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MINIREVIEWS

Dual role of extracellular vesicles in neurodegenerative diseases

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Abstract

Extracellular vesicles (EVs) are cell-to-cell interaction tools that are attracting increasing interest in the literature in two opposing areas. In addition to their role in physiological development, there is growing evidence of their involvement in healing and protective processes. However, EVs also mediate pathological conditions, particularly contributing to the progression of several chronic diseases, such as neurodegenerative diseases. On the other hand, EVs also form the core of a new therapeutic strategy for neuroprotection, which is based on the administration of EVs derived from a wide range of donor cells. In particular, the possibility of obtaining numerous EVs from stem cells of different origins, which is feasible for therapeutic aims, is now under investigation. In this review, we focused on neurodegenerative diseases, in which EVs could have a propagative detrimental effect or could also be exploited to deliver protective factors. This review explores the different hypotheses concerning the dual role of EVs, with the aim of shedding light on the following question: Can vesicles be used to fight vesicle-propagated diseases?

Key Words: Extracellular vesicles; Neurodegenerative diseases; Induced pluripotent stem cells; Mesenchymal stem cells; Neuroprotection; Cellular communication; Biomarkers

Core Tip: An increasing number of studies in the literature have focused on the role of extracellular vesicles (EVs) in the progression of several diseases, particularly neurodegenerative diseases, in which EVs are presumed to transfer pathological molecules to normal cells. Nevertheless, many therapeutic strategies focus on the use of EVs to deliver prosurvival factors; however, apparent discrepancies are noted. In this review, we focused on neurodegenerative diseases to shed light on the dual role that EVs play and explored, in particular, the potential therapeutic role of stem cell-derived EVs.

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INTRODUCTION

The ability of cells to interact and communicate with each other is essential for their survival and for the correct execution of their functions. Based on this premise, an increasing number of studies in the literature have focused on alterations in cellular interactions as the initiating mechanism of different types of diseases. Among the different communication mechanisms, such as gap junctions and tunneling nanotubes[1], extracellular vesicles (EVs) have attracted increasing interest in recent years, with considerable evidence of the involvement of these structures both in common physiological processes (cell maintenance and survival, myelin formation, neurite elongation, and cellular aging) and in the development of pathological implications, such as tumor development, cognitive impairment and neurodegeneration[2-5]. Despite the stronger association of EVs with different pathological conditions, an even larger number of studies have focused on the use of EVs as therapeutic agents, with an apparent paradox: Is it possible to counteract a disease by using the same agents supposedly involved in its onset/progression? This point is particularly interesting for some diseases, such as neurodegenerative diseases, in which both roles of EVs are under investigation and are considered feasible. The answer seems to be positive. With appropriate strategies, exploiting the unique sensitivity of EVs to the culture microenvironment, their potential for manipulation, and carefully selecting the cellular population from which they are derived, positive outcomes can be achieved. In this review, we focused on neurodegenerative diseases, explored the different hypotheses concerning the role of EVs and analyzed, in particular, the stem cell-derived EVs currently proposed as therapeutic options.

BRIEF HISTORY OF EVS

EVs are vesicular structures delimited by a lipidic layer and are unable to replicate[6]. In a thorough review, Couch *et al* [7] described the discovery of these structures, which are now widely studied. Starting from the first report of their existence as a particulate fraction during blood clotting experiments, in approximately 1940[8], Couch *et al*[7] reported different hypotheses on these structures over the years, during which the scientific community gained awareness of their importance in an incremental fashion. From the first hypothesis on their possible role as simple cargo systems for molecules[9], until the current evidence of a dynamic communication system available to the cell was reached, changes in the extracellular environment and proper reactions were detected by adjusting the EV content[1,10,11]. Current guidelines (minimal information to study EVs 2018) have identified and described different types of structures as EVs, mainly on the basis of their biogenesis and dimension[6,12], given the lack of specific molecular markers. In particular, the classification of EVs includes exosomes, microvesicles, and apoptotic bodies[3]. Exosomes are formed (and released) in an endosomal manner, and their dimensions can range from 30 to 150 nm. Microvesicles are larger than exosomes, with dimensions between 100 nm and 1 μm and originate from direct budding of the cell plasmatic membrane, whereas apoptotic bodies are a product of apoptotic cells that are highly variable in size[3]. All EV types contain proteins, lipids and nucleic acids [including regulatory microRNA (miRNAs)], and, based on their size, they can also contain organelles. Although exosomes and microvesicles are released by cells, apoptotic bodies are more exact cellular fragments derived from cell disassembly; in any case, all of these fragments could play important roles in cellular communication[13]. Generally, the key role of EVs relies on what they can transport. The initial hypothesis was that EVs are used by cells to release products designated for elimination in the extracellular space. However, to date, it has been demonstrated that EVs can also exchange several important lipid proteins (*e.g.*, cytokines and trophic factors[14]), cytosolic organelles (*e.g.*, mitochondria[1]), and other important cell regulators (*i.e.*, mRNAs, miRNAs, and small interfering RNAs[15]) with other cells.

