Evaluation of Pathological Perspectives Related to Alzheimer's Disease

Qingyang Song[1,*]

[1]*Catholic Memorial, Boston, 02132, United States*
**corresponding author email：13520040652@163.com*

Abstract: Alzheimer's disease (AD), one of the degenerative diseases and dementias, caused more than millions of people to suffer from it. Over the past few decades, scientists have been putting much effort to study this particular disease in the hope of finding the drug to cure AD. In this condition, two significant hallmarks were discovered, senile plaques and neurofibrillary tangles (NFTs), furthermore leads scientists to focus on Aβ and tau protein to study the pathogenesis of AD. However, the real culprit contributing to AD still remains unknown. Although many amyloid-targeted drugs and tau-targeted drugs are developed, they all failed, causing scientists to cast doubt on the amyloid-related perspective and tau-related perspective. This article will mainly discuss the amyloid hypothesis and the tau hypothesis, the factors driving the formation of senile plaques and NFTs, the scientific data supporting and opposing these two perspectives, the criticisms they are facing, and most importantly the future orientation for scientists to study. Here, after understanding the amyloid-related perspective, tau-related perspective, and other perspectives proposed for AD, we extrapolate that the pathogenesis of AD is multifactorial; moreover, the future AD study should take multiple factors into account.

Keywords: Alzheimer's disease, Aβ, APP, senile plaque, tau protien, NFT.

1. Introduction

Alzheimer's disease (AD) is a type of degenerative disease considered to be the most common form among dementias, causing millions of people to suffer from this disease in 2021[1]. Although scientists have engaged themselves in the study of AD to help worldwide AD patients since the 20th century [2], the determinate pathogenesis for AD still remains unknown. Many neuropathological hallmarks have already been discovered by diligent scientists. Neuropathological hallmarks in an AD patient are the abnormal existence of senile plaques, and the occurrence of neurofibrillary tangles [3], which will translate into the loss of neurons and neurodegeneration in AD patients' brains. In addition to the discoveries of pathological hallmarks of AD, scientists also discovered various potential pathogeneses for AD, such as neuroinflammation, hyperphosphorylation of tau protein, and β-amyloid protein. Here, two well- known perspectives will be mainly discussed in this article, which are the amyloid-related perspective and the tau-related perspective. These two different perspectives focus on the roles of different proteins in the pathogenesis of AD. Moreover, this article will compare two focuses, and evaluate the future possibility of the Alzheimer's disease study related to amyloid and tau protein.

2. Beta-Amyloid and Tau in Alzheimer's Disease

2.1. Beta-Amyloid in AD

The amyloid hypothesis mainly concentrates on the contribution of the effects of amyloid-βon pathogenesis of AD. Senile plaque is extracellular deposition of amyloid beta-peptide (Aβ), Aβ40, and Aβ42, which is cut from amyloid precursor protein (APP) by β- and γ-secretase [4]. Speaking of Aβ, APP is critical for us to know first. The amyloid precursor protein is a transmembrane protein that possesses large extracellular domains, and it belongs to a conserved gene family including amyloid precursor-like proteins, APLP1 and APLP2. It is important to know that only APP can produce amyloidogenic fragments among the family [5].

Normally, β-secretase cuts the APP externally, and γ-secretase cuts it from the cytoplasmic side. Aβ tends to misfold and get sticky. Aggregating misfolded Aβ forms soluble oligomers in the first place, and different forms of Aβ including its oligomers subsequently become senile plaques [4]. After being cut out of the APP, Aβ40 and 42 will be processed by the microglia cells and other cells. In a normal subject's brain, there will be an equal rate between the degradation and the production of Aβ [6]. The cerebrum will clean out all the produced Aβ, whereas, in a subject that is aged or under a pathological state, the cleaning rate will decrease, meaning that this subject's brain cannot clean out an equal amount of Aβ that is being created [7]. Chronically, Aβ will slowly clump together, which exerts negative effects on our brain, including neurotoxicity and neurodegeneration. As Aβ oligomers keep aggregating, they eventually form insoluble senile plaques. It is of note that the presence of Aβ is the earliest pathological change in an AD patient's brain, and the effects it is more than that. When microglia is picking up the Aβ, it will also be activated by it, and subsequently start to release inflammatory cytokine damaging the neurons [8]. Monomers, dimers, higher oligomers, and polymers, are the different forms in which Aβ exists in the brain after being separated from APP [9].

