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Extracellular vesicles in neurodegenerative diseases

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ABSTRACT

Extracellular vesicles (EVs) are released by all neural cells, including neurons, oligodendrocytes, astrocytes, and microglia. The lack of adequate technology has not halted neuroscientists from investigating EVs as a mean to decipher neurodegenerative disorders, still in search of comprehensible pathogenic mechanisms and efficient treatment. EVs are thought to be one of ways neurodegenerative pathologies spread in the brain, but also one of the ways the brain tries to displace toxic proteins, making their meaning in pathogenesis uncertain. EVs, however do reach biological fluids where they can be analyzed, and might therefore constitute clinically decisive biomarkers for neurodegenerative diseases in the future. Finally, if they constitute a physiological inter-cell communication system, they may represent also a very specific drug delivery tool for a difficult target such as the brain. We try to resume here available information on the role of EVs in neurodegeneration, with a special focus on Alzheimer's disease, progressive multiple sclerosis, amyotrophic lateral sclerosis, and Huntington's disease.

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Introduction

Neurodegenerative disorders such as Alzheimer's disease (AD), Parkinson's disease (PD), the progressive phase of multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), and Huntington's disease (HD), constitute a major challenge for biomedical research since they affect an increasing number of individuals in the aging population, and recognize no treatment (Chiti and Dobson, 2017; Kawachi and Lassmann, 2017; Sanabria-Castro et al., 2017; Saudou and Humbert, 2016; Taylor et al., 2016). Recent years have brought many advances in the clinical definition and in the knowledge on pathogenic mechanisms of neurodegenerative diseases, but translation to effective cure is hampered by several factors. The lack of efficient biomarkers, for example, does not allow diagnosing patients in the early stages of the disease when there is still the possibility to maintain acceptable cognitive performance, impedes to assign patients to their disease subtype, and does not allow monitoring disease progression and thus allow a more efficient clinical trial design. Currently, the gold standard biomarker remains brain imaging, either with magnetic resonance imaging (MRI) or positron emission tomography (PET). At least two years of follow-up are needed to appreciate the potential effect of experimental treatments on neurodegeneration with brain imaging, increasing the cost of drug development and dramatically decreasing the number of tested compounds. In general terms, therapeutic strategies for neurodegeneration have been designed to prevent the formation of toxic protein aggregates, present in most neurodegenerative diseases (Shrivastava et al., 2017), to protect neurons from cell death (Hwang et al., 2017), and to modulate concomitant brain inflammation (Heneka et al., 2015; N. P. Rocha et al., 2016). However, despite increasing knowledge on the pathogenic mechanisms leading to formation of toxic protein aggregates, we lack exhaustive information on the final pathways leading to neuronal death and on the role, protective or damaging, of inflammation, to allow the rational design of novel therapeutic strategies.

In this scenario, the first reports describing the detection of extracellular vesicles (EVs) released from neural cells raised enormous interest (Rajendran et al., 2006; Scolding et al., 1989; Verderio et al., 2012). EVs, in fact, were immediately investigated as a potential source of information on neural cells involved in the pathological processes causing neurodegenerative diseases. The possibility to shed light on the mechanisms leading to neuronal death, or to develop biomarkers able to measure neurodegenerative processes in real time have attracted attention and resources from a number of neuroscientists. After initial encouraging reports, however, the field has not developed as quickly as expected, although, as described also here, a number of papers have been

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published. There are, clearly, difficulties that the research on EVs in neurodegeneration shares with the whole field of clinical application of EVs: clear definition of the objects (i.e. exosomes, microvesicles, apoptotic bodies, other), nomenclature (Gould and Raposo, 2013), technological limits in the detection and definition of EVs subtypes (Coumans et al., 2017; Witwer et al., 2013), their biological significance (Colombo et al., 2014). In Fig. 1 we have tried to depict what we hypothesize is, in very general terms, the source and path of EVs to biological fluids before analysis. Current knowledge on most steps is, however, extremely limited, hampering our ability to interpret the significance of EVs levels and content in physiological and pathological conditions. We show in Fig. 1 that neurons, astrocytes, oligodendrocytes and microglia are supposed to be the major source of EVs of neural origin during disease, along with ependymal and leptomeningeal cells when searching the CSF, and brain endothelial cells when searching the blood. Blood-derived infiltrating cells contributing to neuroinflammation during neurodegeneration are also a potential cellular source of EVs. We have limited information, however, on the stimuli inducing the release of EVs from neural cells and on their biological significance. We also ignore what kind of EVs have the ability to travel, and how, in the brain parenchyma and reach biological fluids (blood, CSF) where we can detect them. We have no conclusive data on how EVs are able to cross barriers such as the ependymal cell layer or the basal membrane and the brain endothelium, to gain access to CSF or blood. If EVs are messengers, we need to understand when and why cells release them, what message is delivered, what cells are the target of this communication. If EVs are released by cells to discard unwanted molecules, as a defence mechanism or to change phenotype, we need to understand the cellular pathways involved. Without this information, we cannot properly interpret the significance of their presence in biological fluids an their potential as biomarkers. In this review we try to summarize the knowledge gained in neurodegenerative diseases such as AD, PD, MS, ALS, and HD, focusing on human studies, since the lack of appropriate animal models is another major problem of the field. In Table 1 we report mentioned studies listed according to pathology, if they are human or experimental studies, and we specify techniques and markers used to detect EVs, to provide the reader the possibility to interpret the nature of investigated objects (Table 1).

