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BRAINSTORM STUDENT JOURNAL

REVIEW

The role of exosomes in physiology and pathology

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Abstract

Exosomes have gained the attention of the neuroscience community due to their ability to cell-cell communication and regulate the functions of central nervous system cells. Additionally, exosomes act as "cargo" by transporting proteins, miRNA, and lipids that can modulate cellular functions within recipient cells. However, there is still a need for a better understanding of the precise molecular pathways involved in targeting signaling cascades that lead to the proper phenotype of cells in various mouse models, thereby impacting their behavior. In various diseases, exosomes play a crucial role, such as seeding p-Tau protein in Alzheimer's disease, promoting anti-inflammatory processes in traumatic brain injury, or creating an environment for the development of glioblastoma cells. Indeed, exosomes can be found in biological fluids, including plasma, and hold potential as valuable tools for detecting disease-specific markers and managing patient care in medicine. In this review, we will explore the formation and secretion of exosomes in the extracellular space. Lastly, we will discuss important mechanisms underlying exosome-mediated cell communication in both healthy and diseased conditions.

Keywords

Exosome, cell-cell communications, astrocytes, microglia, Alzheimer diseases, traumatic brain injuries, glioblastoma

Introduction

In multicellular organisms, small extracellular vesicles (EVs) can be released in the extracellular space (1,2). Cells that are able to secrete EVs can be eukaryotic and prokaryotic (3), and recently there has been a growing interest in the field of neurosciences to better understand these EVs. There are three important types of EVs based on their biogenesis and size:

- Exosomes (50 – 150 nm): nanoparticles derived from an invagination of the early endosome membrane.
- Macrovesicles (100 – 1000 nm): derived from evagination of the plasma membrane.
- Apoptotic bodies (1000 – 5000 nm): vesicles that are a product of programmed cell death, subsequently engulfed by macrophages for degradation (4).

The focus of this review will be exosomes. Exosomal membrane contains lipids, such as: cholesterol, sphingolipids, ceramide, and glycerophospholipids. The proportion of these lipids determines membrane fluidity (5). The exosomal signature is provided by several proteins that coat them and allow their identification (6), for instance tetraspanins (CD81, CD63, CD9). Importantly, specific membrane markers are of interest in that they can provide clues as to the origin of the cell itself. Among these markers, L1 cell adhesion molecule (L1CAM) has been studied to obtain neuronal EVs released, but the development of such markers to identify the cell type that releases these exosomes is still ongoing (7). The main function of exosomes is the promotion of intercellular communication, which is essential in maintaining a proper cellular function. Exosomes can transport proteins, miRNAs, which are internalized in different manner by their respective recipient cells to regulate various biological functions, while lipids will anchor in the cell membrane. Interestingly, the content of exosomes differ according to the cell origin (8).

In the central nervous system (CNS) all cells are able to release exosomes (9) in response to various kinds of signal, such as in response to neuronal activity (1). Furthermore, various studies have highlighted that inflammation can also influence the quantity of exosomes released in the inflammatory environment (8,10).

Importantly, exosomes play a role in several diseases. It has been shown that exosomes are involved in the pathogenesis of certain neurodegenerative diseases by promoting the spread of misfolded proteins, including p-Tau, amyloid-β, and α-synuclein (11). Interestingly, exosomes can cross the blood-brain barrier, and have been found in biological fluids such as cerebrospinal fluid (CSF) and plasma. In this context, exosomes have been proposed as biomarkers for medical diagnosis, as this can allow the detection misfolded proteins in these fluids (12).

Methods

Articles were acquired through PubMed and Google scholar searches done for the following terms: Exosome, cell-cell communications, astrocytes, microglia, Alzheimer diseases, traumatic brain injuries, glioblastoma.

Results

Exosome formation and secretion

Exosome formation is initiated by the invagination of the endosomal membrane, leading to the generation of intraluminal vesicles (ILVs). ILVs consist of various sub-fractions of vesicles of varying sizes, including exosomes. The accumulation of several exosomes inside the luminal part leads to a multi-vesicular body (MVB). Once these MVBs are generated, they can have different fates (4). They either go into the lysosome where they are degraded, or they fuse with the plasma membrane to release the exosomes into the extracellular space. This release is known as the

exocytosis of exosomes, which has been discovered with the aid electron microscopy (13).

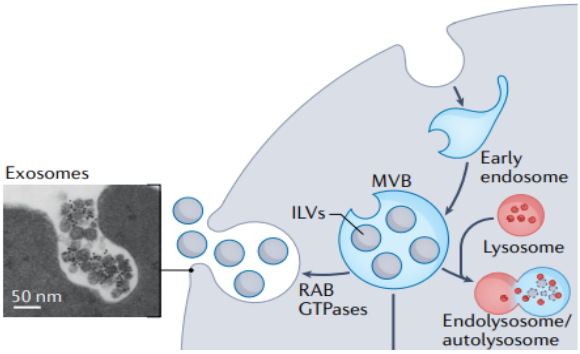

Figure 1. Exosomes trafficking. Exosome biogenesis is a multistep process. It starts by an invagination of the cell membrane that encapsulates extracellular elements and leads to the formation of an early endosome. Early endosomes then mature into late endosomes to form MVBs. At this stage, the membrane of endosomes can also invaginate to generate ILVs inside the MVBs, including exosomes, macrovesicles, and apoptotic bodies. The MVBs are either transported to the lysosome to be degraded or they are translocated at the plasma membrane to release their content. Extracted from Dixson et al. (2023).

Following this, the MVBs are anchored at the plasma membrane by the SNAp Receptor (SNARE) complex which mediates vesicles fusion with the membrane. SNARE complex is involved in the signal-dependent release. The signals that allow this fusion between the MVB membrane and the plasma membrane can be intracellular or extracellular. In neurons, the release of exosomes depends on the influx of calcium, driven by the NMDA and AMPA receptors (1) .

