating reservoirs holds diagnostic potential for diverse conditions. Select molecular targets of relevance for ALS, including DPRs, FUS, SOD1, TDP-43 and miRNAs, have been identified in ALS samples and are further discussed in the text. *Multiple potential mechanisms for the trafficking of EVs from the CNS to blood and vice versa have been discussed elsewhere [133].

investigation of circulating biomarkers with clinical relevance. Both exosomes and ectosomes have been suggested to contain valuable material for diagnostic approaches in many diseases. For example, the body of work reporting their use as diagnostic tools to identify various types of cancer is vast and has been extensively reviewed elsewhere [9–11]. In addition, several examples from cancer-focused work have highlighted the successful isolation and the diagnostic potential of EVs in biological samples as diverse as saliva [12,13], urine [14,15] and cerebrospinal fluid (CSF) [16]. A schematic overview of circulating EVs and of molecular content relevant to ALS discussed below is presented in Fig. 1. Taken together, these findings are only a sub-set of examples showing the impressive body of knowledge reported in recent years on the clinical potential of EVs in the field of cancer and which have helped fuel advances in the development of EVs-associated diagnostic applications in other conditions including neurodegenerative diseases that will be discussed in the next section.

2.2. Extracellular vesicles as diagnostic tools in neurodegenerative diseases

There has also been a marked interest in exploring the molecular contents of EVs for diverse clinical means in a number of neurodegenerative diseases including Alzheimer's disease (AD) and Parkinson's disease (PD). The diagnostic challenges associated with such conditions have supported investigating these circulating reservoirs for the discovery of novel biomarkers. Numerous parameters associated with these reservoirs support their use as diagnostic tools for central nervous system (CNS) disorders and have been discussed elsewhere [17–19]. These notably include the presence of disease-associated molecular footprints found in EVs as well as the relative stability of EV-held cargoes, such as microRNAs, highlighting the diagnostic potential of EVs collected from circulating samples such as blood to monitor underlying pathogenic processes of CNS. Identification of EVs in CSF as well as evidence of their ability to cross the blood-brain barrier (BBB) further justify their potential as a source of biomarkers relevant for CNS conditions. It is nevertheless important to point out that the speed, cost as well as purity of EVs remain inherent challenges associated with the standardization of protocols leveraged to purify these reservoirs and work to address this need has been discussed by others [20,21]. Pioneering studies performed in AD highlighted the likely importance of EVs in neurodegenerative diseases. For example, it was shown that amyloid β peptides, which underlie the formation of amyloid plaques, were released from cells in association with exosomes in AD [22]. This work also revealed an accumulation of exosome-associated proteins in amyloid plaques supporting the potential involvement of these reservoirs in plaque formation. EVs isolated from human and mouse AD plasma samples were shown to promote neuronal toxicity and it was speculated that the EVs-mediated delivery of amyloid β peptides could underlie this observation [23]. A recent study also demonstrated increased levels of oligomeric amyloid β in serum exosomes collected from a transgenic mouse model of AD [24]. Elevated levels of oligomeric amyloid β were also observed in exosomes obtained from post-mortem brain tissues of AD patients [25]. This work additionally provided evidence of amyloid β oligomers internalization and inter-neuronal propagation using co-culture systems. Another AD-relevant protein, tau, was found associated with exosomes isolated from CSF of patients with this condition [26]. Exosome-mediated, neuron-to-neuron, propagation of tau was shown using co-culture of cells with microfluidic devices [27]. Elevated levels of select phosphorylated forms of tau protein were reported in blood exosomes of patients with AD and were associated with their potential to identify AD development several years before its onset [28]. Several examples have also highlighted the potential clinical relevance of EVs in patients diagnosed with PD. Recent work showed elevated plasma levels of exosomes derived from neurons in PD patients when compared to control individuals or patients diagnosed with multiple system atrophy [29]. Furthermore, the value of characterizing exosomal contents of PD-relevant biomolecules, including α-synuclein, has been investigated in various studies. For example, elevated levels of exosomal α-synuclein were reported in PD patients plasma samples and correlated with disease severity [30]. Interestingly, reduced levels of exosomal α-

synuclein were observed in PD patients CSF samples [31]. This work showed that exosomal α-synuclein derived from CSF of PD patients could promote α-synuclein oligomerization in a reporter cell line further supporting the importance of this target in PD. A recent study also reported lower levels of α-synuclein in CNS-derived exosomes purified from serum samples of patients with PD when compared with similar samples from healthy controls or individuals with essential tremor-associated early stage PD [32]. Fluctuating levels of oligomeric α-synuclein in salivary as well as in plasma neural-associated exosomes also highlight the diagnostic potential of this target in PD [33,34]. In addition to α-synuclein, other markers with relevance to neurodegenerative disease have been identified in exosomal fractions collected from PD patients. CNS-derived exosomes were found to contain tau protein in mouse plasma and increased CNS-derived exosomal tau was measured in plasma obtained from PD patients versus control samples [35]. Overall, these studies provide a glimpse of the clinical potential associated with the contents of EVs for patients with a neurodegenerative disease.

3. Amyotrophic lateral sclerosis and extracellular vesicles

3.1. ALS overview and need for early detection

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by selective loss of upper motor neurons (UMN) and lower motor neurons (LMN) ultimately leading to progressive loss of control of voluntary muscles [36,37]. Death occurs from respiratory insufficiency in most persons living with ALS (PALS) three to five years following the onset of symptoms [38,39]. Identification of one to two new cases per year is observed per 100,000 persons annually in most countries [40]. While no single test exists to pose a definite diagnosis of ALS, current approaches to diagnose this condition involve assessment of various clinical parameters aligned with the identification of UMN and LMN signs in the bulbar, thoracic, and/or limb regions [41]. Clinical features of UMN involvement, an important finding to confirm ALS diagnosis, can be challenging to observe in patients with LMN impairment [42]. LMN impairment can be assessed using a variety of approaches including estimation of the motor unit number index (MUNIX) and the neurophysiological index (NI) providing appreciable sensitivity in LMN dysfunction assessment [43]. The use of electromyography (EMG) is important for diagnosis and can help distinguish ALS from similar conditions such as multifocal motor neuropathy or primary lateral sclerosis [44]. EMG-based investigation can yield additional insights notably by detecting denervation and reinnervation characteristics of LMN dysfunction [45]. Nevertheless, PALS frequently exhibit symptoms that are associated with other conditions contributing to a high rate of initial misdiagnosis [46,47], as well as delay in diagnosis.

Early and efficient diagnosis of ALS, including identify the various forms of ALS, thus remains a significant challenge. According to population-based studies, PALS are typically classified as sporadic ALS (sALS) while only approximately 10% present with familial ALS (fALS) [48,49], although emerging genetic findings suggest familial forms may be more common than this. The latter involves a family history frequently associated with hallmark mutations introduced in subsequent sections. However, evidences of a genetic component involving the former are known [50,51] and both share a similar clinical picture. The two predominant clinical forms of ALS are the spinal onset and the bulbar onset [52]. The spinal form is more common with symptoms typically onset asymmetrically in one or more limbs. The bulbar form, associated with speech and/or swallowing impairment at onset, has a less favorable survival prognosis [53,54]. Various phenotypic patterns are recognized in ALS, with a range of involvement of UMN versus LMN, such that some patients have greater spasticity and more mild progression of weakness, whereas others may have more profound muscle atrophy and more rapid progression [55]. It has been reported that as many as 50% of sALS patients have evidence of cognitive impairment, from subtle language impairment to marked frontotemporal dementias [56]. Recent growth in studies of the pathogenesis of ALS has contributed to a better characterization of the clinical spectrum of this condition and numerous molecular biomarkers, including ones for diagnosis, progression or therapy response, have been proposed to identify select forms of ALS [57,58]. Nevertheless, robust biomarkers to diagnose the diverse forms of ALS are needed.

Care provided by a multidisciplinary team of specialists can prolong survival and improve quality of life for PALS [59]. Unfortunately, the therapeutic options available remain sparse. Riluzole, a compound with neuroprotective properties used for ALS treatment, has been linked with improved median survival of patients by a few months [60,61]. Edaravone, a free-radical scavenger and the only other drug approved for the treatment of ALS, appears to demonstrate efficacy yet in limited sub-sets of ALS patients [62,63]. Additional treatments displaying greater efficacy than these options as well as optimization of current clinical trials for ALS remain to be performed [64,65]. The ALSFRS-R (ALS functional rating scale-revised), based on assessment of the level of impairment across a variety of functions, such as walking, speaking, dressing and breathing, can be used to monitor ALS progression [66], and is often used in clinical trials as an outcome measure, along with time to death and/or respiratory failure. Improvement of clinical trials, which sometimes exclude patients with disease duration beyond two years, must be considered. Biomarkers, with diagnostic or prognostic relevance, are therefore necessary to facilitate the early diagnosis of ALS or to monitor response of PALS towards a given compound or therapy. EVs and their contents could be leveraged in the identification of such biomarkers for PALS.