As putative carriers of this wide range of molecules, as stated before and according to several papers, EVs can play important roles in physiological processes in several tissues. In the cardiovascular system, they seem to be involved in blood pressure regulation *via* the transport of vasoactive molecules[16,17]. In the kidney, EVs can transport aquaporin-2, therefore regulating water balance. In the nervous system, they are involved in brain development[17,18]. The ability that makes these structures so interesting is their role in the development of pathological features[16], particularly for those diseases characterized by the propagation of a pathological protein, such as neurodegenerative diseases, which this review is focused.

EVS AS DISEASE MECHANISMS

Many diseases of the nervous system, although characterized by different cellular targets and symptoms, share a common pathological feature, that is, the accumulation of altered proteins, which acquire a toxic function[19-22], as observed in Alzheimer's disease (AD)[23] with β-amyloid and tau; α-synuclein in Parkinson's disease (PD)[15] or huntingtin in Huntington's disease (HD); and superoxide dismutase 1, TDP43 and Fus in amyotrophic lateral sclerosis[24, 25]. This toxic content inside cells quickly spreads to other normal cells, leading to the progressive poisoning of the entire cell population, with the loss of a particular type of cell and overall loss of its function. This type of error propagation involves viral-like diffusion or, rather, prion-like spread, with misfolded proteins inducing alterations in normal proteins [21]. Given that cellular communication is the basis of this form of diffusion, many studies have focused on interaction structures, particularly on EVs, as a mechanism to propagate a "toxic" factor. Eitan *et al*[26] suggested that EV content could cause neuronal damage. Specifically, EVs derived from AD patients or animal disease models, which are therefore considered pathological, can increase and prolong the Ca^{2+} response to glutamate; moreover, they can reduce both basal and maximal mitochondrial respiration and ATP levels. Thus, these EVs can alter both Ca^{2+} homeostasis and mitochondrial function[26], increasing the sensitivity of recipient neurons to excitotoxic stimuli. Similarly, other authors have demonstrated that pathological EVs derived from patients or damaged cells can induce neurotoxic alterations in recipient cells[5,27,28] or at least act as vehicles for the propagation of toxins, which are responsible for proinflammatory cytokine production and the induction of apoptosis. EVs can also contain proteins associated with amyotrophic lateral sclerosis[29] as well as poly-Q and CAG repeats, which are involved in HD and can subsequently lead to neuronal degeneration[30].

The main question arising from these studies revolves around the role of EVs: Are they merely passive mirrors reflecting what happens inside the cell and serving as cargo systems hijacked by pathogenic cells to spread their altered content? Alternatively, could they be considered the triggering factor of the disease? The majority of the literature supports the first hypothesis because of the presence of many peculiar neurotoxic proteins inside EVs. Poehler *et al*[31] reported that some mutations associated with early PD onset, namely, those in the *SNCA* gene, promote both α-synuclein aggregation and its accumulation in EVs, which are then secreted and transferred to other cells that start to show fibril aggregation[31]. Likewise, Zhang *et al*[30] reported the presence of expanded CAG triplets and HD-associated proteins in EVs, whereas Aβ-amyloid peptides have been found in AD patient-derived EVs[26]. In addition to the propagation of misfolded proteins, an unfavorable environment could also alter the EV content, thus further worsening cellular stress. Jeske *et al*[32] reported that the EV content could change in response to inflammatory stimuli, such as lipopolysaccharide or tumor necrosis factor-α, as well as stress stimuli, thus highlighting a detrimental role for EVs. Given that neuroinflammation is a hallmark of neurodegenerative diseases, this could also determine a pathological change in EV content.