A method has been developed to quantify in real time the total amount of exosomes released with the aid of total internal reflection fluorescence microscopy (14). This method is based on tagging the tetraspanin proteins, CD63, with a pH-sensitive fluorescent green protein. This tag, known as CD63-Phluorin, has been used *in vivo* in zebrafish embryos, which are transparent, allowing single-vesicle tracking from their production sites to their destination. This approach might contribute to our understanding of the tropism of exosomes derived from particular cell types (15).

Exosomes in cell-to-cell communication

Once exosomes are released in the extracellular part, they can participate in intercellular communication either at the release site or migrating into other parts of the body, and eventually even crossing the blood brain barrier (16). Exosomes uptake can occur through three ways:

- Endocytosis: which involves the invagination of the plasma membrane to form a vacuole for subsequent uptake of the exosomes.
- Macrophagocytosis: a cellular process in which the plasma membrane forms protrusions that can coated exosomes, and this is actin-dependent process.
- Phagocytosis: an invagination of the plasma membrane, but one that leads to the degradation of exosomes in the lysosome. This process together with macrophagocytosis are actin-dependent, and lead to small movements of the plasma membrane (17).

In the central nervous system (CNS), exosomes can be taken up by all cell types, including the glial cells and neurons. They contribute to the homeostasis of the CNS and the neuron-glial communications. Here, we will review how the uptake of exosomes by glial cells regulates their cellular mechanisms.

Astrocytes

Among glial cells, astrocytes contribute to the CNS formation, provide metabolic support, and regulate synaptic transmission (18). The uptake of exosomes by astrocytes has primarily been studied in cell culture, but recent technological advances have facilitated their investigation in complex organisms. In vivo subcellular localization of exosomes derived from neurons and their uptake by astrocytes in physiological conditions are not yet known. To investigate this, exosomes derived from neurons were studied using a genetically modified mouse

model, Calmodulin-dependent protein kinase II (CaMKII)-CreER+CD63-GFPf/+, where CaMKII is a protein predominantly found in excitatory neurons. Fluorescence emission was induced by intraperitoneal injection of 4-OHT, resulting in clear expression of CD63-GFP-expressing exosomes derived exclusively from excitatory neurons. Simultaneously, the mice were injected with excitatory amino acid transporters (EAAT2)-tdT+ in the sciatic nerve, which is a specific promoter to astrocytes expresses the glutamate transporter, to determine the sub-localization of GFP-labeled exosomes in astrocytes expressing glutamate transporter. In vivo characterization revealed that exosomes derived from excitatory neurons are enriched in miRNA-124, a non-coding RNA that regulates neurobiological function within astrocytes, enabling communication between neurons and astrocytes to regulate cellular mechanisms. One of these cellular mechanisms involves exosomes derived from excitatory neurons, which are enriched in miRNA-124 with the ability to upregulate the expression of the glutamate transporter GLT-1 in astrocytes, playing a crucial role in the uptake of glutamate. This upregulation of GLUT-1 expression in astrocytes has a direct impact on synaptic transmission (19).

Microglia

Microglia, the resident immune cells in the brain, appear to regulate several functions in the CNS. Microglial cells scan the environment, regulate synaptic physiology and also the neuroinflammatory processes (20). How the uptake of exosomes by microglia regulates their functions is still an open question.

A study highlighted that neuronal exosomes could modulate the activity of microglia to promote synapse pruning. To investigate this, the research group stimulated neurons in culture to release and collect exosomes derived from them. Exosomes were added in a Petri dish containing PC12 rat cells derived from pheochromocytoma in co-culture with MG6 cells, both of which are immortalized human microglia. Then, they evaluated the effect of neurite engulfment by MG6 cells allowing the regulatation of synapse pruning. MG6 cells showed an upregulation of pro-phagocytic genes such as C3, indicating their essential role in regulating synapse pruning (21); however, this study has revealed many limitations associated with the use of PC12 and MG6 cells. It is important to note that these cells may not accurately represent the complex physiological conditions that are observed in vivo.

Exosomes in pathology

Alzheimer's disease

Alzheimer's disease (AD) is a neurodegenerative disorder associated with the loss of neuronal structures and functions, ultimately leading to neuronal death. There are two main markers observed in AD. First, patients exhibit an accumulation of senile plaques, also known as β-amyloid plaques. These plaques are formed by the aggregation of β-amyloid peptides, which are produced through successive aberrant proteolytic cleavages of the cell membrane glycoprotein amyloid precursor protein that tend to cluster in the extracellular space. Second, AD is characterized by the formation of neurofibrillary tangles, which result from the accumulation and aggregation of p-Tau proteins inside the cells. This protein is essential for the stabilization of microtubules within the neurites, including dendrites and axons (22,23).

There is a consensus that AD begins in the entorhinal cortex. It has been hypothesized that misfolded proteins can spread through synaptic connections (24). In this context, microglia play a crucial role in clearing misfolded proteins, such as beta-amyloid plaques and neurofibrillary tangles, by engulfing and internalizing them (20). Their involvement in the spreading of tau pathology has gained interest in the past decade. Authors of Asai study used AAV vectors to inject p-Tau protein in the entorhinal cortex, which is thought to be the starting point of AD. This resulted in an accelerated seeding at the level of the dentate gyrus. To demonstrate that microglia played a key role in the seeding of p-Tau protein in the dentate gyrus, they used a chemical inhibitor of microglia known as PLX3397. This resulted in a reduction of p-Tau

protein seeding at the dentate gyrus; however, recent findings suggest that exosomes can also contribute to the spread of misfolded proteins. Inhibition of exosome secretion with the chemical inhibitor GW4869 led to a significant decrease in the spreading of p-Tau around the injection site, suggesting that exosomes play an important role in seeding p-Tau (25). Authors from another study used the P301S model with a microglial deletion of Trem2, a genetic factor related to AD development. They found that this model showed an increase of the spread of exosomes from the entorhinal cortex to the dentate gyrus. This deletion was also related with an increased production of exosomes enriched in p-Tau in the endosome or MVB compartment. These findings suggest that the deletion of Trem2 regulates the exosomes production in microglia (26).