3.2. Extracellular vesicles and proteins relevant for ALS

Several molecular targets with potential relevance to ALS pathogenesis have been characterized over the years. Moreover, various studies indicated their presence or differential expression in circulating EVs. The first genetic mutation associated with ALS was reported on the gene coding for the enzyme Cu/Zn superoxide dismutase-1 (SOD1) [67]. Such mutation, along with additional mutations that were subsequently observed on this target in ALS, can ultimately lead to mutated SOD1 proteins with diverse toxic properties [68]. SOD1 was also detected in exosomes using a mouse motor neuron-like NSC-34 cell model expressing a wild type or a mutated form of this target [69]. Subsequent studies provided further examples of SOD1 secretion in EVs purified from various sources. It was shown that astrocytes expressing mutant SOD1 could transfer mutated SOD1 via exosomes and induce selective death of motor neurons [70]. Misfolded mutant SOD1was also notably demonstrated to be exchanged between NSC-34 cells via exosomes [71]. This study highlighted the propagation of misfolded SOD1 between HEK293 cells using conditioned media as well as in SOD1-overexpressing mouse primary spinal cord cells. Recent work performed on EVs isolated from plasma of sALS patients showed increased SOD1, as well as of other ALS-relevant biomolecules, in microvesicles of sALS patients when compared with SOD1 levels identified in microvesicles from controls supporting further work towards characterizing the ALS-associated SOD1 content of various types of secreted vesicles [72].

Multiple mutations with relevance to ALS have also been identified in the TAR DNA binding protein-43 (TDP-43) gene [73,74]. TDP-43, a member of the heterogeneous nuclear ribonucleoprotein (hnRNP) family and involved in RNA processing, can form insoluble aggregates in the brain of PALS [75]. Early work demonstrated, via immunoblot and mass spectrometry-based approaches, the presence of TDP-43 in CSF exosomal samples obtained from PALS [76]. It was shown that accumulation of TDP-43 oligomers was observed in microvesicles and that this cargo was preferentially internalized by receiving cells of different sources upon which it was more cytotoxic than free TDP-43 [77].

Follow-up work performed to better elucidate the function of monocytes in ALS demonstrated that exosomal TDP-43 was associated with elevated monocytic activation versus exosomes carrying a content that did not promote aggregation [78].

Besides SOD1 and TDP-43, additional targets with relevance for ALS have been characterized and identified as part of secreted EVs albeit to a lesser extent. ALS-related mutations of the fused in sarcoma (FUS) gene can lead to the formation of stress granule-like structures with varying degrees of cytoplasmic mislocalization of FUS [79,80]. Subsequent work revealed FUS interaction with RNA binding proteins Matrin-3 and hnRNPA1 for which mutations have been linked to familial ALS [81]. This study also showed the presence of exosomal FUS supporting the investigation of intercellular dissemination of FUS pathology. C9orf72, an open reading frame with GGGGCC repetition and which appears to be the most common genetic component of ALS [82], underlies trafficking of vesicles in ALS [83,84]. Dipeptide repeat proteins (DPRs), which result from translation of GGGGCC repeat-containing RNA, can form aggregates in the CNS of ALS patients harboring this mutation [85]. It is interesting to note that intercellular spreading of DPRs can occur via exosomes and that DPR transmission was observed in spinal motor neurons isolated from PALS harboring the C9orf72 repeat expansion [86]. Several other genetic mutations with relevance to ALS, which have been reviewed elsewhere [39,87], were identified on targets that include valosin-containing protein (VCP) [88], Sequestosome 1 (SQSTM1) [89] and TANK-Binding Kinase 1 (TBK1) [90] to name a few. Information regarding the possible interplay between these targets and EVs is currently missing. Overall, the examples shown here all support the growing interest and potential of EVs as reservoirs of ALS-associated proteins. A list of such proteins collected from ALS-relevant samples is presented in Table 1.

3.3. Extracellular vesicles and non-coding RNAs relevant for ALS

As exemplified above, several mutations observed in ALS impact genes that encode proteins notably involved in RNA homeostasis including TDP-43, FUS [79,80] and C9orf72 [91,92]. The study of non-coding RNAs, including microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), as a potential family of molecular biomarkers has revealed interesting insights with respect to their diagnostic usefulness for ALS in recent years. Work performed on the former has also brought to light several examples of their presence in diverse circulating samples of clinical interest and the general relevance of miRNAs, small non-coding RNAs capable of regulating the expression of several genes by translational repression or cleavage of mRNA strands [93], in ALS has been reviewed by various teams [94–96]. Pioneering work demonstrated the presence of miRNAs in samples collected from ALS patients. For example, miR-338-3p displayed elevated levels in CSF, serum and spinal cord samples collected from sALS patients when compared with control samples [97]. Follow-up work showed that serum levels of miR-1234-3p and miR-1825 were down-regulated in samples of sALS patients versus serum collected from healthy individuals [98]. Analysis of targets and functions associated with these two miRNAs further revealed multiple common transcript targets as well as a functional network with relevance to ALS common to both miRNAs. A more recent study reported elevated miR-143-3p and miR-206 levels as well as reduced miR-374b-5p levels in serum samples obtained from patients diagnosed with sALS versus healthy individuals [99]. This group also performed longitudinal analysis of miRNA expression in samples collected at different time points and showed increased miR-143-3p as well as decreased miR-374b-5p levels over time supporting the potential of these miRNAs to track disease progression. Several research teams also investigated differentially expressed miRNAs in CSF samples of ALS patients. Multiple TDP-43-targeting miRNAs, including miR-132-3p, miR-132-5p, miR-143-3p, miR-143-5p and miR-574-5p, exhibited varying levels of expression between CSF collected from sALS patients and healthy controls [100]. This work also reported decreased levels of TDP-43-relevant miR-132-3p, miR-132-5p, miR-143-3p, miR-143-5p and let-7b in serum samples obtained from sALS patients versus healthy individuals. A total of 14 deregulated miRNAs were identified in CSF samples obtained from PALS versus unaffected individuals in a subsequent study [101]. MiRNAs obtained from CSF of sALS patients and quantified via small RNA sequencing revealed 11 modulated miRNAs including miR-9-5p [102]. Interestingly, reduced levels of miR-9 and of its precursor were also shown in induced pluripotent stem cells (iPSC) models derived from frontotemporal dementia (FTD)/PALS neurons [103]. Recent studies have highlighted signature of vesicles-associated miRNAs in PALS. A qRT-PCR-based approach showed reduced levels of miR-27a-3p in serum exosomes gathered from ALS patients when compared with the expression observed in control exosomes [104]. A series of differentially expressed miRNAs were also identified in EVs purified from plasma obtained from PALS when quantified by small RNA sequencing [105]. A significant proportion of the deregulated miRNAs detected in this study were down-regulated including miR-9-5p. An overview of EVs-associated miRNAs observed in ALS-relevant samples can be found in Table 2. Since the function of miRNAs is to regulate the expression of mRNAs, it is possible that miRNAs deregulated in ALS exosomes correlate with mRNAs recently found to be modulated in ALS exosomes [106] warranting further investigation.

Besides small non-coding RNAs, long non-coding RNAs (lncRNAs) are also garnering attention for their diagnostic potential in diverse conditions. These non-coding transcripts exceed 200 nucleotides in length and can regulate gene expression in numerous ways and influence a myriad of processes [107]. Several publications have linked lncRNAs with molecular targets relevant to ALS supporting a greater investigation of these RNAs in this condition. For example, elevated levels of the lncRNA NEAT1_2 were observed in human spinal motor neurons obtained from early stage ALS samples [108]. Endogenous mutant FUS levels were also correlated with an increase of NEAT1 isoforms in neuroblastoma SH-SY5Y cells [109]. Several lncRNAs were shown to be deregulated by deep sequencing in peripheral blood mononuclear cells (PBMC) of ALS patients versus healthy controls

Table 1
Proteins with relevance to ALS detected in extracellular vesicles.

Proteins	Observations	Circulating vesicles	Samples / Models	References
SOD1	Secretion via exosomes	Exosomes	NSC-34 cells	[69]
SOD1	Intercellular propagation	Exosomes	NSC-34 cells	[71]
TDP-43	Intercellular exchange	Microvesicles/Exosomes	HEK-293 cells and primary mouse neurons	[77]
FUS	Identification in exosomes	Exosomes	SH-SY5Y and N2A cells	[81]
DPRs	Cell-to-cell spreading	Exosomes	Motor neurons derived from iPSCs of C9orf72-ALS patients	[86]
SOD1	Secretion via exosomes	Exosomes	Primary rat microglial cells	[130]
SOD1, TDP-43, FUS	Elevated levels in ALS versus controls	Microvesicles	Plasma – sALS Patients	[72]

Differentially expressed proteins identified in extracellular vesicles isolated from ALS patients and other ALS-relevant models. Table depicts select key observations reported in the presented articles. Abbreviations: DPR: Dipeptide repeat proteins; FUS: Fused in sarcoma; iPSC: Induced pluripotent stem cells; sALS: Sporadic amyotrophic lateral sclerosis; SOD1: Cu/Zn superoxide dismutase-1; TDP-43: TAR DNA binding protein-43.

Table 2
Non-coding RNAs with interest for ALS detected in extracellular vesicles.