EVs can be exchanged not only between neurons but also between neurons and glial cells[20]. The role of EVs derived from different types of glial cells has been identified as pivotal for neuroimmune communication, the regulation of neuron survival and excitability, and neurite elongation[33] in several experimental models of neurodegenerative diseases[34-36]. However, de Rus Jacquet *et al*[37] reported that a mutation associated with PD can lead to an alteration in the biogenesis of those EVs generally used by astrocytes to support neuronal survival. Deprived of assistance from glial cells, neurons start to develop those alterations, which subsequently trigger the formation and accumulation of misfolded proteins. Further propagation would then be caused by the "hijacked" EVs in a loop causing disease spread escalation.

In addition, other authors have suggested an alternative point of view. Starting from the evidence of the presence of altered/misfolded proteins inside EVs, Hill[14] considered the process as an ultimate attempt of the cell to clear the altered proteins. The pathological contents of EVs should not necessarily be transported but rather seized to eliminate undesired/dangerous proteins[38]. In this context, EVs should represent a protective tool used by the cell. Yuyama *et al* [38] observed the role of EVs in Aβ-amyloid clearance and reported that their downregulation could be related to disease development. This view apparently contradicts the other views previously cited; however, their role, which is initially protective, could change in particular circumstances, *i.e.*, in aged individuals[39]. Upadhya *et al*[39] observed a dysregulation in EV production in aged animals, which could be related to a change in their role; however, the exact mechanisms of such a switch remain unsolved. Therefore, although EVs have not been confirmed to trigger neurodegenerative disease, which often depend on multiple factors, such as oxidative stress, protein misfolding or genetic mutations in familial forms, they are undoubtedly involved in the propagation of the toxic mechanism among cells, similar to how an enemy controls communication systems.

EVS AS A THERAPEUTIC TOOL

If it is certain that EVs play a role in neurodegenerative disease propagation, it is also clear that, because of their features, EVs could be exploited to import every type of molecule into the cell, making them suitable for fighting the same diseases. A possible strategy involves decreasing the number of EVs released, which is associated with disease progression, through the inhibition of the enzymes responsible for their generation[40]. However, increasing evidence suggests the possibility of adding exogenous EVs, which are spontaneously released or engineered to deliver protective factors, to a damaged cell population[39].

The idea of a positive role of EVs was raised first by the evidence that some cells actively contribute to correct nervous system development and maintenance through the release of EVs that modulate neuronal functions[41,42]. Oligodendrocyte-derived EVs contain some proteins essential for myelin formation and axonal support[43]. However, in some cases, microglia can reduce neuroinflammation and oxidative stress through EV release[44]. In addition, Yuyama *et al*[38]

demonstrated that hippocampal neurons release some EVs that are able to reduce Aβ peptide accumulation *in vivo*, thus protecting mouse synaptic activity.

Despite these interesting observations, endogenous EVs, which may be released during physiological development and homeostasis, clearly fail to protect against damage for the reasons mentioned above. In contrast, the exogenous administration of EVs with a protective effect could better support a therapeutic effect. A limiting factor is, however, represented by the need for a sufficient number of EVs to achieve valid protection, which is not easy to obtain.

The first step to overcome such a problem was recently achieved based on research on EVs paired with that of stem cells. Over recent decades, the protective effect of different types of stem cells has been confirmed in many *in vitro* and *in vivo* models, suggesting that the release of rescue factors (such as neurotrophic factors) is a pivotal mechanism. In particular, several authors observed that these cells were able to protect other cellular populations through the release of EVs, thus using them not only as a simple communication system but also to exchange pivotal factors such as antioxidant molecules and mitochondria[1,15,45]. To date, EVs from mesenchymal stem cells (MSCs) are the most studied, and findings obtained using these cells not only corroborate the putative protective role of EVs but also introduce the possibility of their use as a cell-free therapy[4]. In fact, with respect to stem cells, EVs present several advantages because they: (1) Do not induce an immune response; (2) Can be obtained in large amounts; (3) Can be easily stored/functionalized to produce supporting factors, which has already been demonstrated to be beneficial[46]; and (4) Can cross the blood-brain barrier (BBB). Overall, EVs cannot replicate; thus, they are more suitable and safer than cell therapy is[47].