Despite the hurdles and the technical difficulties, all the promises of EVs research in neurodegeneration are still intact. Current knowledge, that we hope to summarize here, sets the stage for exciting developments in the near future.

As mentioned, nomenclature is an issue, and as recommended by the reference Society (Gould and Raposo, 2013), we use here the term extracellular vesicles (EVs) whenever we have not clear indication from cited papers on a more specific nature of investigated objects, namely exosomes or microvesicles.

Alzheimer disease and other cognitive impairment

While the pathogenesis of Alzheimer disease (AD) remains unclear, all forms of AD appear to share overproduction and/or decreased clearance of amyloid beta peptides. The pathogenesis of AD also involves a second protein, tau. EVs are studied both in the pathogenesis of AD as well as possible biomarker able to predict conversion from Mild Cognitive Impairment (MCI) to overt AD. According to the current view, the accumulation of altered proteins (amyloid beta and tau) is toxic to neurons and EVs-mediated transmission of their pathologic forms between neurons has been proposed to account for the spread of AD in the brain (Guo and Lee, 2011; Iba et al., 2013; Medina and Avila, 2014). The potential role of EVs in AD is object of debate and evidences for both a beneficial and a detrimental role have been reported. More than ten years ago, it was first demonstrated that proteins and peptides (i.e. APP, APPC-terminal fragments, APP intra-cellular domain, Aβ) associated with AD are released in association with exosomes (Perez-Gonzalez et al., 2012; Rajendran et al., 2006; Sharples et al., 2008; Vingtdeux

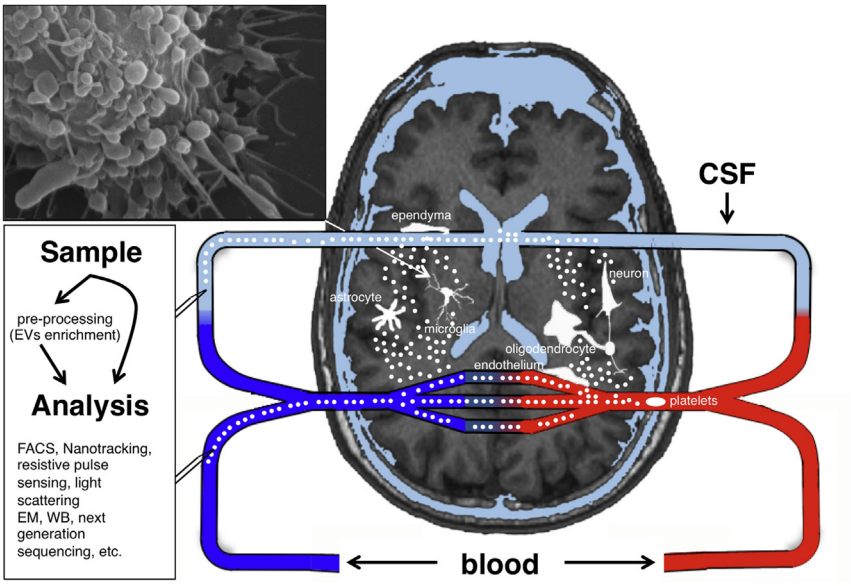

Fig. 1. EVs are released by all neural cells, those depicted and labeled here (neurons, oligodendrocytes, astrocytes, microglia, ependymal cells, brain endothelial cells), but in pathological conditions also blood-derived infiltrating inflammatory cells, or activated circulating cells such as monocytes and platelets may modulate EVs release. In the upper left panel we show a scanning electron microscopy of a human microglia cell-line (CHME-5), stimulated with ATP to release EVs. We ignore the precise nature of the stimuli and the biology of EVs release from neural cells in vivo. In the same way, we do not have a clear view on the path followed by EVs to reach biological fluids, namely the cerebrospinal fluid (CSF) or the circulation. Blood or CSF samples can be pre-processed (centrifuged, column-purified, etc.), to enrich for EVs and eliminate objects (proteic aggregates, other cell debris) that might interfere with the analysis. Freezing the sample for preservation will eliminate larger microvesicles and also some exosomes, with an unknown bias. Samples can be then analyzed by flow cytometry, nano tracking, light scattering, resistive pulse sensing, electron microscopy, western blot, next generation sequencing, etc.

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