Glioblastoma

Zeng's study has found that glioblastoma, which arises due to several mutations in glial cells, can secrete EVs that modify its environment, promoting angiogenesis and an immunosuppressive effect that facilitates the growth of glioma cells. These EVs were then taken up by the astrocytes in culture samples. The EVs derived from glioblastoma transformed matured astrocytes into pre-neoplastic astrocytes by inducing changes in their proliferation and growth. The study also reported a trend toward an increase of gene expression, glucose metabolism, and oxidative metabolism. Taken together these results indicate that the exosomes derived from glioblastoma are able to change astrocytes into tumor-like cells (27)

Traumatic brain injury

Neuro-glial communication has been extensively studied, but what about communication among glial cells themselves? In case of post-traumatic brain injury (TBI) in a mouse model, exosomes derived from astrocytes appear to regulate the inflammatory phenotype in microglia. By using a transcriptomic approach, they identified that exosomes are enriched in lncRNA 4933431K23Rik enabling to regulate some neuroinflammatory processes. Among them, lncRNA 4933431K23Rik appear to regulate the Samd7 gene expression in microglia by reducing the gene level of Samd7. The Samd7 gene inhibits the Nf-Kb pathway, allowing to downregulate the inflammation of microglia to improve the recovery post-TBI and prevent spatial cognitive deficits (28).

Conclusion

This review highlights the crucial role of exosomes in maintaining body homeostasis, starting by revisiting exosome biogenesis. Further research is still needed to identify the constitutive secretion of exosomes. Exosomes are also involved in cell-to-cell communication, through which they regulate a number of neurobiological functions. There is an ongoing effort to better understand how exosomal content influences CNS functions. It is known that the content of exosomes varies depending on factors such as inflammation, aging, and several diseases such as AD (29). Moreover, the role of exosomes in the propagation of misfolded proteins observed in neurodegenerative disorders is reviewed here, with a focus on the p-Tau protein in AD. All in all, there is a growing interest on the study of exosomes, for instance the presence of different miRNAs. Indeed, since they can cross the blood brain barrier, exosomes and their content can be used as biomarkers for the detection of pathological conditions as exosomes can be extracted from blood plasma and their miRNA content analyzed. This would ultimately help clinicians to make more accurate diagnoses and delivering treatments personalized to meet patient needs (30).

References

(1) Fauré J, Lachenal G, Court M, Hirrlinger J, Chatellard-Causse C, Blot B, et al. Exosomes are released by cultured cortical neurones. Mol Cell Neurosci. avr 2006;31(4):642‑8.

(2) Taylor AR, Robinson MB, Gifondorwa DJ, Tytell M, Milligan CE. Regulation of heat shock protein 70 release in astrocytes: Role of signaling kinases. Dev Neurobiol. nov 2007;67(13):1815-29.

(3) Deatherage BL, Cookson BT. Membrane Vesicle Release in Bacteria, Eukaryotes, and Archaea: a Conserved yet Underappreciated Aspect of Microbial Life. Andrews-Polymenis HL, éditeur. Infect Immun. juin 2012;80(6):1948-57.

(4) Dixson AC, Dawson TR, Di Vizio D, Weaver AM. Context-specific regulation of extracellular vesicle biogenesis and cargo selection. Nat Rev Mol Cell Biol

(5) Raposo G, Stoorvogel W. Extracellular vesicles: Exosomes, microvesicles, and friends. J Cell Biol. 18 févr

(6) Pegtel DM, Gould SJ. Exosomes. Annu Rev Biochem. 20 juin 2019;88(1):487-514.

(7) Gomes DE, Witwer KW. L1CAM-associated extracellular vesicles: A systematic review of nomenclature, sources, separation, and characterization. J Extracell : 1(3)

(8) Zhang N, He F, Li T, Chen J, Jiang L, Ouyang XP, et al. Role of Exosomes in Brain Diseases. Front Cell Neurosci. 13 sept 2021;15:743353.

(9) Sharma P, Schiapparelli L, Cline HT. Exosomes function in cell–cell communication during brain circuit development. Curr Opin Neurobiol. déc 2013;23(6):997-1004.

(10) Tian Y, Cheng C, Wei Y, Yang F, Li G. The Role of Exosomes in Inflammatory Diseases and Tumor-Related Inflammation. Cells. 16 mars 2022;11(6):1005.

(11) Xiao T, Zhang W, Jiao B, Pan CZ, Liu X, Shen L. The role of exosomes in the pathogenesis of Alzheimer' disease. Transl Neurodegener. déc 2017;6(1):3.

(12) Yin Q, Ji X, Lv R, Pei JJ, Du Y, Shen C, et al. Targetting Exosomes as a New Biomarker and Therapeutic Approach for Alzheimer's Disease. Clin Interv Aging. 23 avr 2020;15:195-205.

(13) van Niel G, D'Angelo G, Raposo G. Shedding light on the cell biology of extracellular vesicles. Nat Rev Mol Cell Biol. avr 2018;19(4):213-28.

(14) Bebelman MP, Bun P, Huveneers S, van Niel G, Pegtel DM, Verweij FJ. Real-time imaging of multivesicular body–plasma membrane fusion to quantify exosome release from single cells. Nat Protoc. janv 2020;15(1):102-21.