MiRNAs	Observations	Circulating vesicles	Samples/Models	References
miR-124, miR-146a, and miR-155	Secretion or modulation in recipient cells	Exosomes	NSC-34 and N9 cells	[131]
miR-27a-3p	Reduced levels in ALS versus controls	Exosomes	Serum – ALS Patients	[104]
miR-9-5p, miR-183-5p, miR-338-3p, miR-1246 and others	Elevated levels of 5 miRNAs and reduced levels of 22 miRNAs in ALS versus controls	Extracellular vesicles	Plasma – ALS Patients	[105]
miR-1268a, miR-2861, miR-4700-5p, miR-4736 and others	Elevated levels of 13 miRNAs and reduced levels of 17 miRNAs in ALS versus controls	Extracellular vesicles	Plasma – ALS Patients	[132]

Modulated miRNAs observed in circulating vesicles collected from ALS patients and additional models leveraged for ALS study. Select results of interest identified in the articles are presented in this table.

[110]. Interestingly, a smaller number of lncRNAs was observed by the authors in patients harboring mutations in genes coding for FUS, TDP-43 and SOD1. Unlike for miRNAs, information pertaining to the differential lncRNA expression in EVs collected from PALS is lacking and this knowledge gap should be addressed. Overall, it is expected that the molecular investigation of EVs in ALS samples will only increase in the next few years despite foreseen challenges [111], including the accurate quantification of small amounts of select RNA targets, associated with the characterization of RNA content in these reservoirs.

4. Perspectives and conclusion

4.1. Extracellular vesicles as reservoirs of biomolecules: Beyond diagnostic applications

While this review presented multiple examples of the relevance of EVs as diagnostic tools in diverse conditions, it is important to stress the potential importance of these reservoirs for other means including their use in drug response assessment as well as for therapeutic purposes. Several studies have supported the former application including one that reported the fluctuations of exosomal proteins and TGF-β1 levels in plasma of patients diagnosed with acute myeloid leukemia (AML) treated with chemotherapeutic agents such as anthracycline and cytarabine that could correlate with response to the administered compounds [112]. Recent work also identified a signature of modulated exosomal miRNAs that was correlated with response to IFN-β treatment in relapsing-remitting multiple sclerosis (MS) patients [113]. The relative potential of EVs for treatment response or disease progression in neurodegenerative diseases has been proposed by others [114,115] and additional studies highlighting such applications of EVs in these conditions are expected in upcoming years.

Meanwhile, several reports have also reviewed the benefits and limitations of EVs for therapeutic purposes [116–118]. Specific applications of EVs for neurodegenerative diseases are starting to emerge. Select examples include the exosomal-mediated delivery of siRNA targeting α-synuclein in a mouse model via peripheral injection that was ultimately associated with significant reduction of intraneuronal protein aggregates of this target [119]. Similarly, siRNA aimed at BACE1, a relevant target for patients with AD, was delivered via exosomes in mice and was associated with substantial reduction of target transcript and protein levels [120]. Interestingly, intranasal administration of exosomes loaded with a catalase cargo was correlated with neuroprotective benefits in a PD mouse model [121]. Brain administration of exosomes obtained from primary rodent cortical neurons in a transgenic mice model overexpressing the amyloid precursor protein, a model used to investigate AD, was notably associated with reduction of amyloid β pathology [122]. Concurrent work also demonstrated that exosomes obtained from mouse neuroblastoma cells and injected into mouse brains could sequester amyloid β peptide [123]. Exosomes collected from adipose-derived stem cells could reduce aggregation of mutant Huntingtin protein in neuronal cells obtained from a mouse model of Huntington's disease (HD) [124] providing yet another example of the therapeutic potential of these circulating reservoirs in a neurodegenerative disease. As exosomes collected from mouse stromal cells were shown to possess cytoprotective properties in NSC-34 cells confronted to oxidative stress, the potential role of EVs for ALS treatment has also been proposed even though additional experimental studies highlighting this application are scarce [125,126]. These studies all support the need to better characterize the potential benefits of EVs in various neurodegenerative conditions. It is nevertheless important to mention that multiple underlying challenges exist in the development of EV-based therapeutics including the yield of EVs that can be isolated from sources such as cell lines [127], the selection of optimal isolation methods to generate homogenous EV populations [128] as well as the many factors that can influence EV delivery to target site [129] to name a few. Such parameters will be essential to address when developing a bona fide EV-based therapeutic application to treat PALS.

In conclusion, the diagnostic, prognostic and even therapeutic potential of EVs in ALS were investigated to different extents in the current review. Characterizing the molecular footprints associated with these circulating reservoirs is of utmost importance to strengthen their potential use as clinical tools. Numerous challenges are foreseen before the routine use of EVs-focused diagnostic approaches becomes a standard procedure in detecting and managing ALS. Nevertheless, the benefits outlined in this work appear to outweigh the hurdles and should further encourage the research community to strive to better characterize ALS-associated EVs footprints.

Acknowledgements

Laboratory work performed on ALS was supported by an ALS Canada and Brain Canada Discovery Grant awarded to COC and PJM. DS is supported by a CRMUS salary award from the Faculty of Medicine and Health Sciences of Université de Sherbrooke as well as a Maritime SPOR SUPPORT Unit (MSSU) bursary.

Declaration of Competing Interest

None.

References

[1] E. Cocucci, J. Meldolesi, Ectosomes and exosomes: shedding the confusion between extracellular vesicles, Trends Cell Biol. 25 (6) (2015) 364–372.
[2] J. Meldolesi, Exosomes and Ectosomes in intercellular communication, Curr. Biol. 28 (8) (2018) R435–R444.
[3] C. Théry, K.W. Witwer, E. Aikawa, M.J. Alcaraz, J.D. Anderson, R. Andriantsitohaina, A. Antoniou, T. Arab, F. Archer, G.K. Atkin-Smith, D.C. Ayre, J.M. Bach, D. Bachurski, H. Baharvand, L. Balaj, S. Baldacchino, N.N. Bauer, A.A. Baxter, M. Bebawy, C. Beckham, et al., Minimal information for studies of extracellular vesicles 2018 (MISEV2018): a position statement of the International Society for Extracellular Vesicles and update of the MISEV2014 guidelines, J. Extracell. Vesicles 7 (1) (2018) 1535750.
[4] F. Momen-Heravi, L. Balaj, S. Alian, P.Y. Mantel, A.E. Halleck, A.J. Trachtenberg, C.E. Soria, S. Oquin, C.M. Bonebreak, E. Saracoglu, J. Skog, W.P. Kuo, Current methods for the isolation of extracellular vesicles, Biol. Chem. 394 (10) (2013) 1253–1262.
[5] M.Y. Konoshenko, E.A. Lekchnov, A.V. Vlassov, P.P. Laktionov, Isolation of extracellular vesicles: general methodologies and latest trends, Biomed. Res. Int. 2018 (2018) 8545347.