Different authors have highlighted the important role of endogenous EVs in the correct maintenance of neural functions, such as the transport of myelin-associated proteins, neurotransmitters and trophic factors for neuronal survival [48]. However, a promising therapeutic role has also been assigned to exogenous EVs. Jeske *et al*[32] compared the therapeutic potential of EVs derived from several types of induced pluripotent stem cells (iPSCs) for different neurodegenerative diseases. EVs extracted from normal oligodendrocytes reduce the damage observed in an AD model by sequestering Aβ amyloid and then promoting its clearance by microglia, whereas EVs derived from macrophages reduce reactive oxygen species (ROS) levels and promote neuronal survival[32].

Several authors have reported that MSC-derived EVs can counteract several alterations responsible for cellular senescence and age-related diseases, such as inflammation and oxidative stress[49]. In particular, EVs from MSCs have been demonstrated to reduce oxidative stress and ROS production in several *in vitro* models by modulating important pathways, such as the Wnt/β-catenin pathway[50], signal transducer and activator of transcription 3 pathway[51], Akt signaling pathway[52], and the cascade involving nuclear factor erythroid 2-related factor 2[53], which are pivotal regulators of oxidative stress, inflammation and cell survival. EVs also act as regulators of other central nervous system cells, such as microglia. In an AD model, Ding *et al*[54] demonstrated that neurons release triggering molecules, namely, alarmins, which subsequently activate microglia to a proinflammatory phenotype in a detrimental loop. In this context, the content of MSC-derived EVs could stop this chain through the modulation of tumor necrosis factor-α and interleukin-1β *vs* interleukin-10 and transforming growth factor-beta. In addition to inflammation and oxidative stress, multiomics analysis has revealed that EVs contain many proteins and regulatory miRNAs involved in autophagy and apoptosis regulation, as well as several trophic factors, such as brain-derived neurotrophic factor, glial cell line-derived neurotrophic factor, and vascular endothelial growth factor, which are important for neuronal survival, axonal guidance and angiogenesis[45,47,55], thus increasing the likelihood of exploiting EVs for therapeutic purposes.

MSC-derived EVs have also been demonstrated to be useful in different *in vivo* models of neurological diseases, such as stroke[56], traumatic brain injury[57], and cisplatin-dependent cochlear damage[58,59]. They also counteract brain aging. For example, Zhang *et al*[60] administered EVs once a month for 3 months in a mouse model, reporting increased sirtuin 1 expression, as well as decreased apoptosis and ROS levels. In an *in vivo* model of cisplatin-induced neuropathy, intranasally injected EVs derived from MSCs were able to reverse drug-dependent cognitive impairment and most molecular alterations, restoring synaptic integrity and mitochondrial morphology[45].

Nevertheless, all these encouraging results obtained both *in vitro* and *in vivo* are limited by several important critical points. First, the large heterogeneity of the outcomes, mainly due to batch-to-batch variability in MSCs, highlights the current unreliability of this approach, as demonstrated by the small number of clinical trials that have reached phase 3 [61]. In addition to variability, a further problem is represented by the large number of MSCs necessary to obtain an amount of EVs sufficient for therapeutic treatment[62]. To overcome these limitations, research has moved from the use of MSCs to the use of iPSCs or, even better, to the use of MSCs derived from iPSCs, so-called iPSC-derived MSCs (iMSCs). The switch to these cells could allow a more effective system to achieve a usable number of EVs, and currently, several protocols can be used to obtain iMSCs[62]. Some iMSCs were derived from embryonic stem cells, which may be cocultured with other cells, such as OP9 (a mouse bone marrow stroma cell line), or directed to the formation of embryoid bodies under particular culture conditions[62]. In contrast, other studies used somatic cells, such as fibroblasts, and then reprogrammed them into iMSCs using a cocktail of mitogen-activated protein kinases inhibitors and growth factors. Therefore, both the use of embryonic cells, together with their related ethical and safety problems, and safer cells, which undergo important manipulations, are needed[62]. To better characterize the differences among MSCs, iPSCs and iMSCs and their effectiveness, several authors have compared these cells in terms of effects and contents. Table 1 summarizes the main features of the different cells.

