Extracellular Vesicles and Synaptic Dysfunction in Alzheimer's Disease

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Alzheimer's disease (AD) is considered by many to be a synaptic failure. Synaptic function is in fact deeply affected in the very early disease phases and recognized as the main cause of AD-related cognitive impairment. In the brain, extracellular vesicles (EVs) are secreted by all cell types, including glial cells and neurons. They can affect the synapse and propagate synaptic alterations among connected cells in a way that poses them as attractive therapeutic targets.

Alzheimer's disease | extracellular vesicles | synaptic dysfunction

1. EVs Released by Microglia

Microglia, the innate immunity cells resident in the brain, are essential regulators of synaptic function and neuronal network formation [1]. They react to the smallest stimulus, being able to assume a various and complex range of activation states [2]. When brain homeostasis is endangered, microglia orchestrate a weighted response to re-establish the status quo [3]. Under sustained brain alterations, as in the case of AD (Alzheimer's disease), microglia undergo a neurodegenerative/disease-associated (MGnd/DAM) phenotypic change [4][5][6] and become determinants of disease pathogenesis [7]. Accumulating evidence suggests that DAM might play a positive and protective role in early disease pathology while in late AD stages, DAM might become dysregulated and accelerate the disease [8][9]. The central role of microglia in AD [10] and related synaptic dysfunction [11][12][13][14] has long been known, and the fact that many AD risk genes pertain to microglia and their functions strengthens this concept [10][15][16][17][18].

Several studies indicated that extracellular vesicles (EVs) released by microglia can influence synapse formation, inducing new spines at sites of contact with neurons [19], emulating what happens at microglia–synapse contact sites [20][21]. In addition, cultured neurons exposed to large EVs derived from primary rat microglia show an increase in miniature excitatory postsynaptic current (mEPSC) frequency in a dose-dependent manner, without changes in their amplitude [22]. Analysis of paired-pulse recordings showed that EVs mostly act at the presynaptic site, increasing neurotransmitter release probability [22] and the availability of synaptic vesicles for release [23]. The effect of microglial EVs was confirmed in vivo in cingulate cortex slices from the mouse brain [24], as well as in the rat visual cortex, where injection of large EVs caused an acute increase in the amplitude of field potentials evoked by visual stimuli [22]. Furthermore, a subsequent study showed that microglial large EVs are enriched in endocannabinoids, which are capable of inducing a decrease in miniature inhibitory post-synaptic currents (mIPSCs) targeting CB1 receptors on GABA-ergic cells [25]. More importantly, when microglia are exposed to an

inflammatory stimulus, they become detrimental for synaptic function by releasing EVs, which are enriched in a set of miRNAs that regulate the expression of key synaptic proteins. In particular, it can be demonstrated that large EVs from microglia activated by a cocktail of pro-inflammatory cytokines transfer miR-146a-5p to neurons, leading to the suppression of synaptotagmin 1, a pre-synaptic protein, and neuroligin 1, a postsynaptic adhesion protein that maintains synaptic stability and plays a key role in dendritic spine formation, with detrimental effects on synaptic strength and dendritic spine remodelling [26]. Similar effects on dendritic spines are mediated by small EVs released by primary mouse microglia inflamed after saturated fatty acid palmitate exposure, a model of a high-fat diet [27]. These findings link inflammatory microglia and enhanced EV production to loss of excitatory synapses.

This link was recently confirmed in models of AD, where the implication of large and small microglial EVs in synaptic dysfunction has also been demonstrated.

In a seminal paper, Asai and colleagues used a model of rapid tau propagation from the entorhinal cortex–EC to the dentate gyrus of the hippocampus–DG, together with in vitro systems, to demonstrate that tau propagates between these two regions, causing reduced excitability in DG cells as well as cytopathic changes [11]. Interestingly, tau spreading was limited by both microglia depletion and EV synthesis inhibition [11], while the working and contextual memory deficits were rescued in the P301S tau transgenic mouse model by treatment with a P2 × 7 receptor antagonist, which blocks EV release from microglia [28].

In line with these findings, microglial immune receptor Trem2 deletion in mice (*Trem2* KO), a condition known to aggravate tau pathology, enhances tau spreading from the EC to the hippocampus through small EVs, which coincides with impaired synaptic function and memory behaviour [29]. *TREM2* is in fact a risk gene for AD and an important regulator of microglia response to pathological changes. *R47H* heterozygous mutation of *TREM2* is linked to late onset AD, and small EVs released by microglia-like cells differentiated from iPSCs in patients carrying this variant (*R47Hhet* EVs) have been characterized. These EVs contain more inflammatory and DAM-associated proteins than common variant EVs (Cv EVs) [30]; they lose the ability to promote neurite outgrowth and neuronal metabolism; and lose their protective functions against AD-related insults to neurons [31].