[6] S. Keerthikumar, D. Chisanga, D. Ariyaratne, H. Al Saffar, S. Anand, K. Zhao, M. Samuel, M. Pathan, M. Jois, N. Chilamkurti, L. Gangoda, S. Mathivanan, ExoCarta: a web-based compendium of exosomal cargo, J. Mol. Biol. 428 (4) (2016) 688–692.
[7] M. Pathan, P. Fonseka, S.V. Chitti, T. Kang, R. Sanwlani, J. Van Deun, A. Hendrix, S. Mathivanan, Vesiclepedia 2019: a compendium of RNA, proteins, lipids and metabolites in extracellular vesicles, Nucleic Acids Res. 47 (D1) (2019) D516–D519.
[8] O.D. Murillo, W. Thistlethwaite, J. Rozowsky, S.L. Subramanian, R. Lucero, N. Shah, A.R. Jackson, S. Srinivasan, A. Chung, C.D. Laurent, R.R. Kitchen, T. Galeev, J. Warrell, J.A. Diao, J.A. Welsh, K. Hanspers, A. Riutta, S. Burgstaller-Muehlbacher, R.V. Shah, A. Yeri, et al., exRNA Atlas analysis reveals distinct extracellular RNA cargo types and their carriers present across human biofluids, Cell 177 (2) (2019) 463–477.
[9] W. Li, C. Li, T. Zhou, X. Liu, X. Liu, X. Li, D. Chen, Role of exosomal proteins in cancer diagnosis, Mol. Cancer 16 (1) (2017) 145.
[10] H. Mirzaei, A. Sahebkar, M.R. Jaafari, M. Goodarzi, H.R. Mirzaei, Diagnostic and therapeutic potential of exosomes in cancer: the beginning of a new tale? J. Cell. Physiol. 232 (12) (2017) 3251–3260.
[11] R. Xu, A. Rai, M. Chen, W. Suwakulsiri, D.W. Greening, R.J. Simpson, Extracellular vesicles in cancer — implications for future improvements in cancer care, Nat. Rev. Clin. Oncol. 15 (10) (2018) 617–638.
[12] Y. Sun, C. Huo, Z. Qiao, Z. Shang, A. Uzzaman, S. Liu, X. Jiang, L.-Y. Fan, L. Ji, X. Guan, C.-X. Cao, H. Xiao, Comparative proteomic analysis of exosomes and microvesicles in human saliva for lung cancer, J. Proteome Res. 17 (3) (2018) 1101–1107.
[13] A. Zlotogorski-Hurvitz, B.Z. Dekel, D. Malonek, R. Yahalom, M. Vered, FTIR-based spectrum of salivary exosomes coupled with computational-aided discriminating analysis in the diagnosis of oral cancer, J. Cancer Res. Clin. Oncol. 145 (3) (2019) 685–694.
[14] Y. Zhan, L. Du, L. Wang, X. Jiang, S. Zhang, J. Li, K. Yan, W. Duan, Y. Zhao, L. Wang, Y. Wang, C. Wang, Expression signatures of exosomal long non-coding RNAs in urine serve as novel non-invasive biomarkers for diagnosis and recurrence prediction of bladder cancer, Mol. Cancer 17 (1) (2018) 142.
[15] F. Yazarlou, M.H. Modarressi, S.J. Mowla, V.K. Oskooei, E. Motevaseli, L.F. Tooli, L. Nekoohesh, M. Eghbali, S. Ghafouri-Fard, M. Afsharpad, Urinary exosomal expression of long non-coding RNAs as diagnostic marker in bladder cancer, Cancer Manag. Res. 10 (2018) 6357–6365.
[16] R. Shi, P.-Y. Wang, X.-Y. Li, J.-X. Chen, Y. Li, X.-Z. Zhang, C.-G. Zhang, T. Jiang, W.-B. Li, W. Ding, S.-J. Cheng, Exosomal levels of miRNA-21 from cerebrospinal fluids associated with poor prognosis and tumor recurrence of glioma patients, Oncotarget 6 (29) (2015) 26971–26981.
[17] K.M. Kanninen, N. Bister, J. Koistinaho, T. Malm, Exosomes as new diagnostic tools in CNS diseases, Biochim. Biophys. Acta 1862 (3) (2016) 403–410.
[18] A.G. Thompson, E. Gray, S.M. Heman-Ackah, I. Mäger, K. Talbot, S.E. Andaloussi, M.J. Wood, M.R. Turner, Extracellular vesicles in neurodegenerative disease – pathogenesis to biomarkers, Nat. Rev. Neurol. 12 (6) (2016) 346–357.
[19] A.T. Jan, M.A. Malik, S. Rahman, H.R. Yeo, E.J. Lee, T.S. Abdullah, I. Choi, Perspective insights of exosomes in neurodegenerative diseases: a critical appraisal, Front. Aging Neurosci. 9 (2017) 317.
[20] K.W. Witwer, E.I. Buzás, L.T. Bemis, A. Bora, C. Lässer, J. Lötvall, E.N. Nolte-'t Hoen, M.G. Piper, S. Sivaraman, J. Skog, C. Théry, M.H. Wauben, F. Hochberg, Standardization of sample collection, isolation and analysis methods in extracellular vesicle research, J. Extracell. Vesicles 2 (1) (2013) 20360.
[21] C. Soekmadji, A.F. Hill, M.H. Wauben, E.I. Buzás, D. Di Vizio, C. Gardiner, J. Lötvall, S. Sahoo, K.W. Witwer, Towards mechanisms and standardization in extracellular vesicle and extracellular RNA studies: results of a worldwide survey, J. Extracell. Vesicles 7 (1) (2018) 1535745.
[22] L. Rajendran, M. Honsho, T.R. Zahn, P. Keller, K.D. Geiger, P. Verkade, K. Simons, Alzheimer's disease β-amyloid peptides are released in association with exosomes, Proc. Natl. Acad. Sci. U. S. A. 103 (30) (2006) 11172–11177.
[23] E. Eitan, E.R. Hutchison, K. Marosi, J. Comotto, M. Mustapic, S.M. Nigam, C. Suire, C. Maharana, G.A. Jicha, D. Liu, V. Machairaki, K.W. Witwer, D. Kapogiannis, M.P. Mattson, Extracellular vesicle-associated Aβ mediates trans-neuronal bioenergetic and Ca^{2+}-handling deficits in Alzheimer's disease models, NPJ Aging Mech. Dis. 2 (2016) 16019.
[24] H. Rosas-Hernandez, E. Cuevas, J.B. Raymick, B.L. Robinson, S.F. Ali, J. Hanig, S. Sarkar, Characterization of serum exosomes from a transgenic mouse model of Alzheimer's disease, Curr. Alzheimer Res. 16 (2019).
[25] M. Sardar Sinha, A. Ansell-Schultz, L. Civitelli, C. Hildesjö, M. Larsson, L. Lannfelt, M. Ingelsson, M. Hallbeck, Alzheimer's disease pathology propagation by exosomes containing toxic amyloid-beta oligomers, Acta Neuropathol. 136 (1) (2018) 41–56.
[26] S. Saman, W. Kim, M. Raya, Y. Visnick, S. Miro, S. Saman, B. Jackson, A.C. McKee, V.E. Alvarez, N.C.Y. Lee, G.F. Hall, Exosome-associated tau is secreted in tauopathy models and is selectively phosphorylated in cerebrospinal fluid in early Alzheimer disease, J. Biol. Chem. 287 (6) (2012) 3842–3849.
[27] Y. Wang, V. Balaji, S. Kaniyappan, L. Krüger, S. Irsen, K. Tepper, R. Chandupatla, W. Maetzler, A. Schneider, E. Mandelkow, E.M. Mandelkow, The release and trans-synaptic transmission of Tau via exosomes, Mol. Neurodegener. 12 (1) (2017) 5.
[28] M.S. Fiandaca, D. Kapogiannis, M. Mapstone, A. Boxer, E. Eitan, J.B. Schwartz, E.L. Abner, R.C. Petersen, H.J. Federoff, B.L. Miller, E.J. Goetzl, Identification of pre-clinical Alzheimer's disease by a profile of pathogenic proteins in neurally-derived blood exosomes: a case-control study, Alzheimers Dement. 11 (6) (2015) 600–607.