(15) Verweij FJ, Revenu C, Arras G, Dingli F, Loew D, Pegtel DM, et al. Live Tracking of Inter-organ Communication by Endogenous Exosomes In Vivo. Dev Cell. févr 2019;48(4):573-589.e4.

(16) Banks WA, Sharma P, Bullock KM, Hansen KM, Ludwig N, Whiteside TL. Transport of Extracellular Vesicles across the Blood-Brain Barrier: Brain Pharmacokinetics and Effects of Inflammation. Int J Mol Sci. 21 juin 2020;21(12):4407.

(17) Mayor S, Pagano RE. Pathways of clathrin-independent endocytosis. Nat Rev Mol Cell Biol. août 2007;8(8):603-12.

(18) Santello M, Toni N, Volterra A. Astrocyte function from information processing to cognition and cognitive impairment. Nat Neurosci. févr 2019;22(2):154-66.

(19) Men Y, Yelick J, Jin S, Tian Y, Chiang MSR, Higashimori H, et al. Exosome reporter mice reveal the involvement of exosomes in mediating neuron to astroglia communication in the CNS. Nat Commun. 12 sept 2019;10(1):4136.

(20) Hickman S, Izzy S, Sen P, Morsett L, El Khoury J. Microglia in neurodegeneration. Nat Neurosci. oct 2018;21(10):1359-69.

(21) Bahrini I, Song J hoon, Diez D, Hanayama R. Neuronal exosomes facilitate synaptic pruning by up-regulating complement factors in microglia. Sci Rep. 23 janv 2015;5(1):7989.

(22) Lau V, Ramer L, Tremblay MÈ. An aging, pathology burden, and glial senescence build-up hypothesis for late onset Alzheimer's disease. Nat Commun. 25 mars 2023;14(1):1670.

(23) Selkoe DJ. Cell biology of protein misfolding: The examples of Alzheimer's and Parkinson's diseases. Nat Cell Biol. 1 nov 2004;6(11):1054-61.

(24) Miyoshi E, Bilousova T, Melnik M, Fakhrutdinov D, Poon WW, Vinters HV, et al. Exosomal tau with seeding activity is released from Alzheimer's disease synapses, and seeding potential is associated with amyloid beta. Lab Invest. déc 2021;101(12):1605-17.

(25) Asai H, Ikezu S, Tsunoda S, Medalla M, Luebke J, Haydar T, et al. Depletion of microglia and inhibition of exosome synthesis halt tau propagation. Nat Neurosci. nov 2015;18(11):1584-93.

(26) Zhu B, Liu Y, Hwang S, Archuleta K, Huang H, Campos A, et al. Trem2 deletion enhances tau dispersion and pathology through microglia exosomes. Mol Neurodegener. 2 sept 2022;17(1):58.

(27) Zeng A, Wei Z, Rabinovsky R, Jun HJ, El Fatimy R, Deforzh E, et al. Glioblastoma-Derived Extracellular Vesicles Facilitate Transformation of Astrocytes via Reprogramming Oncogenic Metabolism. iScience. août 2020;23(8):101420.

(28) He X, Huang Y, Liu Y, Zhang X, Wang Q, Liu Y, et al. Astrocyte-derived exosomal lncRNA 4933431K23Rik modulates microglial phenotype and improves post-traumatic recovery via SMAD7 regulation. Mol Ther. févr 2023;S1525001623000631.

(29) Kahroba H, Davatgaran-Taghipour Y. Exosomal Nrf2: From anti-oxidant and anti-inflammation response to wound healing and tissue regeneration in aged-related diseases. Biochimie. avr 2020;171-172:103-9.

(30) Gurunathan S, Kang MH, Jeyaraj M, Qasim M, Kim JH. Review of the Isolation, Characterization, Biological Function, and Multifarious Therapeutic Approaches of Exosomes. Cells.3 avr 20

BRAINSTORM STUDENT JOURNAL

LETTER

About holistic approaches in neuroscience

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A holistic approach is a methodological position that emphasizes the interconnection of pieces of information pertaining to a certain topic on different levels, in order to give a more global perspective on the topic only when they are taken as a whole. In the field of neuroscience, breaking down knowledge into isolated compartments is a limitation when it comes to elucidating brain-wide functions. As a consequence, finding the biological substrates underlying mental states and cognition poses a major challenge in neuroscience. In other words, describing cellular processes that take place in certain neuronal sub-populations remains essential to but insufficient in explaining complex brain functions. Similarly, exploring behavior while overlooking the biology behind it offers an incomplete picture, thereby preventing a full understanding of the observed phenomenon. Therefore, adopting a more holistic approach to neuroscience might be the key to unlocking answers to pertinent and unresolved questions in the field. In spite of the potential of such an approach, the scientific system seems reluctant to enable deep, structured collaborations between research teams working on a certain domain at different planes.

A collaborative approach that prioritizes networking among research teams and interdisciplinary collaboration has the potential to facilitate a more profound comprehension of brain functions.. An example of an initiative following this school of thought is the 'Marie Sklodowska-Curie Doctoral Networks' – in particular, the 'Cerebellum and Emotional Network', working on cerebellar research. This network brings together researchers from different countries and disciplines to investigate the cerebellum, a brain region that has traditionally been viewed as a simple motor structure, but is now known to be involved in many other functions, including cognition and emotion. By taking a holistic approach that combines cellular, systemic, and behavioral levels of analysis, this network aims to better understand the cerebellum's role in these diverse functions. Importantly, adopting a holistic approach does not necessitate the need for all scientists to be specialists in every aspect. Furthermore, such networks can avoid

duplication of research efforts and encourage interdisciplinary approaches, ultimately accelerating the pace of scientific progress.