2.2. Amyloid-Related Illness

The amyloid precursor protein gene is on chromosome 21, and the mutation of the APP gene leads to a higher likelihood of Aβ production and aggregation. Indeed, an increase in the production of Aβ is associated with mutations of APP. Some studies built upon this topic seem to be potent evidence to support the rightness of the direction of previous work. For example, scientists have discovered that the mutation in the component of γ-secretase, presenilin, will lead to the abnormal increase in the production of Aβ42 in familial Alzheimer's disease (FAD) patients' cerebrum [10]. Extra Aβ will accumulate into senile plaques and then translate into senile plaques, resulting in the loss of neurons and neurodegeneration. Another study has discovered the vital role of APP genetic mutations in early-onset familial Alzheimer's disease (EOFAD), a rare case in AD patients occupying 5% of the total AD patient population and characterized by an early episode of AD [11]. The Aβ and APP have also widely studied. It is notable that through the study done on overexpressed APP, scientists suggest that in the region with high neuronal activity, the production of Aβ from APP may be increased, and Aβ42 rather than 40 is likely to produce a depression of synaptic transmission [12]. This experiment may indicate a positive correlation between high neuronal activity, Aβ production, and synaptic depression. Although several discoveries, such as the positive correlation between the level of total Aβ and the progression of dementia [13], appear to consolidate the belief of digging the underlying role of Aβ in the pathogenesis of AD, there are more recent discoveries disapproving it, which puts it into the controversy.

2.3. Tau Protein

Tau protein is a microtubule-associated protein (MAP) with a high soluble property [3]. Tau protein plays many roles in our cerebrum, including boosting microtubule growth and bundling, stabilizing microtubule [14], and so on. Although tau serves many functions, its function of stabilizing microtubules is what most are familiar with. The formation of axons and dendrites is unachievable without the existence of stabilized microtubules that generate the cytoplasmic extensions [15], and as mentioned earlier, tau is one of the MAPs stabilizing microtubule.

2.4. Tau Phosphorylation in AD

Despites the positive functions of tau, the dominant composition of neurofibrillary tangles (NFTs) is phosphorylated tau, which is one of the pathological hallmarks of AD [16]. The other hallmark, is the presence of senile plaques. Paired helical filament (PHF) was discovered to be the component of NFTs, and it is partially made up by tau. Precisely, PHF is an intracellular deposit with insoluble property and filamentous form composed of hyperphosphorylated tau [17]. Therefore, it becomes legible that NFTs are predominantly composed of aggregated phosphorylated tau. Notably, NFT is not formed by the complete phosphorylation of tau protein. In the normal physiological condition, tau phosphorylated in 2-3 residues. Under pathological circumstance, however, the phosphorylation of tau is anomalously higher than that [18]. The aberrant presence of NFT, therefore, causes the destruction of microtubule, which further leads to the structural disintegration of the neuron. Another problem discovered in the models is the characteristics of trans-synaptic propagation of tau's pathological state, meaning tauopathies are able to spread across the synapse [19]. The presence of pathological form of tau is not merely a pathological feature for AD but also a renowned pathological hallmark in many neurological diseases, including Pick's disease, frontotemporal dementia linked to chromosome 17, Down's syndrome, sporadic frontotemporal dementias, Parkinsonism linked to chromosome 17, and so on [20-22]. All these diseases related with aberrant tau are called collectively as tauopathy.

The impacts of tau protein dysfunction have been broadly studied and conjectured. It is now conclusive that the hyperphosphorylated tau has negative influences on the affinity of tau to microtubules, and will aggregate in vitro to form helical filaments similar to those observed in vivo [23], which furthermore promotes the NFT formation. Besides, it is also demonstrated that soluble tau protein will have a neurotoxic function in AD patients' brains, which is resulted from the structural change altered by an aggregation of phosphorylated tau [24]. The phosphorylation of tau, nevertheless, does not always serve as a negative effect on the brain. Another experiment has shown that the phosphorylation of tau protein exerts a protective purpose on neurons in the first place, which is inhibiting the toxicity of Aβ [25].