[29] T. Ohmichi, M. Mitsuhashi, H. Tatebe, T. Kasai, O.M. Ali El-Agnaf, T. Tokuda, Quantification of brain-derived extracellular vesicles in plasma as a biomarker to diagnose Parkinson's and related diseases, Parkinsonism Relat. Disord. 61 (2019) 82–87.
[30] M. Shi, C. Liu, T.J. Cook, K.M. Bullock, Y. Zhao, C. Ginghina, Y. Li, P. Aro, R. Dator, C. He, M.J. Hipp, C.P. Zabetian, E.R. Peskind, S.-C. Hu, J.F. Quinn, D.R. Galasko, W.A. Banks, J. Zhang, Plasma exosomal α-synuclein is likely CNS-derived and increased in Parkinson's disease, Acta Neuropathol. 128 (5) (2014) 639–650.
[31] A. Stuendl, M. Kunadt, N. Kruse, C. Bartels, W. Moebius, K.M. Danzer, B. Mollenhauer, A. Schneider, Induction of α-synuclein aggregate formation by CSF exosomes from patients with Parkinson's disease and dementia with Lewy bodies, Brain 139 (2016) 481–494.
[32] X. Si, J. Tian, Y. Chen, Y. Yan, J. Pu, B. Zhang, Central nervous system-derived exosomal alpha-synuclein in serum may be a biomarker in Parkinson's disease, Neuroscience (2019), https://doi.org/10.1016/j.neuroscience.2019.05.015.
[33] Z. Cao, Y. Wu, G. Liu, Y. Jiang, X. Wang, Z. Wang, T. Feng, α-Synuclein in salivary extracellular vesicles as a potential biomarker of Parkinson's disease, Neurosci. Lett. 696 (2019) 114–120.
[34] Z.-H. Zhao, Z.-T. Chen, R.-L. Zhou, X. Zhang, Q.-Y. Ye, Y.-Z. Wang, Increased DJ-1 and α-synuclein in plasma neural-derived exosomes as potential markers for Parkinson's disease, Front. Aging Neurosci. 10 (2019) 438.
[35] M. Shi, A. Kovac, A. Korff, T.J. Cook, C. Ginghina, K.M. Bullock, L. Yang, T. Stewart, D. Zheng, P. Aro, A. Atik, K.F. Kerr, C.P. Zabetian, E.R. Peskind, S.C. Hu, J.F. Quinn, D.R. Galasko, T.J. Montine, W.A. Banks, J. Zhang, CNS tau efflux via exosomes is likely increased in Parkinson's disease but not in Alzheimer's disease, Alzheimers Dement. 12 (11) (2016) 1125–1131.
[36] D.W. Cleveland, J.D. Rothstein, From Charcot to Lou Gehrig: deciphering selective motor neuron death in ALS, Nat. Rev. Neurosci. 2 (2001) 806–819.
[37] M.A. van Es, O. Hardiman, A. Chio, A. Al-Chalabi, R.J. Pasterkamp, J.H. Veldink, L.H. van den Berg, Amyotrophic lateral sclerosis, Lancet 390 (10107) (2017) 2084–2098.
[38] F.J. Mateen, M. Carone, E.J. Sorenson, Patients who survive five years or more with ALS in Olmsted County, 1925–2004, J. Neurol. Neurosurg. Psychiatry 81 (10) (2010) 1144–1146.
[39] J.P. Taylor, R.H. Brown, D.W. Cleveland, D.W. Cleveland, Decoding ALS: from genes to mechanism, Nature 539 (7628) (2016) 197–206.
[40] A. Al-Chalabi, O. Hardiman, The epidemiology of ALS: a conspiracy of genes, environment and time, Nat. Rev. Neurol. 9 (2013) 617–628.
[41] B.R. Brooks, R.G. Miller, M. Swash, T.L. Munsat, World Federation of Neurology Research Group on Motor Neuron Diseases, El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis, Amyotroph. Lateral Scler. Other Motor Neuron Disord. 1 (5) (2000) 293–299.
[42] M. de Carvalho, Testing upper motor neuron function in amyotrophic lateral sclerosis: the most difficult task of neurophysiology, Brain 135 (Pt 9) (2012) 2581–2582.
[43] M.L. Escorcio-Bezerra, A. Abrahao, K.F. Nunes, N.I. De Oliveira Braga, A.S.B. Oliveira, L. Zinman, G.M. Manzano, Motor unit number index and neurophysiological index as candidate biomarkers of presymptomatic motor neuron loss in amyotrophic lateral sclerosis, Muscle Nerve 58 (2) (2018) 204–212.
[44] N.C. Joyce, G.T. Carter, Electrodiagnosis in persons with amyotrophic lateral sclerosis, PM R 5 (Suppl. 5) (2013) S89–S95.
[45] M. de Carvalho, R. Dengler, A. Eisen, J.D. England, R. Kaji, J. Kimura, K. Mills, H. Mitsumoto, H. Nodera, J. Shefner, M. Swash, Electrodiagnostic criteria for diagnosis of ALS, Clin. Neurophysiol. 119 (3) (2008) 497–503.
[46] J.M. Belsh, P.L. Schiffman, The amyotrophic lateral sclerosis (ALS) patient perspective on misdiagnosis and its repercussions, J. Neurol. Sci. 139 (Suppl) (1996) 110–116.
[47] S. Paganoni, E.A. Macklin, A. Lee, A. Murphy, J. Chang, A. Zipf, M. Cudkowicz, N. Atassi, Diagnostic timelines and delays in diagnosing amyotrophic lateral sclerosis (ALS), Amyotroph. Lateral Scler. Frontotemp. Degener. 15 (2014) 453–456.
[48] S. Byrne, C. Walsh, C. Lynch, P. Bede, M. Elamin, K. Kenna, R. McLaughlin, O. Hardiman, Rate of familial amyotrophic lateral sclerosis: a systematic review and meta-analysis, J. Neurol. Neurosurg. Psychiatry 82 (6) (2011) 623–627.
[49] K. Boylan, Familial amyotrophic lateral sclerosis, Neurol. Clin. 33 (4) (2015) 807–830.
[50] J. Gamez, M. Corbera-Bellalta, G. Nogales, N. Raguer, E. García-Arumí, M. Badia-Canto, E. Lladó-Carbó, J. Álvarez-Sabín, Mutational analysis of the Cu/Zn superoxide dismutase gene in a Catalan ALS population: should all sporadic ALS cases also be screened for SOD1? J. Neurol. Sci. 247 (2006) 21–28.
[51] J. Cooper-Knock, C. Hewitt, J.R. Highley, A. Brockington, A. Milano, S. Man, J. Martindale, J. Hartley, T. Walsh, C. Gelsthorpe, L. Baxter, G. Forster, M. Fox, J. Bury, K. Mok, C.J. McDermott, B.J. Traynor, J. Kirby, S.B. Wharton, P.G. Ince, J. Hardy, P.J. Shaw, Clinico-pathological features in amyotrophic lateral sclerosis with expansions in C9ORF72, Brain 135 (2012) 751–764.
[52] L.C. Wijesekera, P.N. Leigh, Amyotrophic lateral sclerosis, Orphanet J. Rare Dis. 4 (1) (2009) 3.
[53] A.M. Chancellor, J.M. Slattery, H. Fraser, R.J. Swingler, S.M. Holloway, C.P. Warlow, The prognosis of adult-onset motor neuron disease: a prospective study based on the Scottish Motor Neuron Disease Register, J. Neurol. 240 (6) (1993) 339–346.
[54] G. Logroscino, B.J. Traynor, O. Hardiman, A. Chio, P. Couratier, J.D. Mitchell, R.J. Swingler, E. Beghi, Descriptive epidemiology of amyotrophic lateral sclerosis: new evidence and unsolved issues, J. Neurol. Neurosurg. Psychiatry 79 (2008) 6–11.
[55] N.G. Simon, M.R. Turner, S. Vucic, A. Al-Chalabi, J. Shefner, C. Lomen-Hoerth,