Billing *et al*[63] demonstrated that MSCs and iMSCs are very similar but not identical. Specifically, iMSCs are more useful for axon support and for reducing multiple sclerosis progression, whereas MSCs better support vascular development. Importantly, iMSCs fail to differentiate into adipose cells, an essential prerequisite for identifying MSCs, as established by Dominici *et al*[64]. A similar approach was used by Branscome *et al*[65] and Barreca *et al*[47], who both compared the effectiveness of EVs derived from MSCs and iPSCs. They both identified a similar protective role for these EVs in different cellular models. However, Branscome *et al*[65] specified that iPSC-derived EVs could have a delayed effect, thus resulting in less suitability. More generally, the comparison among all these cells revealed that although some

Table 1 Comparison among mesenchymal stem cells, induced pluripotent stem cells and induced pluripotent stem cell-derived mesenchymal stem cells

	MSCs	iPSCs	iMSCs
Differentiation potential	Differentiate into the 3 mesengenic lineages	Pluripotent	Do not differentiate into adipose cells
Proliferative potential	Low-medium	High	High
Immunomodulation	Immunomodulation properties	Immunomodulation properties	Immunomodulation properties
Gene signature	Age-related gene pathway	Rejuvenation-associated gene pathway	Age-related gene pathway
Variability	Donor and batch-dependent	Single-clone derivation	Single-clone derivation
Soluble factor release	Higher vascular development	Delayed effect	Neurological symptoms
Safety	No safety issues	Safety issues	Safety issues

MSC: Mesenchymal stem cell; iPSC: Induced pluripotent stem cells; iMSC: Induced pluripotent stem cell-derived mesenchymal stem cells.

differences were detected, their EVs are able to reduce apoptosis, inflammation and oxidative stress. These EVs are particularly enriched in growth factors, which are able to stimulate synaptic plasticity through the extracellular signal-regulated kinase pathway, and miRNAs with regenerative potential[66].

From this starting point, different authors have attempted to modify the content of EVs, with the aim of improving the therapeutic strategy, by functionalizing them to transfer specific molecules (or drugs)[67-70]. Moreover, several techniques aimed at the de novo generation of EVs have been developed to obtain large-scale production of specific EVs, thus optimizing the release and exchange of a specific cell target[71]. Finally, some authors have suggested the use of specific hydrogels to stabilize EVs and enhance their retention[72]. This approach has demonstrated efficacy since the encapsulated EVs were able to promote endogenous neurogenesis in a model of damaged nerves[73], reduce inflammation and oxidative stress[74] and promote angiogenesis[75].

EVS AS BIOMARKERS/BIOCARRIERS

To date, some clinical trials have focused on EV use in the context of neurological diseases, although the majority have proposed EVs as biomarkers for disease detection (http://www.clinicaltrials.gov). In fact, regardless of whether their role is detrimental or defensive, some molecules are present inside EVs, and their presence is certainly attributed to the disease. This content paves the way for the use of these structures as "predictors", which are suitable for the early detection of diseases using a minimally invasive method given that EVs are present in almost every body fluid, such as blood, urine, or saliva[76], and noticeable improvements in the current diagnostic techniques, particularly for neurological diseases. Furthermore, since the EV content may change during different stages of the disease, EVs could also be used as prognostic biomarkers or, at least, to classify the disease stage[67].

A alternative approach was offered by You *et al*[22], who identified some differences among EVs derived from different human iPSCs. By demonstrating that EVs are not identical, the authors suggested the possibility of discriminating a specific EV signature for different diseases, as previously suggested by Fiandaca *et al*[77]. In particular, in a proteomic study, You *et al*[22] demonstrated that activated astrocytes release particular EVs that contain proteins strongly associated with AD, such as SLC7A2 and S100A6, which are highly expressed in astrocytes around Aβ plaques. This could be particularly useful for selectively blocking the entry of a class of pathological EVs inside the cell, thus arresting or at least limiting disease spread, as suggested by Wang *et al*[5]. These authors investigated insulin resistance-associated cognitive impairment and demonstrated that EVs carrying a particular miRNA (miR-9-3p) induce synaptic loss. The design of proteins that are able to specifically recognize these EVs and prevent their internalization potentially represent an innovative therapeutic approach. In parallel, it would be possible to exploit other classes of EVs as important biocarriers loaded with protective and/or trophic molecules. In this way, EVs could be particularly attractive because of their ability to cross the BBB by transcytosis or through endothelial cell junctions, as reported in several studies summarized in a review by Li *et al*[78], which revealed that EVs are more helpful than entire cells.