In addition to the advantages to science and the economy, adopting a holistic approach to neuroscience can also boost individual careers by providing training to researchers in various fields relevant to their subject. As scientific research becomes increasingly interdisciplinary, researchers with expertise in multiple areas are becoming increasingly valuable. By participating in collaborative networks and taking a holistic approach to their research, neuroscientists can gain expertise in a wider range of methods and techniques, making them more attractive to potential employers and collaborators. Moreover, a more holistic approach can lead to more creative and innovative research, which can open up new areas of inquiry and lead to exciting new breakthrough discoveries. Scientific profiles that have been cultivated in a range of disciplines could introduce perspectives leading to refined and sophisticated ideas. In other words, they are likely to understand better the limitations that lie in the intersection of their disciplines of expertise, as well as propose solutions that minimize them.

While science is not meant to be profitable in the traditional sense, optimizing efforts and resources can still bring objective benefits. Investing in creating links between laboratories across different domains is compatible with both progress and preventing competitiveness. This not only benefits the scientific community, but also has practical implications in healthcare and technology. The absence of fundamental science undermines the foundation for applied science. Ultimately, the main goal of scientific research is to advance our understanding of the natural world. Holistic approaches seem like a promising strategy to make this progress possible, not only within the Neuroscience community but also beyond the frontiers between science and society.

DISSEMINATION ARTICLE

Alzheimer's disease: towards new treatments?

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This section has been created in collaboration with the Maison du Cerveau, an association that brings together all those involved with diseases from the nervous system. Our goal is to increase visibility and to provide information about these pathologies, treatments, and research advancements for the general public.

Discovered by Alois Alzheimer in 1906, Alzheimer's disease (AD) is a neurodegenerative disease, affecting around 10% of the population aged over 65 years old. It is the most common cause of dementia, characterized by memory loss and serious cognitive decline that appear with aging (1). The symptoms become worse progressively, from an early mild stage to a late severe stage when the patient must depend on others in his daily life. Diverse types of AD exist, from genetic origins to environmental factors such as lack of physical activity, wrong diet, or strong stress (1). Nowadays we have solutions to improve the symptoms but still no disease-modifying treatments. One of the main reasons is because the intervention is often too late: AD diagnosis is not simple and until date, early biomarkers (biological products by which the pathology can be identified) were not well defined. In this short article, we will focus on several new targets that would offer innovative therapies.

AD has two main features: plaques of amyloid beta (Aβ) and aggregation of the protein Tau (1). One of the main hypotheses in AD development is the Aβ theory, telling that Aβ are the first ones to appear and induce Tau accumulation (2). Extracellularly, amyloid is formed from Amyloid Precursor Protein, cut by two different enzymes (β and γ secretase) to become the Aβ. The degradation of Aβ decreases with age in AD patients leading to accumulation (2). When Aβ plaques are formed, neuronal communication is disrupted. On the other side, Tau protein contained inside the cells is involved in protein motility, but in AD it becomes hyperphosphorylated and dissociated, accumulating to form tangles (paired filaments). Tau aggregation is causing an impaired axonal transport which impaired neuronal communication, causing their early death (3). To counter this abnormal accumulation of protein, the immune cells of the brain, microglia, are activated to try to clean it up. Microglia become highly recruited but are not sufficient to destroy the plaques. At a severe stage of the disease, microglia enter a pro-inflammatory state that even increases neuronal damage, aggravating AD phenotype. Considering

the complexity of this neurodegenerative disease, implicating Aβ, Tau and inflammation, we can understand the lack of actual treatment to cure AD (1).

Following the major Aβ theory for AD development, the first logical target for disease-modifying treatment and biomarkers is the amyloid plaques. Recently, pre-clinical studies have shown the efficiency of passive immunotherapy. This "vaccine" is made of an antibody that targets abnormal Aβ and facilitates its removal from the brain (3,4). In 2014, two different therapies were tested but showed improved cognitive scores only when administrated in patients with early stages of AD. New monoclonal antibodies are currently used in clinical trials to try to improve their efficiency at any stage. Another strategy is to target enzymes responsible for the production of Aβ to inhibit the cleavage of the precursor peptide. Currently, multiple drugs acting on BACE1 (essential for the production of Aβ) are in development. First results in pre-clinical studies have shown a reduction of 40-fold in plaques levels. Despite a time-consuming and costly administration, Aβ immunotherapy is one of the most promising treatment types with a proved efficiency, especially in elderly people, and safety. Some vaccines also exist to target Tau accumulation but very few have reached the clinical test until now (4).

As mentioned before, microglia are important in AD development. They have a two-dimensional role, where they are helpful at early stage to become harmful at late stage of the disease (5). When microglia are overactivated, they induce an inflammatory response by destroying synapses, producing toxic products that accumulates and form an intracellular complex leading to cell death (6). By blocking the assembly of this complex, AD symptoms were improved in a rodent model, with a reduced Aβ accumulation, neuronal death, and inflammation. This complex also seems to be a very good biomarker, present more than 10 years before the onset of the disease. For clinical applications, a trial is currently undergoing since 2020.

Another strategy is to focus on the improvement of the symptoms more than to cure the causes of the disease. Cognitive-enhancement treatment is aiming at boosting cognitive function in AD patients, to improve their daily life (1). Accumulation of Aβ leads to impaired neurotransmitter activities that are crucial for a normal cognition. This therapy should re-establish the altered function by drug administration. Two main drugs have already been used in AD patients: cholinesterase inhibitors and memantine (3). Cholinesterase inhibitors work by reducing the cleavage of acetylcholine in the brain, which is important in neuronal communication. Memantine blocks the excessive excitatory activity in the brain observed in AD. A combination of these two chemicals provide benefits but has also some adverse effects (nausea, muscle twitching, diarrhoea, headache). Fixed-dose combinations of the two agents are available on the market. However, even if patients observed a cognitive improvement, in many others it only delayed their decline for a few months. This treatment is thus a provisional solution that increases the quality of life of AD patients.