2.5. Causes and Impacts of Tau Phosphorylation

Studies have shown various factors contributing to the phosphorylation of tau. An experiment on genetically modified rats, causing them to lack sod2, showed that oxidative stress would translate into tau phosphorylation [26]. Scientists also find that fibrillar Aβ will induce the phosphorylation of tau to proceed in primary rat and human neurons, and the induced phosphorylated tau will resemble PHF-associated tau's dysfunction of microtubules affinity [27], which aggregates into NFT later on. Moreover, manganese ions can also be a factor that leads to hyperphosphorylation of intracellular tau protein through the activation of ERK or MAPK, which is protein kinase [28]. Astrocytes was discovered to be a critical mediator for tau phosphorylation [29]. Factors causing tau phsphorylation are always more than that, and there are still many factors contributing to the phosphorylation of tau, and some of them are still waiting to be explored in the future.

3. Discussion

The discovery of NET and Aβ seem to open a promising door for the future prospect of this field. Interestingly, the importance of tau in the pathogenesis of AD seems to be ignored by that time under scientists' great mass fervor toward Aβ. A few decades ago, scientists' main interest in AD study was the beta-amyloid protein. As more amyloid-targeting drugs failed, however, scientists began to realize the importance of tau protein's role in the pathogenesis of AD. Therefore, the hyperphosphorylation, aggregation, and truncation of tau are now widely studied and are considered to be the main pathogenesis of many dementias by many scientists, including AD [30]. The reason for the shift from the amyloid-related perspective to the tau-related perspective or tau hypothesis is varied. This shift becomes increasingly obvious in recent decades as more and more studies have shown the importance of tau in the pathogenesis of AD. A significant factor that makes many scientists start realizing tau's role is the continuous failures in the development of amyloid beta-targeted or anti-amyloid drugs, they either failed or did not reach scientists' expectations.

The first trial of drug focusing on activating immune response stopped as brain and meninges inflammation happened in some recipients, and the trial on the inhibitor of γ-secretase, semagacestat, also failed due to the occurrence of skin cancer and the worsening cognition in participants, because γ-secretase also cut out other proteins [31]. Such cases are countless in the development of AD drugs. It is very important to know that such cases are not merely happening to the drug focusing on provoking the immune system but also happening to other anti-amyloid drugs [32]. However, the explanation given by scientists suggests that the bad timing of giving drugs is the culprit for such drug's failure. It seems to be a potent justification since there is a long preclinical stage for AD before the manifestation of pathological symptoms, and this pre-manifestation period gives plenty of time for the process causing NFT and neuronal injury or death [33]; therefore, the timing of receiving drug seems to be critical. Until 2022, still, no drug can be able to completely cure this disease, which is a very strong evidence that opposes this false timing explanation. If the timing is the reason for the failure, the subsequent trials should be able to avoid the timing issue and succeed. Nevertheless, later trials are still failing, indicating that timing is not the chief culprit for the failure. This phenomenon has persuaded many scientists that there must be other reasons explaining the developmental failure of AD drugs. Some scientists believe that although Aβ accumulation is in parallel with AD progression, it is not the primary pathogenesis, and amyloid-centric therapies will fail continuously [34].

In addition to the position of Aβ in the pathogenesis of AD, its neurotoxicity has also been challenged. It has already known that without the presence of tau protein pathology, imposing amyloid pathology solely will not lead to dementia, which suggests that the neurotoxicity of Aβ depends on the pathological tau [30]. Other studies have demonstrated that some subjects with abundant senile plaques and a large amyloid burden in the brain suffer from neither dementia nor cognitive impairment [35, 36]. Such studies indicate that Aβ is not itself a substance that exerts neurotoxicity solely, and might just be part of the normal aging process. Therefore, the focus of the AD study starts shifting from amyloid to tau protein.

Many scientists begin to believe that tau is the major pathogenesis for AD; therefore, tau-targeted drugs are in full development. The outcome, however, does not reach scientists' anticipation, because there are still too many unsolved puzzles. It has been shown that neuronal loss occurs before the existence of NFT [37]. Beyond that, just like Aβ, NFT presents anomalously inside the brain of some subjects with normal cognitive ability [36]. Just like anti- amyloid drugs, the development of anti-tau therapy keeps failing and discouraging people. For example, GSK-3β is a protein kinase that promotes tau phosphorylation, which makes it to become a feasible target for anti-tau therapy, hence, tideglusib was created based on this knowledge [38]. Tideglusib, a GSK-

3β inhibitor, however, did not show significant therapeutic efficacy in phase II clinical trials [39].