CONCLUSION

It is important to keep in mind the existence of a dual role of EVs in the context of current scientific research on neurodegenerative diseases, and understanding what could tip the scale toward a protective or detrimental role is fundamental for EV applications in the clinic. It is plausible and realistic to counteract a disease using EVs, which carry key factors, such as growth factors, regulatory miRNAs, antiapoptotic factors, anti-inflammatory factors and antioxidative factors, to support neuronal survival. In addition, EVs can be manipulated, and their content can be adjusted by changing the cellular microenvironment or the stimuli to which the cell is exposed. In any case, with respect to the clinical use of EVs,

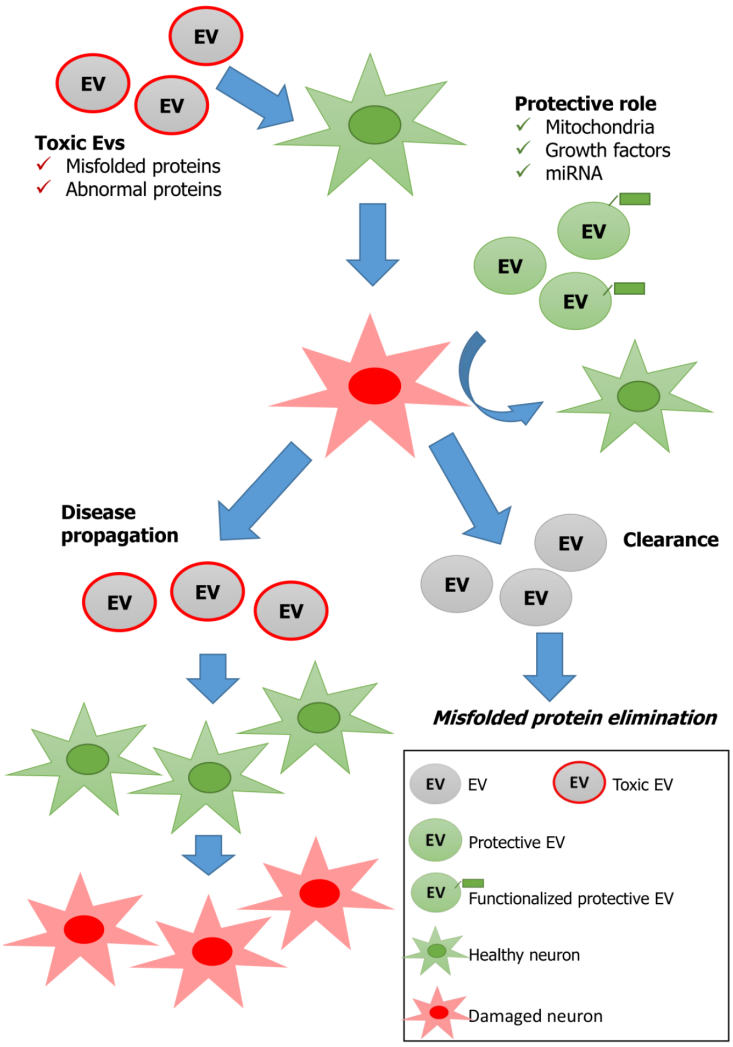

Figure 1 The different roles and actions of extracellular vesicles. EV: Extracellular vesicle; miRNA: MicroRNA.

attention should be given to their putative disadvantages and our limited knowledge of many important parameters, such as the duration of their effects, how to adjust the EV content for different neurodegenerative diseases and, overall, their dual role. Neurodegenerative diseases, even more than other therapeutic areas, could benefit from treatments based on EVs because of their ability to cross the BBB, a peculiarity that could be further addressed through specific modifications of EVs[78,79]. A long list of challenges needs to be addressed in order to obtain robust data, starting from the choice of the best donor cell type for each therapeutic approach and moving toward the establishment of robust protocols for EV production and isolation[79,80]. Progress in EV research, particularly in *in vivo* studies, could help to improve the potential therapeutic role of EVs. Long-term studies should exclude the possibility that exogenous EVs administered with a therapeutic aim could also be hijacked by the body and turned into Trojan horses. Figure 1 recapitulates the different putative actions of EVs most frequently suggested by the papers considered in this review. The large amount of data presented in the literature should be critically analyzed to standardize culture conditions as well as characterization and extraction methods as much as possible, which may affect the results.

A concluding remark should be made about the EV administration route. Many *in vivo* studies systemically provide EVs; however, several authors have demonstrated that systemic administration causes retention of EVs in the lungs, with a consequent reduction in their effectiveness[57]. Currently, local administration, particularly intranasal administration, should be employ standardize procedures that reduce EV clearance[81]. In conclusion, once the biological properties of EVs are completely elucidated, they have the potential for use as a disruptive and innovative therapeutic tool for several different diseases.

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