Plasma extracellular vesicles from the periphery as spreading vectors of Alzheimer's disease pathogenesis?

Bruno Vincent [a,b]*

[a]Institute of Molecular Biosciences, Mahidol University, Nakhon Pathom 73170, Thailand
[b]Centre National de la Recherche Scientifique, 2 rue Michel Ange, Paris 75016, France

eBioMedicine 2022;78: 103961
Published online xxx
https://doi.org/10.1016/j.ebiom.2022.103961

The incessant and inevitable increase in the aging of the population makes Alzheimer's disease (AD) a major public health problem, with the multifactorial nature of this neurodegenerative disorder adding extra complexity in the search for effective therapies. Nevertheless, it is widely recognized that a loss of balance in the metabolism of the β-amyloid precursor protein (βAPP) by the catalytic activities called "secretases" is among the early triggering events of the disease and happens to be the basis of the amyloid hypothesis.[1] However, the old concept that the built up of amyloidose is neuron-centric and takes place in a static and local way (each cell/brain area contributes, independently of the others, to its own production of amyloid peptides) has been long debated[2] and was further called into question by the evidence of the existence of AD-related protein-containing brain-derived extracellular vesicles[3] that may eventually contribute to the dissemination of amyloidogenesis from one to another brain area.[4] Indeed, pEV have long been described as important inter-cellular communication factors that can easily cross the blood brain barrier[5] and have more recently been proposed for therapeutic purposes[6] and as a possible source of biomarkers.[7]

In this issue of eBioMedicine, Lee and co-workers have undertaken to purify, quantify and characterize plasma extracellular vesicles (pEV) from AD patients according to their secretase contents and they have investigated the route taken by these vesicles, prepared from cell lines and injected into mice, to eventually reach the brain from the periphery.[8] They first reported an abnormally high number (>100-fold) of pEV in AD patients (AD-pEV) when compared to control individuals. Moreover, they showed that these AD-pEV, in addition to being particularly rich in pro-inflammatory factors, contain excessive amounts of catalytically active α-, β- and γ-secretases, which could possibly lead to an increased metabolism of βAPP in target neurons. In their following attempt to determine if and how these AD-pEV can access the brain from the periphery, Lee et al. injected aluminum chloride-induced EV (Al_3-EV) purified from hepatocytes in the tail of mice. They showed that these vesicles, similar to AD-pEV in factor content, can reach hippocampal neurons via hyaluronan-dependent docking to the choroide plexus and they proposed that this could potentially exert detrimental effects when reaching target cells at high levels and for extended time periods.

As a whole, the study by Lee et al. brings a new concept by suggesting the existence of a hitherto unknown communication axis that would allow peripherally produced pEV to enter the limbic system and more especially the hippocampus that is particularly affected in AD. Notably, these vesicles show a high load of proteases involved in βAPP metabolism (ADAM10, ADAM17, BACE1 and the catalytic core of γ-secretase presenilin 1) and neuroinflammation (ADAM10 and ADAM17), two events closely linked to the pathogenesis of AD. However, due to the antagonism of the amyloidogenic (β/γ) and non-amyloidogenic (α) pathways with regard to the development of the disease,[9] and considering that they are all highly upregulated in AD-pEV, the respective contributions of these activities and the net balance at the target site of action would certainly be informative. In this context, establishing the full profile of production of βAPP-derived secretase-forming metabolites (sAPPα, C83, sAPPβ, C99) would help to clarify this point.

Despite the notable differences observed between the Alzheimer's samples and the controls the limited number of human plama (3-6AD/2-4CT depending on the parameters measured) and more especially brain (3AD/3CT) samples used in this study does not make it possible to guarantee in a certain way the formal implication of pEV in the progression of AD. Moreover, the convincing demonstration that cell line-derived Al_3-pEV reach the hippocampus via the choroid plexus in mice does

DOI of original article: http://dx.doi.org/10.1016/j.ebiom.2022.103903

*Correspondence to: Institute of Molecular Biosciences, Mahidol University, Nakhon Pathom 73170, Thailand.
E-mail address: bruno.vin@mahidol.ac.th

not allow us to affirm with certainty that this happens in the same way in humans.