Microglia large EVs have been shown to promote the solubilisation of amyloid beta (Aβ) aggregates, thus shifting equilibrium from an almost inert insoluble form of the peptide toward soluble and neurotoxic species [32][33][34]. In addition, when exposed to Aβ 1–42, microglia release large EVs already carrying neurotoxic Aβ species on their surface and in their lumen [19][32][33]. Once injected into the mouse EC, these Aβ-loaded EVs (Aβ–EVs) reduce synaptic transmission and consequently inhibit long-term potentiation (LTP). Interestingly, these effects are first detected in the vicinity of the injection site, but synaptic dysfunction then propagates from the EC to the hippocampus [19]. The spreading of synaptic dysfunction was ascribed to the ability of Aβ–EVs to move on the neuron surface, along axonal projections connecting the EC to the DG. Indeed, when Aβ–EV motility was inhibited, no propagation of LTP deficit along the entorhinal–hippocampal circuit occurred [19]. Although it has been reported that tau can be released inside microglia large EVs [35], no data are currently available on the role of such EVs in tau spreading.

Supporting an interplay between tau and Aβ in AD pathogenesis, the release of small tau-carrying EVs is higher from microglia surrounding Aβ plaques that phagocyte hyper-phosphorylated plaque-associated tau, as well as apoptotic neurons and synapses [36]. Notably, microglia phagocyte AD misfolded proteins and apoptotic structures aiming at their clearance [37], and exploited EV release at least in part as a disposal mechanism [19][32], as other cells do [38][39][40][41].

In accordance with all these studies, large EV production from myeloid cells (microglia/macrophages) is very high in AD patients and correlates with white matter lesions and hippocampal atrophy in prodromal AD, the preeminent expression of neuronal damage in the human brain [42]. In addition, the neurodegenerative microglia signature is enriched in brain-derived small EVs from CAST.APP/PS1 AD mice [43].

2. EVs Released by Astrocytes

Astrocytes play important roles in neuronal support, maintaining brain homeostasis of ions and neurotransmitters. They represent a fundamental component of the synapse, being part of the so-called "tripartite synapse" together with the pre-synaptic terminal and the post-synaptic compartment [44][45]. Astrocytes are involved in synapse formation, can regulate synaptic transmission, and can also eliminate synapses. Accordingly, similarly to microglial EVs, large EVs released by astrocytes promote excitatory synaptic transmission [22] and move extracellularly, inducing spine formation at sites of stable contact [46], while small EVs carry the neuroprotectant neuroglobin [47], promote neurite outgrowth and neuron survival, and also stimulate synaptic transmission and formation [48][49]. Nevertheless, upon interleukin 1β exposure of donor rat or human primary astrocytes, released small EVs undergo neuronal uptake more frequently than EVs from control cells and are able to inhibit neurite outgrowth, neuronal branching, and firing [48][50].

Like microglia, astrocytes are central players in AD pathology [51] and show early changes in the disease [10][52]. Those close to dystrophic neurites or Aβ plaques alter their morphology, becoming hypertrophic or atrophic [53], as well as their gene and protein expression, displaying a heterogeneous range of activation states [54][55]. In tauopathies, mouse model astrocytes display early functional deficits and lose their neuro-supportive function [56]. In addition, tau accumulation in astrocytes of the DG of the hippocampus, a phenomenon also found in the brain of AD-affected individuals, has been found to cause neuronal dysfunction and memory deficits in mice [57].

Astrocytes are very efficient in engulfing dead cells, synapses, and protein aggregates (e.g., of Aβ) [58][59][60][61][62][63][64], and astrocytes with high Aβ load are frequently found in the AD-affected brain [65]. However, as opposed to microglia, astrocytes are extremely inefficient at degrading phagocytosed material [66], including Aβ 1–42 protofibrils [67]. Aβ accumulation in astrocytes over a very long time further affects endosomal and lysosomal function and induces the release of EVs carrying Aβ (in its N-terminal truncated form) and ApoE to favour elimination of undegraded materials [67][68][69][70]. Furthermore, the Aβ 1–42 proxy Aβ 25–35 induces phosphorilated-tau overproduction in human astrocytes in culture and increases its release within small EVs [71]. EVs carrying Aβ/phosphorylated tau are neurotoxic, causing synaptic loss, axonal swelling, vacuolization of

neuronal cell bodies, severe mitochondrial impairment, cholesterol deposits in lysosomal compartments, and apoptosis [68].