As we can observe, many different targets are studied to find efficient and safe disease-modifying treatments for AD. Scientists are focusing on different steps in order to identify the best suited therapy that could actually combine several strategies. AD is one of the most common neurodegenerative diseases, explaining the urge to establish treatments. Fortunately, many clinical trials are ongoing, with some very promising ideas.

References

(1) Masters, C. L., Bateman, R., Blennow, K., Rowe, C. C., Sperling, R. A., & Cummings, J. L. (2015). Alzheimer's disease. Nature reviews. Disease primers, 1, 15056. https://doi.org/10.1038/nrdp.2015.56

(2) Breijyeh, Z., & Karaman, R. (2020). Comprehensive Review on Alzheimer's Disease: Causes and Treatment. Molecules (Basel, Switzerland), 25(24), 5789. https://doi.org/10.3390/molecules25245789

(3) Weller, J., & Budson, A. (2018). Current understanding of Alzheimer's disease diagnosis and treatment. F1000Research, 7, F1000 Faculty Rev-1161. https://doi.org/10.12688/f1000research.14506.1

(4) Briggs, R., Kennelly, S. P., & O'Neill, D. (2016). Drug treatments in Alzheimer's disease. Clinical medicine (London, England), 16(3), 247–253. https://doi.org/10.7861/clinmedicine.16-3-247

(5) Hansen, D. V., Hanson, J. E., & Sheng, M. (2018). Microglia in Alzheimer's disease. The Journal of cell biology, 217(2), 459–472. https://doi.org/10.1083/jcb.201709069

(6) Zhang, Y., Dong, Z. & Song, W. NLRP3 inflammasome as a novel therapeutic target for Alzheimer’s disease. Sig Transduct Target Ther 5, 37 (2020). https://doi.org/10.1038/s41392-020-0145-7

INTERVIEW

I see, therefore I want

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[1]Glia-neuron interactions team, Neurocentre Magendie, University of Bordeaux

In this new section of BrainStorm you will find interviews extracted from the website www.neuronhub.org founded by one of the members of the Editorial Board of BrainStorm (Juan Garcia-Ruiz).

What's neuronhub? It is an outreach website hosting interviews with researchers from all corners of the planet about their work in the field of neuroscience. The idea is that you get something from people who have a long career in science, that you learn something new and cool, and above all that you don't lose track of the latest discoveries in neuroscience that are being made in other parts of the world.

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I see, therefore I want

A man can do what he wills but cannot will what he wills.

Arthur Schopenhauer

Have you ever felt that they don't value your work as much as they should? Have you felt that they've gotten used to you just doing things right? If so, you'll agree that it's not nice. Well, you do the same thing! You undervalue the work your brain does inside your skull day in and day out, from the time you get out of bed until you get back into it! Just stop to think about how many things your brain ponders when someone asks you how you are doing. It's a vague question, too vague. But yes, it's true that the answer can be simple. Sometimes, if you don't feel like talking, a couple of words is enough. Doing well. Doing bad. Getting by. But it doesn't mean that your brain is a lazy ass! The reality is that there is a great deal of processing behind these simple words. Then, what do you mean when you say you're fine?

When you are asked how you are doing you are asked about your current state. That's to say, whatever you are experiencing at the very moment you are asked the question. Where you are, what you see, what you hear, how healthy you are, how cold, hot, hungry or thirsty you are. But your current state is also everything that happened to you lately with your loved ones and friends, how was work, how well or badly you slept the night before, or how badly you need holidays.

But there's so much more to it than that. It turns out even these factors influence each other. For example, if you're extremely cold, you're probably not as thirsty as if you were hot. Or if you have a problem with your boss, you might not feel like eating as much. And if you're walking past the window of a chocolate shop, it might whet your appetite even if you weren't hungry before you walked by.

In short, how we are depends on many things. For example, it's not as simple as I need nutrients, so I'm hungry, or conversely, I just ate, so I'm not hungry. Our final answer is the result of the computation of multiple factors. Your brain is responsible for the integration of all the information to give rise to an overall state. It integrates visceral signals that come from inside our body, but also signals that come from our perception and our interaction with the world. It's exciting. It really is. But I can't tell you as much about it, because I haven't been studying it for years like Mark Andermann. Mark Andermann's lab, at Harvard University, tries to understand how our dietary needs can influence what we perceive (or not) in the environment. And conversely, how what we perceive can influence what we need.

Juan Garcia Ruiz: You try to understand how our needs are shaped by what we perceive. How would you explain this research topic to a child?

Mark Andermann: Sometimes when you see food you become hungry. So sometimes when people ask me about what I do, I tell them that I study that. The way neuroscience had built this idea was slightly different: when you need calories, you become hungry. And then when you see food you get a desire to eat it. What I think is that there is really an interesting dialogue between our experience of the world and our feelings of hunger. Our brains are designed to get everything we need. But the brain knows that we won't necessarily have access to everything all the time. So when the brain suddenly encounters food, it prioritizes it and seeks it. About a decade ago, we started studying the hypothalamus, one of the most ancient parts of the brain that we share with lizards. That part of the brain is related to the drive to seek food. What we discovered together with other groups was that when a mouse sees a picture of food, that very exposure could modulate the hypothalamus. So there was no distinction between parts of the brain that control our drives and that perceive the availability of that food in the world: they were all working through the same brain circuits.