M.C. Kiernan, Quantifying disease progression in amyotrophic lateral sclerosis, Ann. Neurol. 76 (5) (2014) 643–657.
[56] G.M. Ringholz, S.H. Appel, M. Bradshaw, N.A. Cooke, D.M. Mosnik, P.E. Schulz, Prevalence and patterns of cognitive impairment in sporadic ALS, Neurology 65 (4) (2005) 586–590.
[57] M.R. Turner, M.C. Kiernan, P.N. Leigh, K. Talbot, Biomarkers in amyotrophic lateral sclerosis, Lancet Neurol. 8 (1) (2009) 94–109.
[58] U.G. Vijayakumar, V. Milla, M.Y. Cynthia Stafford, A.J. Bjourson, W. Duddy, S.M. Duguez, A systematic review of suggested molecular strata, biomarkers and their tissue sources in ALS, Front. Neurol. 10 (2019) 400.
[59] B.J. Traynor, M. Alexander, B. Corr, E. Frost, O. Hardiman, Effect of a multidisciplinary amyotrophic lateral sclerosis (ALS) clinic on ALS survival: a population based study, 1996–2000, J. Neurol. Neurosurg. Psychiatry 74 (9) (2003) 1258–1261.
[60] G. Bensimon, L. Lacomblez, V. Meininger, The A.S. Group, A controlled trial of riluzole in amyotrophic lateral sclerosis, N. Engl. J. Med. 330 (9) (1994) 585–591.
[61] L. Lacomblez, G. Bensimon, P.N. Leigh, P. Guillet, V. Meininger, Dose-ranging study of riluzole in amyotrophic lateral sclerosis. Amyotrophic Lateral Sclerosis/Riluzole Study Group II, Lancet 347 (9013) (1996) 1425–1431.
[62] The Writing Group on behalf of the Edaravone (MCI-186) ALS 19 Study Group, Safety and efficacy of edaravone in well defined patients with amyotrophic lateral sclerosis: a randomised, double-blind, placebo-controlled trial, Lancet Neurol. 16 (7) (2017) 505–512.
[63] H. Sawada, Clinical efficacy of edaravone for the treatment of amyotrophic lateral sclerosis, Expert. Opin. Pharmacother. 18 (7) (2017) 735–738.
[64] D. Petrov, C. Mansfield, A. Moussy, O. Hermine, ALS clinical trials review: 20 years of failure. Are we any closer to registering a new treatment? Front. Aging Neurosci. 9 (2017) 68.
[65] R.P.A. van Eijk, H.-J. Westeneng, S. Nikolakopoulos, I.E. Verhagen, M.A. van Es, M.J.C. Eijkemans, L.H. van den Berg, Refining eligibility criteria for amyotrophic lateral sclerosis clinical trials, Neurology 92 (5) (2019) e451–e460.
[66] J.M. Cedarbaum, N. Stambler, E. Malta, C. Fuller, D. Hilt, B. Thurmond, A. Nakanishi, The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function. BDNF ALS Study Group (Phase III), J. Neurol. Sci. 169 (1–2) (1999) 13–21.
[67] D.R. Rosen, T. Siddique, D. Patterson, D.A. Figlewicz, P. Sapp, A. Hentati, D. Donaldson, J. Goto, J.P. O'Regan, H.-X. Deng, Z. Rahmani, A. Krizus, D. McKenna-Yasek, A. Cayabyab, S.M. Gaston, R. Berger, R.E. Tanzi, J.J. Halperin, B. Herzfeldt, R. Van den Bergh, W.-Y. Hung, T. Bird, G. Deng, D.W. Mulder, C. Smyth, N.G. Laing, E. Soriano, M.A. Pericak-Vance, J. Haines, G.A. Rouleau, J.S. Gusella, H.R. Horvitz, R.H. Brown, Mutations in Cu/Zn superoxide dismutase gene are associated with familial amyotrophic lateral sclerosis, Nature 362 (6415) (1993) 59–62.
[68] O. Pansarasa, M. Bordoni, L. Diamanti, D. Sproviero, S. Gagliardi, C. Cereda, SOD1 in amyotrophic lateral sclerosis: "ambivalent" behavior connected to the disease, Int. J. Mol. Sci. 19 (5) (2018) 1345.
[69] C. Gomes, S. Keller, P. Altevogt, J. Costa, Evidence for secretion of Cu,Zn superoxide dismutase via exosomes from a cell model of amyotrophic lateral sclerosis, Neurosci. Lett. 428 (1) (2007) 43–46.
[70] M. Basso, S. Pozzi, M. Tortarolo, F. Fiordaliso, C. Bisighini, L. Pasetto, G. Spaltro, D. Lidonnici, F. Gensano, E. Battaglia, C. Bendotti, V. Bonetto, Mutant copper-zinc superoxide dismutase (SOD1) induces protein secretion pathway alterations and exosome release in astrocytes: implications for disease spreading and motor neuron pathology in amyotrophic lateral sclerosis, J. Biol. Chem. 288 (22) (2013) 15699–15711.
[71] L.I. Grad, J.J. Yerbury, B.J. Turner, W.C. Guest, E. Pokrishevsky, M.A. O'Neill, A. Yanai, J.M. Silverman, R. Zeineddine, L. Corcoran, J.R. Kumita, L.M. Luheshi, M. Yousefi, B.M. Coleman, A.F. Hill, S.S. Plotkin, I.R. Mackenzie, N.R. Cashman, Intercellular propagated misfolding of wild-type Cu/Zn superoxide dismutase occurs via exosome-dependent and -independent mechanisms, Proc. Natl. Acad. Sci. U. S. A. 111 (9) (2014) 3620–3625.
[72] D. Sproviero, S. La Salvia, M. Giannini, V. Crippa, S. Gagliardi, S. Bernuzzi, L. Diamanti, M. Ceroni, O. Pansarasa, A. Poletti, C. Cereda, Pathological proteins are transported by extracellular vesicles of sporadic amyotrophic lateral sclerosis patients, Front. Neurosci. 12 (2018) 487.
[73] E. Kabashi, P.N. Valdmanis, P. Dion, D. Spiegelman, B.J. McConkey, C. Vande Velde, J.-P. Bouchard, L. Lacomblez, K. Pochigaeva, F. Salachas, P.-F. Pradat, W. Camu, V. Meininger, N. Dupre, G.A. Rouleau, TARDBP mutations in individuals with sporadic and familial amyotrophic lateral sclerosis, Nat. Genet. 40 (5) (2008) 572–574.
[74] J. Sreedharan, I.P. Blair, V.B. Tripathi, X. Hu, C. Vance, B. Rogelj, S. Ackerley, J.C. Durnall, K.L. Williams, E. Burratti, F. Baralle, J. de Belleroche, J.D. Mitchell, P.N. Leigh, A. Al-Chalabi, C.C. Miller, G. Nicholson, C.E. Shaw, TDP-43 mutations in familial and sporadic amyotrophic lateral sclerosis, Science 319 (5870) (2008) 1668–1672.
[75] T. Arai, M. Hasegawa, H. Akiyama, K. Ikeda, T. Nonaka, H. Mori, D. Mann, K. Tsuchiya, M. Yoshida, Y. Hashizume, T. Oda, TDP-43 is a component of ubiquitin-positive tau-negative inclusions in frontotemporal lobar degeneration and amyotrophic lateral sclerosis, Biochem. Biophys. Res. Commun. 351 (2006) 602–611.
[76] E. Feneberg, P. Steinacker, S. Lehnert, A. Schneider, P. Walther, D.R. Thal, M. Linsenmeier, A.C. Ludolph, M. Otto, Limited role of free TDP-43 as a diagnostic tool in neurodegenerative diseases, Amyotroph. Lateral Scler. Front. Degener. 15 (5–6) (2014) 351–356.
[77] M.S. Feiler, B. Strobel, A. Freischmidt, A.M. Helferich, J. Kappel, B.M. Brewer, D. Li, D.R. Thal, P. Walther, A.C. Ludolph, K.M. Danzer, J.H. Weishaupt, TDP-43 is intercellularly transmitted across axon terminals, J. Cell Biol. 211 (4) (2015) 897–911.