The first evidence of the involvement of EVs released by astrocytes in AD progression came from the finding that, in response to Aβ, astrocytes release small EVs containing prostate apoptosis response 4 (PAR4) and ceramide, which induce apoptosis in other astrocytes upon internalization, likely contributing to neurodegeneration [72]. Interestingly, vesicular ceramide was later found to be responsible for astrocyte small EVs' ability to aggregate Aβ peptides [73]. Subsequently, phosphorylated tau and proteins of the Aβ 1–42 peptide-generating system were found in astrocyte-derived small EVs extracted from the plasma of AD patients [74] as well as various complement proteins that are central players in synaptic pruning [75][76]. In line with this evidence, when isolated from AD patients, astrocyte EVs were more efficient than neuron EVs in inducing complement-mediated neurotoxicity and in reducing neurite density and decreasing cell viability in either cultured neurons or human iPSC-derived neuron-like cells [77].

Additional proofs of the implication of astrocyte EVs in AD progression came from: (i) the enrichment in astrocyte-derived molecules in AD EVs compared to EVs from mild cognitive impairment (MCI) patients [78][79], and (ii) the most significant association of a protein module enriched in astrocyte-specific EV markers with AD pathology and cognitive impairment compared to the proteome of other brain cell-derived AD EVs [80].

Despite extensive evidence suggesting important roles for EVs released by astrocytes in AD synaptopathy evolution, further studies will be necessary to gain a clearer understanding of their early action on the synapse.

3. EVs Released by Neurons

During development, neural stem cells can secrete EVs capable of affecting the proliferation and differentiation of neighbouring cells through the propagation of specific miRNAs able to reprogram multiple cellular mechanisms in recipient cells [81][82]. In the mature nervous system, neurons maintain their ability to produce EVs and use these vesicles to communicate with other cells and to regulate several phenomena such as homeostasis, immune response, and synaptic plasticity [83][84]. Although neuronal-derived EVs have been shown to interact with glial cells and affect microglia phagocytic activity [85] and the expression of the glutamate transporter GLT1 in astrocytes [86], in vitro studies suggested that EVs secreted by cortical neurons preferentially bind to other neurons [87], allowing neuron-to-neuron diffusion of specific cargoes. In addition, EV release has been shown to be strongly modulated by synaptic activity [88][89][90].

Neuron-derived EVs could be differentiated from the ones produced by other cell types by the expression of specific markers, such as the L1 cell adhesion molecule (L1CAM), the GluR2/3 subunits of the glutamate receptors, and the GPI-anchored prion protein [88][91]. However, the prion protein was also later identified in astrocyte-derived EVs [46][92].

Given their ability to move from cell to cell, neuronal EVs have been hypothesized to be able to spread along a neural network of connections in a trans-synaptic manner and contribute to the propagation of misfolded proteins in neurodegenerative diseases such as AD.

Indeed, the amyloid precursor protein (APP) and its metabolites, including the Aβ peptide, have been shown to be secreted within neuron-derived small EVs [93][94][95][96][97]. In addition, Sardar Sinha and colleagues [98] demonstrated that the impairment of the formation/secretion of small EVs can suppress the diffusion of Aβ oligomers to other neurons.

Interestingly, as opposed to microglial large EVs, neuronal and neuroblastoma cell line small EVs seem to promote amyloidogenesis of soluble Aβ through the binding of the amyloid peptide to the glycosphingolipid glycans [34][99][100] and to the cellular prion protein (PrP^C) [101][102] present on their surface. Neuronal small EVs contain higher levels of glycosphingolipid glycans in their membrane compared to small EVs secreted by other cell types, and this significantly increases Aβ affinity for neuronal-derived EVs [103][104]. The interaction between the Aβ peptide and neuronal EVs can lead to accelerated Aβ fibril formation and, therefore, drive conformational changes in the Aβ to form nontoxic amyloid fibrils [99]. Indeed, small EV markers such as Alix have been observed to be concentrated in senile Aβ plaque in AD brains [93]. Furthermore, PrP^C on small EVs negatively regulates Aβ 1–42 uptake by neuronal cells [102] while, on the other hand, neuron-derived small EVs can be efficiently internalized by microglia and promote Aβ degradation, suggesting an overall protective effect of neuron-derived EVs against AD pathology [99][105], as opposed to microglia large EVs [32]. This suggests that neuronal small EVs and microglia large EVs may play very distinct roles in neurodegeneration. In agreement with this hypothesis, protective effects against Aβ-induced pathology and synaptic transmission have been observed following chronic administration of small EVs derived from neuroblastoma cells or primary neurons in the hippocampus [100][103], and a significant rescue of Aβ-induced LTP impairment has been observed after the intracerebroventricular infusion of small EVs in rats [106], strengthening the link between neuronal-derived EVs and neuroprotection. In contrast, EVs released from cultured human neurons and cell lines harbouring familial AD presenilin 1 mutations show neurotoxicity towards cultured wild type neurons in terms of intracellular calcium regulation, mitochondrial functions, and sensibility to excitotoxicity [38].