JGR: Let's see it now the other way around, the way neuroscience built this idea. If we perceive what we need (instead of we perceive, therefore we desire) and our nutritional needs change during the day, could this mean that the focus of our perception changes accordingly?

MA: There are parts of our brain that are there to defend against starvation that only care about calories, whether they're from fats or from carbohydrates. But there are other reasons that might explain why in the morning you want to have more bread and carbohydrates, and in the evening you want to have more fats. And that's possibly because fats are easier to store while carbohydrates are easier to burn right away when you know you're going to need them. As soon as the brain needs something, it will pay attention to that specific kind of thing. Even a baby can do this. There's something called the wisdom of the body, that was coined to define how a baby would discover from eating broccoli which mineral was missing. And then next time the baby misses that mineral, it will look for broccoli. One of the most interesting outcomes is that when it comes to processed foods, where instead of broccoli you have a package with broccoli powder in it, we can no longer understand the relationship between the food we eat and the ingredients that it provides to our body. So we no longer are able to make the same kinds of learned predictions that we evolved to make.

JGR: You study food perception and needs in rodents. Our case as human beings is a bit different because we don't need to hunt or to look for food in nature. We have supermarkets. Is our perception, as human

beings, shaped by our needs like it is for other species like mice? I guess we don't need to struggle to get what we need so we don't need to engage our perception as much as animals that hunt for example.

MA: It is not an easy question. The easy availability of food is only about 200 years old phenomenon, but our brains haven't really changed much in 200 years or so. That doesn't mean that there isn't cultural transmission and other environmental factors that we can learn over our lifetime about food availability. And that may affect what we care about and what we perceive for sure, that's true. But when it's late at night and you're very tired, all the basic instincts that evolved before supermarkets take over. And then there's another layer that we've developed particularly well as humans to say "no, no, I can wait until later even if I see the food now, this isn't what I'm supposed to be eating". But those circuits can be weak unless parents and schools train them early in life.

JGR: Needs are not only shaping what we perceive, but also what we learn and remember. Is that right?

MA: Over the course of evolution, parts of the brain, like the cortex, have expanded a lot more than the core of need drivers in the hypothalamus, in the bottom of the brain. But that expansion hasn't occurred so that we can watch Pokemon. The expansion is simply to help us meet our needs better. And one way that we can do a better job of meeting our needs is to become more sophisticated in how we search for food. So if we have very good memory that allows us to think about where we found a source of food not only a day ago, but even a month ago, we will have a greater chance of finding that source of food again. That's how memory helps us to survive. Similarly, we have ways of learning that depend on what we need. It is the case for flies. If they are starved, they can learn about sources of food while they won't learn about potential situations where they can be punished, because what really matters to them at that moment is calories. So everything about how we learn depends on what we need.

JGR: What are the specific questions that your team is trying to answer right now?

MA: I received training on the study of external senses like hearing, touch and vision. Then I started to realize that we have a limited understanding in how our brains sense signals related to hunger and thirst, so I decided to focus on that. The reason why it's so poorly understood is because while we've used televisions to study vision and fancy sound systems to study hearing, we have no equivalent way of controlling the signals that go from our body to our brain. At least until very recently. What we're trying to understand as a lab is how the brain senses all of the signals in the body in a holistic way. By holistic, what I mean is not just from the heart, the stomach, or the bladder, but from all of the regions of the body including even the bloodstream, and not just through nerves that innervate the body and send signals to the brain. We think that there are regions in the brain that are integrating all possible information about the body and using that as a kind of context. For instance when you're in the supermarket, you get really hungry for the food you see. That's a spatial context. But a lot of the signals from the body together create an interoceptive context. That context is critical for understanding drives, but also for understanding addiction and withdrawal states.

JGR: What are the black boxes of your field of study?

MA: I think one of the frontiers is that we have studied many motivational drives separately in isolation, but we haven't studied how they compete with each other. We don't really understand how it is that we change from one goal to another. This idea requires us to merge many different fields and to ask questions more holistically. Similarly, we are not just feeling hungry. We are not just feeling pain. We are feeling all

those things. So how is it that we actually perceive one at a given moment and not another. The field has focused in general on both vision and other sensory systems of the cortex. But we and others are discovering that an important part of perception is this shutting down of information transfer right at door into the brain. And that's a frontier idea, because there's a lot to be done to understand it.

JGR: What's the best advice you were given during your career?

MA: I was very lucky to have a PhD mentor named Chris Moore. His advice to me was to be courageous and not to be fearful of risk because if you take risks, individually you will fail a lot but collectively you will have a chance to succeed. But if you don't take risks then definitely you will fail.

JGR: What makes a good scientist?

MA: I think that science is hard and not always appreciated by society or by governments. But it is an incredible privilege to get up in the morning and know that your job is to figure out how something works. To me the scientists that I believe are the most fulfilled and probably the most productive, are the ones who are so appreciative of the gift of being able to focus their life on discovery that they see this as the number one payment. I think it is the responsibility of the government and of scientists to educate taxpayers that certain basic economic realities should motivate them to fund science, rather than trying to convince taxpayers that understanding of knowledge is so valuable that they should pay for it. Even though I believe that's the most important reason, it is easier to just go by the facts. And the fact is that at least in the United States, every dollar invested in federal research has saved in the past half a century many dollars in health care costs. Even though only a tiny percentage of the projects ever funded ended up resulting in a medication or a cure, statistically it is an extremely good investment. In terms of giving people the ability to convince parents and friends of the value of research, it is important to educate yourself on situations like the development of AIDS therapies. Because the therapies basically came from people that were studying very strange viruses that were not particularly relevant to anything. And they stumbled upon something that ended up being the foundation for incredibly important therapies. There are many other examples including the discovery of insulin, that really came from training people to just care about how the world works and as a byproduct helping society. I think the other reason to care about research is to consider science as a guiding light that continues to teach generations of people how to think about evidence. Without science, this critical thinking could fade and then we would be in big trouble.