[78] L. Zondler, M.S. Feiler, A. Freischmidt, W.P. Ruf, A.C. Ludolph, K.M. Danzer, J.H. Weishaupt, Impaired activation of ALS monocytes by exosomes, Immunol. Cell Biol. 95 (2) (2017) 207–214.
[79] T.J. Kwiatkowski, D.A. Bosco, A.L. Leclerc, E. Tamrazian, C.R. Vanderburg, C. Russ, A. Davis, J. Gilchrist, E.J. Kasarskis, T. Munsat, P. Valdmanis, G.A. Rouleau, B.A. Hosler, P. Cortelli, P.J. de Jong, Y. Yoshinaga, J.L. Haines, M.A. Pericak-Vance, J. Yan, N. Ticozzi, T. Siddique, D. McKenna-Yasek, P.C. Sapp, H.R. Horvitz, J.E. Landers, R.H. Jr Brown, Mutations in the FUS/TLS gene on chromosome 16 cause familial amyotrophic lateral sclerosis, Science 323 (5918) (2009) 1205–1208.
[80] C. Vance, B. Rogelj, T. Hortobágyi, K.J. De Vos, A.L. Nishimura, J. Sreedharan, X. Hu, B. Smith, D. Ruddy, P. Wright, J. Ganesalingam, K.L. Williams, V. Tripathi, S. Al-Saraj, A. Al-Chalabi, P.N. Leigh, I.P. Blair, G. Nicholson, J. de Belleroche, J.-M. Gallo, C.C. Miller, C.E. Shaw, Mutations in FUS, an RNA processing protein, cause familial amyotrophic lateral sclerosis type 6, Science. 323 (5918) (2009) 1208–1211.
[81] M. Kamelgarn, J. Chen, L. Kuang, A. Arenas, J. Zhai, H. Zhu, J. Gal, Proteomic analysis of FUS interacting proteins provides insights into FUS function and its role in ALS, Biochim. Biophys. Acta 1862 (10) (2016) 2004–2014.
[82] E. Majounie, A.E. Renton, K. Mok, E.G.P. Dopper, A. Waite, S. Rollinson, A. Chiò, G. Restagno, N. Nicolaou, J. Simon-Sanchez, J.C. van Swieten, Y. Abramzon, J.O. Johnson, M. Sendtner, R. Pamphlett, R.W. Orrell, S. Mead, K.C. Sidle, H. Houlden, J.D. Rohrer, K.E. Morrison, H. Pall, K. Talbot, O. Ansorge, T.C. 9-A. Chromosome 9-ALS/FTD Consortium, T.F. research network on French research network on FTLD/FTLD/ALS, T.I. ITALSGEN Consortium, D.G. Hernandez, S. Arepalli, M. Sabatelli, G. Mora, M. Corbo, F. Giannini, A. Calvo, E. Englund, G. Borghero, G.L. Floris, A.M. Remes, H. Laaksovirta, L. McCluskey, J.Q. Trojanowski, V.M. Van Deerlin, G.D. Schellenberg, M.A. Nalls, V.E. Drory, C.-S. Lu, T.-H. Yeh, H. Ishiura, Y. Takahashi, S. Tsuji, I. Le Ber, A. Brice, C. Drepper, N. Williams, J. Kirby, P. Shaw, J. Hardy, P.J. Tienari, P. Heutink, H.R. Morris, S. Pickering-Brown, B.J. Traynor, Frequency of the C9orf72 hexanucleotide repeat expansion in patients with amyotrophic lateral sclerosis and frontotemporal dementia: a cross-sectional study, Lancet Neurol. 11 (4) (2012) 323–330.
[83] M.A. Farg, V. Sundaramoorthy, J.M. Sultana, S. Yang, R.A. Atkinson, V. Levina, M.A. Halloran, P.A. Gleeson, I.P. Blair, K.Y. Soo, A.E. King, J.D. Atkin, C9ORF72, implicated in amytrophic lateral sclerosis and frontotemporal dementia, regulates endosomal trafficking, Hum. Mol. Genet. 23 (13) (2014) 3579–3595.
[84] Y. Aoki, R. Manzano, Y. Lee, R. Dafinca, M. Aoki, A.G.L. Douglas, M.A. Varela, C. Sathyaprakash, J. Scaber, P. Barbagallo, P. Vader, I. Mäger, K. Ezzat, M.R. Turner, N. Ito, S. Gasco, N. Ohbayashi, S. El Andaloussi, S. Takeda, M. Fukuda, K. Talbot, M.J.A. Wood, C9orf72 and RAB7L1 regulate vesicle trafficking in amyotrophic lateral sclerosis and frontotemporal dementia, Brain 140 (4) (2017) 887–897.
[85] K. Mori, S.-M. Weng, T. Arzberger, S. May, K. Rentzsch, E. Kremmer, B. Schmid, H.A. Kretzschmar, M. Cruts, C. Van Broeckhoven, C. Haass, D. Edbauer, The C9orf72 GGGGCC repeat is translated into aggregating dipeptide-repeat proteins in FTLD/ALS, Science 339 (6125) (2013) 1335–1338.
[86] T. Westergard, B.K. Jensen, X. Wen, J. Cai, E. Kropf, L. Iacovitti, P. Pasinelli, D. Trotti, Cell-to-cell transmission of dipeptide repeat proteins linked to C9orf72-ALS/FTD, Cell Rep. 17 (3) (2016) 645–652.
[87] P. Corcia, P. Couratier, H. Blasco, C.R. Andres, S. Beltran, V. Meininger, P. Vourc'h, Genetics of amyotrophic lateral sclerosis, Rev. Neurol. (Paris) 173 (5) (2017) 254–262.
[88] J.O. Johnson, J. Mandrioli, M. Benatar, Y. Abramzon, V.M. Van Deerlin, J.Q. Trojanowski, J.R. Gibbs, M. Brunetti, S. Gronka, J. Wuu, J. Ding, L. McCluskey, M. Martinez-Lage, D. Falcone, D.G. Hernandez, S. Arepalli, S. Chong, J.C. Schymick, J. Rothstein, F. Landi, Y.-D. Wang, A. Calvo, G. Mora, M. Sabatelli, M.R. Monsurrò, S. Battistini, F. Salvi, R. Spataro, P. Sola, G. Borghero, ITALSGEN Consortium, G. Galassi, S.W. Scholz, J.P. Taylor, G. Restagno, A. Chiò, B.J. Traynor, Exome sequencing reveals VCP mutations as a cause of familial ALS, Neuron 68 (5) (2010) 857–864.
[89] F. Fecto, J. Yan, S.P. Vemula, E. Liu, Y. Yang, W. Chen, J.G. Zheng, Y. Shi, N. Siddique, H. Arrat, S. Donkervoort, S. Ajroud-Driss, R.L. Sufit, S.L. Heller, H.-X. Deng, T. Siddique, SQSTM1 mutations in familial and sporadic amyotrophic lateral sclerosis, Arch. Neurol. 68 (11) (2011) 1440–1446.
[90] A. Freischmidt, T. Wieland, B. Richter, W. Ruf, V. Schaeffer, K. Müller, N. Marroquin, F. Nordin, A. Hübers, P. Weydt, S. Pinto, R. Press, S. Millecamps, N. Molko, E. Bernard, C. Desnuelle, M.-H. Soriani, J. Dorst, E. Graf, U. Nordström, M.S. Feiler, S. Putz, T.M. Boeckers, T. Meyer, A.S. Winkler, J. Winkelman, M. de Carvalho, D.R. Thal, M. Otto, T. Brännström, A.E. Volk, P. Kursula, K.M. Danzer, P. Lichtner, I. Dikic, T. Meitinger, A.C. Ludolph, T.M. Strom, P.M. Andersen, J.H. Weishaupt, Haploinsufficiency of TBK1 causes familial ALS and fronto-temporal dementia, Nat. Neurosci. 18 (5) (2015) 631–636.
[91] M. DeJesus-Hernandez, I.R. Mackenzie, B.F. Boeve, A.L. Boxer, M. Baker, N.J. Rutherford, A.M. Nicholson, N.A. Finch, H.F. Gilmer, J. Adamson, N. Kouri, A. Wojtas, P. Sengdy, G.-Y.R. Hsiung, A. Karydas, W.W. Seeley, K.A. Josephs, G. Coppola, D.H. Geschwind, Z.K. Wszolek, H. Feldman, D. Knopman, R. Petersen, B.L. Miller, D. Dickson, K. Boylan, N. Graff-Radford, R. Rademakers, Expanded GGGGCC hexanucleotide repeat in non-coding region of C9ORF72 causes chromosome 9p-linked frontotemporal dementia and amyotrophic lateral sclerosis, Neuron 72 (2) (2011) 245–256.
[92] A.E. Renton, E. Majounie, A. Waite, J. Simón-Sánchez, S. Rollinson, J.R. Gibbs, J.C. Schymick, H. Laaksovirta, J.C. van Swieten, L. Myllykangas, H. Kalimo, A. Paetau, Y. Abramzon, A.M. Remes, A. Kaganovich, S.W. Scholz, J. Duckworth,