By means of immunoassays specifically designed to detect the full-length tau protein, considered to be the aggregation-competent form, Guix and colleagues [107] revealed that small EVs secreted by human iPSC-derived neurons or present in human biofluids are highly enriched in full-length tau compared to the extracellular solution, indicating that neuronal EVs carry aggregation-competent tau proteins. In addition, neuronal small EVs could mediate the trans-synaptic propagation of tau protein regardless of its phosphorylation state, in an activity-dependent manner [108], but unfortunately their neurophysiological correlates in vivo have not been explored yet. Interestingly, in analysing neuronal EVs isolated from the plasma of AD and frontotemporal dementia patients, a correlation between the vesicular levels of some synaptic proteins and patients' cognitive status have been defined, mirroring the decrease in synaptic proteins and the synaptic dysfunction in the affected brain [109][110].

4. Mixed EV Populations Isolated from Body Fluids or Brain Tissue

In an increasing number of papers, small EVs isolated from the interstitial space of brain tissue or body fluids (mainly cerebrospinal fluid (CSF) and plasma) have been investigated. These samples represent a real liquid biopsy of the system (animal or human) they are coming from and a window on the microenvironment of specific tissues/compartments in these organisms in a particular situation (e.g., stage of pathology). For this reason, these specimens have been particularly useful for the study of biomarkers for the diagnosis and prognosis of different diseases, including AD and related cognitive defects [39][74][75][111][112][113][114][115][116]. On the other hand, EVs from brain tissue and body fluids are mixed populations of EVs of different cell origins, and the extraction of cell-type-specific EVs is possible only after an additional step of immunoisolation (e.g., in [117]).

As mentioned above (EVs released from astrocytes), small EVs isolated from AD brains typically express more glia- than neuron-derived molecules compared to EVs from healthy subjects [111], and those isolated from the brain of AD mouse models indicate that Aβ can be processed and oligomerized in EVs [118]. Studies on small EVs from human plasma and CSF corroborated the prevalent exposure of Aβ peptides on the surface of EVs [38][119]. A fascinating hypothesis is that binding to the EV surface may be the basis for the low CSF levels of Aβ 1–42 that typically correlate with AD [34]. On the other hand, small oligomeric globular tau, together with other isoforms, phosphorylated or not, have been found inside EVs from tauopathy mice models and AD patients [11][78][98][108][111][112][120] and display an elevated tau seeding activity [78][108][121]. Tau particles have been visualized in the inner leaflet of the EV membranes by electron microscopy [11], and the exposure of even a small portion of tau oligomers on the outer membrane leaflet is highly controversial [78].

Joshi and colleagues were the first to report that EVs isolated from the CSF of AD patients affect neuronal calcium homeostasis and are neurotoxic [32]. A subsequent study showed that small EVs from AD CSF samples are internalized by neurons and affect mitochondrial function, making the cells more vulnerable to excitotoxicity [38]. After internalization, small EVs can be degraded into lysosomes or transfer their content to the cytosol. However, two independent studies recently revealed that small EVs from mouse models and AD patients can avoid disassembly and, still intact, can transport Aβ and tau in an anterograde manner along axons and migrate trans-synaptically to a connected neuron in vitro [98][122] (**Figure 2**). Interestingly, this might occur also in vivo: small EVs isolated from the plasma of healthy mice and injected into the DG of the hAPP-J20 AD mouse model were engulfed by microglia surrounding Aβ plaques. However, a fraction of them not engulfed by microglia propagated through the hippocampus and up to the cortex in 20 days [123].

A first clue that small EVs are able to induce and propagate neurophysiological dysfunction in the AD brain came from a study from Dr. Ikezu's laboratory. In this work, Ruan et al. showed significant spreading of abnormally phosphorylated tau in both the contralateral and ipsilateral hippocampus 4.5 months after inoculation of EVs derived from the brain of prodromal AD and AD patients in the outer membrane layer of the DG [78]. Unexpectedly, tau was mainly found in the GAD67+ interneurons and GluR2/3+ mossy cells in the hilus region of the hippocampus. On the other hand, tau oligomers and fibrils isolated from the same subjects and injected in equal

amounts caused very limited tau pathology. Importantly, these phenomena were associated with intrinsic synaptic dysfunction of CA1 pyramidal neurons and reduced input from interneurons and were mediated by tau seeding caused by inoculated EVs.

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