JGR: Do you have a final message you would like to share?

MA: I think that the one thing that I want to clarify is that I am a white male, and I grew up very sheltered. A lot of the words that I said about the importance of just being inspired and pursue joy in science, I am very aware I can say them because I am very privileged because my family could support itself without worrying about where the next paycheck was coming from, which allowed me to take risks in my training and afterwards. I think there is definitely an awareness that the same fuel that can inspire people to stay in science, is not a fuel that society allows everyone to partake in. That's why I think there is a bigger role for understanding science in all these other ways, so there's not only just people like me that can say how satisfied I am with my career. It should be something really available to everyone.

For more interviews, visit www.neuronhub.org

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Neuro-horoscope

Sara Carracedo, 2nd year PhD student at the Institute of Neurodegenerative Diseases (IMN)

Aries

Love: Mixing love and lab might lead to more spills than chemistry

Money: your wallet is on diet, sponsored by the PhD

Lab: Keep your lab notebooks organized, you will need them to redo the experiment

Taurus

Love: you'll find the love in the CROUS

Money: your bank account seems to have disappeared

Lab: experiments that make you question if you accidentally joined a lab-themed circus

Gemini

Love: stable as a well-controlled experiment

Money: your financial situation is in need of some magic

Lab: go check your contaminated cultures

Cancer

Love: Love's centrifugation might spin you in unexpected directions

Money: your wallet feels as dry as a desert

Lab: your lab experiments are a chaotic comedy show

Leo

Love: Be cautious not to set the Bunsen burner of your heart too high, or you might get burned

Money: your bank account forgot to join the party

Lab: PCR reactions that amplify frustration

Virgo

Love: love might be outside the lab

Money: your budget requires creative solutions

Lab: mice would not cooperate this week

Libra

Love: remember that love doesn't always follow rules

Money: huge dreams, limited funds

Lab: cells have a dark sense of humor

Scorpio

Love: keep conducting experiments until you find the formula for love

Money: PhD stipend evaporating faster than water

Lab: Western blots that resemble abstract art

Sagittarius

Love: unconventional love as your scientific theories

Money: you will develop financial creativity

Lab: contamination and fashionable lab coats

Capricorn

Love: Beware of falling for a lab partner who believes pipetting is a dance move

Money: you will ask for money to your parents

Lab: the lab equipment is conspiring against you

Aquarius

Love: dramatic love life, like your experiments

Money: your salary is a rare species, always in extinction

Lab: you are more burned than the primers

Pisces

Love: Your love life might need some optimization, just like your experiments

Money: a cup of instant noodles feels like a five-star meal

Lab: no significant p-values

Results from last issue

Cell-personality at the Neurocampus

60% astrocyte

37% neuron

3% microglia

Editorial board

Sara Carracedo

Sara is a PhD student at the Neurodegénératives Diseases Institute (IMN). She comes from Pontevedra, Spain and holds a Veterinary Bachelor's degree from the University of Santiago de Compostela, Spain and she did the NeuroBIM Master's in Neurosciences. Her PhD is focused on understanding the role of P2X4 receptor in ALS pathogenesis and biomarker in which she is interested in neuroinflammation and receptor trafficking.

Khadija Inam

Khadija is a Pakistani student currently pursuing a training as a Clinical Research Associate at the University of Bordeaux. She graduated with a Bachelor's degree in Applied Biosciences from the National University of Sciences and Technology, and later the NeuroBIM Master's degree in Neurosciences from the University of Bordeaux. Her research interests are in the scope of pharmacology and neurological disorders.

Louise Eygret

Born in Gien, France, Louise did her Bachelor's in Life Sciences followed by the NeuroBIM Master's in Neurosciences. Currently, she is pursuing a PhD focused on the neural substrates underlying odor modulation of food intake regulating neuronal circuits. Her research interests are primarily in nutrition, olfaction and hypothalamus.

Juan Garcia-Ruiz

With two Bachelor's degree, in Psychology and Biochemistry, and the NeuroBIM Master's degree in Neurosciences, Juan is now pursuing a PhD where he is focuses on the role of lactate in basal synaptic transmission, which allows him to combine his research interests in biochemistry, electrophysiology and neurometabolics. Although he speaks near-perfect French, Juan comes from Huelva, Spain. He is also the co-founder of neuronhub (www.neuronhub.org).

Simon Lecomte

Simon is originally from Lyon, France. He did his Bachelor's of Psychology from Strasbourg, after which he did the International Master of Neuroscience from Bordeaux. He is a PhD student studying how the Fragile X Syndrome impacts the presynaptic mechanisms at the DG-CA3 synapses from which one can guess that his interests lie in memory, synaptic communication and the hippocampus. He also runs a blog "Astrocytes et traumatismes crâniens juvéniles".

How can you participate?

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Are you a MSc or a PhD student in neuroscience? Then you are more than welcome to participate in our journal.

You can write either a short-review on a topic of your choice, or a one-page letter (a reflection, a project or an insight you would like to share with the scientific community), a dissemination article about clinical neuroscience (neurodegeneration, neurodevelopmental or psychiatric disorders…) with the aim to reach a more general public, or a neurojoke.

Don't start to worry, you won't be alone! You will work hand-by-hand with our editors and we will send you guidelines and a template to make your life easier. Perhaps you would like to know that the best review will get a special prize by June 2023.

If writing is not your thing and you prefer to express yourself through art, we have a place for you too! For each issue we recruit an artist to design the cover page illustration. And remember that microscopic images are also a form of art!

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