J. Ding, D.W. Harmer, D.G. Hernandez, et al., A hexanucleotide repeat expansion in C9ORF72 is the cause of chromosome 9p21-linked ALS-FTD, Neuron 72 (2) (2011) 257–268.
[93] D.P. Bartel, MicroRNAs: target recognition and regulatory functions, Cell 136 (2) (2009) 215–233.
[94] F. Cloutier, A. Marrero, C. O'Connell, P. Jr Morin, MicroRNAs as potential circulating biomarkers for amyotrophic lateral sclerosis, J. Mol. Neurosci. 56 (1) (2015) 102–112.
[95] C. Ricci, C. Marzocchi, S. Battistini, MicroRNAs as biomarkers in amyotrophic lateral sclerosis, Cells 7 (11) (2018) 219.
[96] G. Joilin, P.N. Leigh, S.F. Newbury, M. Hafezparast, An overview of microRNAs as biomarkers of ALS, Front. Neurol. 7 (10) (2019) 186.
[97] B. De Felice, A. Annunziata, G. Fiorentino, M. Borra, E. Biffali, C. Coppola, R. Cotrufo, J. Brettschneider, M.L. Giordana, T. Dalmay, G. Wheeler, R. D'Alessandro, miR-338-3p is over-expressed in blood, CFS, serum and spinal cord from sporadic amyotrophic lateral sclerosis patients, Neurogenetics 15 (4) (2014) 243–253.
[98] A. Freischmidt, K. Müller, L. Zondler, P. Weydt, B. Mayer, C.A.F. von Arnim, A. Hübers, J. Dorst, M. Otto, K. Holzmann, A.C. Ludolph, K.M. Danzer, J.H. Weishaupt, Serum microRNAs in sporadic amyotrophic lateral sclerosis, Neurobiol. Aging 36 (9) (2015) (2660.e15-2660.e20).
[99] R. Waller, E.F. Goodall, M. Milo, J. Cooper-Knock, M. Da Costa, E. Hobson, M. Kazoka, H. Wollff, P.R. Heath, P.J. Shaw, J. Kirby, Serum miRNAs miR-206, 143-3p and 374b-5p as potential biomarkers for amyotrophic lateral sclerosis (ALS), Neurobiol. Aging 55 (2017) 123–131.
[100] A. Freischmidt, K. Müller, A.C. Ludolph, J.H. Weishaupt, Systemic dysregulation of TDP-43 binding microRNAs in amyotrophic lateral sclerosis, Acta Neuropathol. Commun. 1 (2013) 42.
[101] M. Benigni, C. Ricci, A.R. Jones, F. Giannini, A. Al-Chalabi, S. Battistini, Identification of miRNAs as potential biomarkers in cerebrospinal fluid from amyotrophic lateral sclerosis patients, NeuroMolecular Med. 18 (4) (2016) 551–560.
[102] R. Waller, M. Wyles, P.R. Heath, M. Kazoka, H. Wollff, P.J. Shaw, J. Kirby, Small RNA sequencing of sporadic amyotrophic lateral sclerosis cerebrospinal fluid reveals differentially expressed miRNAs related to neural and glial activity, Front. Neurosci. 11 (2018) 731.
[103] Z. Zhang, S. Almeida, Y. Lu, A.L. Nishimura, L. Peng, D. Sun, B. Wu, A.M. Karydas, M.C. Tartaglia, J.C. Fong, B.L. Miller, R.V. Jr Farese, M.J. Moore, C.E. Shaw, F.-B. Gao, Downregulation of microRNA-9 in iPSC-derived neurons of FTD/ALS patients with TDP-43 mutations, PLoS One 8 (2013) e76055.
[104] Q. Xu, Y. Zhao, X. Zhou, J. Luan, Y. Cui, J. Han, Comparison of the extraction and determination of serum exosome and miRNA in serum and the detection of miR-27a-3p in serum exosome of ALS patients, Intractable Rare Dis. Res. 7 (1) (2018) 13–18.
[105] D. Saucier, G. Wajnberg, J. Roy, A.-P. Beauregard, S. Chacko, N. Crapoulet, S. Fournier, A. Ghosh, S.M. Lewis, A. Marrero, C. O'Connell, R.J. Ouellette, P. Jr Morin, Identification of a circulating miRNA signature in extracellular vesicles collected from amyotrophic lateral sclerosis patients, Brain Res. 1708 (2019) 100–108.
[106] K. Otake, H. Kamiguchi, Y. Hirozane, Identification of biomarkers for amyotrophiclateral sclerosis by comprehensive analysis of exosomal mRNAs in human cerebrospinal fluid, BMC Med. Genet. 12 (1) (2019) 7.
[107] T. Nagano, P. Fraser, No-nonsense functions for long noncoding RNAs, Cell 145 (2) (2011) 178–181.
[108] Y. Nishimoto, S. Nakagawa, T. Hirose, H.J. Okano, M. Takao, S. Shibata, S. Suyama, K.-I. Kuwako, T. Imai, S. Murayama, N. Suzuki, H. Okano, The long non-coding RNA nuclear-enriched abundant transcript 1_2 induces paraspeckle formation in the motor neuron during the early phase of amyotrophic lateral sclerosis, Mol. Brain 6 (2013) 31.
[109] H. An, L. Skelt, A. Notaro, J.R. Highley, A.H. Fox, V. La Bella, V.L. Buchman, T.A. Shelkovnikova, ALS-linked FUS mutations confer loss and gain of function in the nucleus by promoting excessive formation of dysfunctional paraspeckles, Acta Neuropathol. Commun. 7 (2019) 7.
[110] S. Gagliardi, S. Zucca, C. Pandini, L. Diamanti, M. Bordoni, D. Sproviero, M. Arigoni, M. Olivero, O. Pansarasa, M. Ceroni, R. Calogero, C. Cereda, Long non-coding and coding RNAs characterization in peripheral blood mononuclear cells and spinal cord from amyotrophic lateral sclerosis patients, Sci. Rep. 8 (2018) 2378.
[111] B. Mateescu, E.J.K. Kowal, B.W.M. van Balkom, S. Bartel, S.N. Bhattacharyya, E.I. Buzás, A.H. Buck, P. de Candia, F.W.N. Chow, S. Das, T.A.P. Driedonks, L. Fernández-Messina, F. Haderk, A.F. Hill, J.C. Jones, K.R. Van Keuren-Jensen, C.P. Lai, C. Lässer, I. di Liegro, T.R. Lunavat, M.J. Lorenowicz, S.L.N. Maas, I. Mäger, M. Mittelbrunn, S. Momma, K. Mukherjee, M. Nawaz, D.M. Pegtel, M.W. Pfaffl, R.M. Schiffelers, H. Tahara, C. Théry, J.P. Tosar, M.H.M. Wauben, K.W. Witwer, E.N.M. Nolte-'t Hoen, Obstacles and opportunities in the functional analysis of extracellular vesicle RNA - an ISEV position paper, J. Extracell. Vesicles 6 (1) (2017) 1286095.
[112] C.-S. Hong, L. Muller, T.L. Whiteside, M. Boyiadzis, Plasma exosomes as markers of therapeutic response in patients with acute myeloid leukemia, Front. Immunol. 5 (2014) 160.
[113] I. Manna, E. Iaccino, V. Dattilo, S. Barone, E. Vecchio, S. Mimmi, E. Filippelli, G. Demonte, S. Polidoro, A. Granata, S. Scannapieco, I. Quinto, P. Valentino, A. Quattrone, Exosome-associated miRNA profile as a prognostic tool for therapy response monitoring in multiple sclerosis patients, FASEB J. 32 (8) (2018) 4241–4246.
[114] V.K. Harris, S.A. Sadiq, Biomarkers of therapeutic response in multiple sclerosis: current status, Mol. Diagn. Ther. 18 (6) (2014) 605–617.
[115] Y. Kitamura, M. Kojima, T. Kurosawa, R. Sasaki, S. Ichihara, Y. Hiraku, H. Tomimoto, M. Murata, S. Oikawa, Proteomic profiling of exosomal proteins for blood-based biomarkers in Parkinson's disease, Neuroscience. 392 (2018) 121–128.
[116] S. El Andaloussi, I. Mäger, X.O. Breakefield, M.J.A. Wood, Extracellular vesicles: biology and emerging therapeutic opportunities, Nat. Rev. Drug Discov. 12 (2013) 347–357.
[117] J.P. Armstrong, M.N. Holme, M.M. Stevens, Re-engineering extracellular vesicles as smart nanoscale therapeutics, ACS Nano 11 (1) (2017) 69–83.
[118] A.T. Reiner, K.W. Witwer, B.W.M. van Balkom, J. de Beer, C. Brodie, R.L. Corteling, S. Gabrielsson, M. Gimona, A.G. Ibrahim, D. de Kleijn, C.P. Lai, J. Lötvall, H.A. Del Portillo, I.G. Reischl, M. Riazifar, C. Salomon, H. Tahara, W.S. Toh, M.H.M. Wauben, V.K. Yang, Y. Yang, R.W.Y. Yeo, H. Yin, B. Giebel, E. Rohde, S.K. Lim, Concise review: developing best-practice models for the therapeutic use of extracellular vesicles, Stem Cells Transl. Med. 6 (8) (2017) 1730–1739.
[119] M. Cooper, P.B.O. Wiklander, J.Z. Nordin, R. Al-Shawi, M.J. Wood, M. Vithlani, A.H.V. Schapira, J.P. Simons, S. El-Andaloussi, L. Alvarez-Erviti, Systemic exosomal siRNA delivery reduced alpha-synuclein aggregates in brains of transgenic mice, Mov. Disord. 29 (12) (2014) 1476–1485.
[120] L. Alvarez-Erviti, Y. Seow, H. Yin, C. Betts, S. Lakhal, M.J.A. Wood, Delivery of siRNA to the mouse brain by systemic injection of targeted exosomes, Nat. Biotechnol. 29 (4) (2011) 341–345.
[121] M.J. Haney, N.L. Klyachko, Y. Zhao, R. Gupta, E.G. Plotnikova, Z. He, T. Patel, A. Piroyan, M. Sokolsky, A.V. Kabanov, E.V. Batrakova, Exosomes as drug delivery vehicles for Parkinson's disease therapy, J. Control. Release 207 (2015) 18–30.
[122] K. Yuyama, H. Sun, S. Usuki, S. Sakai, H. Hanamatsu, T. Mioka, N. Kimura, M. Okada, H. Tahara, J. Furukawa, N. Fujitani, Y. Shinohara, Y. Igarashi, A potential function for neuronal exosomes: sequestering intracerebral amyloid-β peptide, FEBS Lett. 589 (1) (2015) 84–88.
[123] K. Yuyama, H. Sun, S. Sakai, S. Mitsutake, M. Okada, H. Tahara, J. Furukawa, N. Fujitani, Y. Shinohara, Y. Igarashi, Decreased amyloid-β pathologies by intracerebral loading of glycosphingolipid-enriched exosomes in Alzheimer model mice, J. Biol. Chem. 289 (35) (2014) 24488–24498.
[124] M. Lee, T. Liu, W. Im, M. Kim, Exosomes from adipose-derived stem cells ameliorate phenotype of Huntington's disease in vitro model, Eur. J. Neurosci. 44 (4) (2016) 2114–2119.
[125] R. Bonafede, I. Scambi, D. Peroni, V. Potrich, F. Boschi, D. Benati, B. Bonetti, R. Mariotti, Exosome derived from murine adipose-derived stromal cells: Neuroprotective effect on in vitro model of amyotrophic lateral sclerosis, Exp. Cell Res. 340 (1) (2016) 150–158.
[126] R. Bonafede, R. Mariotti, ALS pathogenesis and therapeutic approaches: the role of mesenchymal stem cells and extracellular vesicles, Front. Cell. Neurosci. 11 (2017) 80.
[127] C. Charoenviriyakul, Y. Takahashi, M. Morishita, A. Matsumoto, M. Nishikawa, Y. Takakura, Cell type-specific and common characteristics of exosomes derived from mouse cell lines: yield, physicochemical properties, and pharmacokinetics, Eur. J. Pharm. Sci. 96 (2017) 316–322.
[128] A. Bobrie, M. Colombo, S. Krumeich, G. Raposo, C. Thery, Diverse subpopulations of vesicles secreted by different intracellular mechanisms are present in exosome preparations obtained by differential ultracentrifugation, J. Extracell. Vesicles 1 (2012) 18397.
[129] O.P. Wiklander, J.Z. Nordin, A. O'Loughlin, Y. Gustafsson, G. Corso, I. Mager, P. Vader, Y. Lee, H. Sork, Y. Seow, N. Heldring, L. Alvarez-Erviti, C.I. Smith, K. Le Blanc, P. Macchiarini, P. Jungebluth, M.J. Wood, S.E. Andaloussi, Extracellular vesicle in vivo biodistribution is determined by cell source, route of administration and targeting, J. Extracell. Vesicles 4 (2015) 26316.
[130] F. Massenzio, E. Peña-Altamira, S. Petralla, M. Virgili, G. Zuccheri, A. Miti, E. Polazzi, I. Mengoni, D. Piffaretti, B. Monti, Microglial overexpression of fALS-linked mutant SOD1 induces SOD1 processing impairment, activation and neurotoxicity and is counteracted by the autophagy inducer trehalose, Biochim. Biophys. Acta Mol. basis Dis. 1864 (12) (2018) 3771–3785.
[131] S. Pinto, C. Cunha, M. Barbosa, A.R. Vaz, D. Brites, Exosomes from NSC-34 cells transfected with hSOD1-G93A are enriched in miR-124 and drive alterations in microglia phenotype, Front. Neurosci. 11 (2017) 273.
[132] M. Katsu, Y. Hama, J. Utsumi, K. Takashina, H. Yasumatsu, F. Mori, K. Wakabayashi, M. Shoji, H. Sasaki, MicroRNA expression profiles of neuron-derived extracellular vesicles in plasma from patients with amyotrophic lateral sclerosis, Neurosci. Lett. 708 (2019) 134176, https://doi.org/10.1016/j.neulet.2019.03.048.
[133] J. Matsumoto, T. Stewart, W.A. Banks, J. Zhang, The transport mechanism of extracellular vesicles at the blood-brain barrier, Curr. Pharm. Des. 23 (40) (2017) 6206–6214.