The directions arising from this work could be of several kinds. Firstly, although Lee et al. stated that the observed drastic increase in pEV in AD samples are unlikely to originate from the central nervous system since any high secretory activity of diseased brain cells has been reported so far, additional investigations are obviously necessary to determine precisely the nature of the peripheral cells/organs that genuinely produce these AD-pEV vesicles in addition to hepatocytes, as suggested by the authors. Secondly, establishing the spatio-temporal profile of the secretase-dependent production of βAPP metabolites, i.e. determine whether it occurs predominantly before the release of EV by peripheral cells/organs, in pEV during its transportation to the brain (as suggested by the presence of Aβ in these structures[10]) or at site once the hippocampal targeted cells are reached, would certainly shed more light on the overall new concept proposed by Lee et al. Finally, demonstrating that the peripheral injection of AD-like pEV (Al3-pEV) induces AD-like events (amyloidogenesis, learning and memory impairment, neuroinflammation) in aged wild-type mice, and establishing that it accelerates AD pathogenesis in transgenic mouse models of the disease would bring the definitive proof of a causative role of pEV in AD.

In summary, beyond the possible use of pEV release from the brain to the plasma as a source of AD biomarkers, whether these structures can also, remotely and in the opposite direction, participate to the propagation of the disease was speculative so far. In this context, Lee et al. brought an additional stone to the concept of a dynamic relationship between the periphery and the CNS regarding AD pathogenesis by showing that peripheral EV can reach the brain *in vivo*. This exciting discovery obviously deserves more investigations to establish a genuine causal roles of pEV in the retrograde dissemination of AD.

Contributors

BV is the sole author.

Declaration of interests

The author declares no conflict of interests.

Acknowledgements

BV is funded by Mahidol University (grant NDFR-13/2564).

References

1 Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. *Science*. 2002;297(5580):353–356. https://doi.org/10.1126/science.1072994.
2 De Strooper B, Karran E. The cellular phase of Alzheimer's disease. *Cell*. 2016;164(4):603–615. https://doi.org/10.1016/j.cell.2015.12.056.
3 Fiandaca MS, Kapogiannis D, Mapstone M, et al. Identification of preclinical Alzheimer's disease by a profile of pathogenic proteins in neurally derived blood exosomes: a case-control study. *Alzheimers Dement*. 2015;11(6):600. https://doi.org/10.1016/j.jalz.2014.06.008. -7 e1.
4 Hill AF. Extracellular vesicles and neurodegenerative diseases. *J Neurosci*. 2019;39(47):9269–9273. https://doi.org/10.1523/jneurosci.0147-18.2019.
5 Arraud N, Linares R, Tan S, et al. Extracellular vesicles from blood plasma: determination of their morphology, size, phenotype and concentration. *J Thromb Haemost*. 2014;12:614–627. https://doi.org/10.1111/jth.12554.
6 Iannotta D, Yang M, Celia C, et al. Extracellular vesicle therapeutics from plasma and adipose tissuse. *Nano Today*. 2021;39: 101159. https://doi.org/10.1016/j.nantod.2021.101159.
7 Palviainen M, Saraswat M, Varga Z, et al. Extracellular vesicles from human plasma and serum are carriers of extracellular cargo-implications for biomarker discovery. *PLoS One*. 2020;15:(8) e0236439. https://doi.org/10.1371/journal.pone.0236439.
8 Lee JH, Ostalecki C, Oberstein T, et al. Alzheimer's disease protease-containing plasma extracellular vesicles transfer to the hippocampus via the choroid plexus. *eBioMedicine*. 2022;77: 103903. https://doi.org/10.1016/j.ebiom.2022.103903.
9 Schaduangrat N, Prachayasittikul V, Choomwattana S, et al. Multidisciplinary approaches for the targeting of the secretase protein family as a therapeutic route for Alzheimer's disease. *Med Res Rev*. 2019;39(5):1730–1778. https://doi.org/10.1002/med.21563.
10 Rajendran L, Honsho M, Zahn TR, et al. Alzheimer's disease beta-amyloid peptides are released in association with exosomes. *Proc Natl Acad Sci USA*. 2006;103(30):11172–11177. https://doi.org/10.1073/pnas.0603838103.