Although the amyloid-related perspective and tau-related perspective are both being challenged, the tau-related perspective is still considered as a better orientation to study and is still flourishing. Maybe it's because we have undergone so many failures in developing anti-amyloid drugs, and thus, became disappointed. It is not clear which one is a better target to study. Just like what has been mentioned previously, Aβ will induce tau phosphorylation causing NFTs [27], and the neurotoxicity of Aβ will not exist without the existence of pathological tau [30]. The pathogenesis of AD is still a mystery, however, it is clear that the pathogenesis of AD is multifactor, indicating that merely focusing on one or two perspectives does not reach the goal of understanding and curing the disease. For example, many studies suggested that melatonin can effectively reduce the hyperphosphorylation of tau protein, and can exert positive effects in protecting the cholinergic system and in anti-inflammation [40]. The multifactor pathogenesis of AD indicates that the amyloid protein and tau do play a role in the pathogenesis of AD, but not solely. It does not mean that future studies and the development of drugs should ignore these two perspectives but means that scientists should focus on multiple perspectives to study AD because past experiences have taught us that focusing on one perspective to develop AD drugs will eventually fail. Although it might be a hard road to explore, the payback will eventually come and the drug will be more complete.

4. Conclusion

Alzheimer's disease has been studied since the last century, and people have discovered two major hallmarks for AD, senile plaques and NFTs. Ever since, most scientists start developing the experiment and drugs around these two hallmarks. However, as more experiment, and more failures of developing amyloid-targeted and tau-targeted drugs for curing AD, the pathogenesis of AD formed a debate. Efforts made on curing AD with single target seem to be inadequeate based on the past experiences. Meanwhile, many studies proposed that there are various factors causeing Aβ deposites and tau protein phosphorylation. Therefore, the study focusing on multifactorial seems to be a better option to take.

References

[1] *Gauthier, S., Rosa-Neto, P., Morais, J. A., & Webster, C. (2021). World Alzheimer Report 2021: Journey through the diagnosis of dementia. Alzheimer's Disease International.*

[2] *Selkoe, D. J., & Hardy, J. (2016). The amyloid hypothesis of Alzheimer's disease at 25 years. EMBO Molecular Medicine, 8(6), 595–608. https://doi.org/10.15252/emmm.201606210*

[3] *Mohandas, E., Rajmohan, V., & Raghunath, B. (2009). Neurobiology of Alzheimer's disease. Indian journal of psychiatry, 51(1), 55–61. https://doi.org/10.4103/0019-5545.44908*

[4] *Chen, G. F., Xu, T. H., Yan, Y., Zhou, Y. R., Jiang, Y., Melcher, K., & Xu, H. E. (2017). Amyloid beta: structure, biology and structure-based therapeutic development. Acta Pharmacologica Sinica, 38(9), 1205–1235. https://doi.org/10.1038/aps.2017.28*

[5] *O'Brien, R. J., & Wong, P. C. (2011). Amyloid Precursor Protein Processing and Alzheimer's Disease. Annual Review of Neuroscience, 34(1), 185–204. https://doi.org/10.1146/annurev-neuro-061010-113613*

[6] *Lee, C. Y. D., & Landreth, G. E. (2010). The role of microglia in amyloid clearance from the AD brain. Journal of Neural Transmission, 117(8), 949–960. https://doi.org/10.1007/s00702-010-0433-4*

[7] *Kametani, F., & Hasegawa, M. (2018). Reconsideration of Amyloid Hypothesis and Tau Hypothesis in Alzheimer's Disease. Frontiers in Neuroscience, 12. https://doi.org/10.3389/fnins.2018.00025*

[8] *Hansen, D. V., Hanson, J. E., & Sheng, M. (2017). Microglia in Alzheimer's disease. Journal of Cell Biology, 217(2), 459–472. https://doi.org/10.1083/jcb.201709069*

[9] *SELKOE, D. J. (2006). Toward a Comprehensive Theory for Alzheimer's Disease. Hypothesis: Alzheimer's Disease Is Caused by the Cerebral Accumulation and Cytotoxicity of Amyloid β-Protein. Annals of the New York Academy of Sciences, 924(1), 17–25. https://doi.org/10.1111/j.1749-6632.2000.tb05554.x*

[10] Chávez-Gutiérrez, L., Bammens, L., Benilova, I., Vandersteen, A., Benurwar, M., Borgers, M., Lismont, S., Zhou, L., van Cleynenbreugel, S., Esselmann, H., Wiltfang, J., Serneels, L., Karran, E., Gijsen, H., Schymkowitz, J., Rousseau, F., Broersen, K., & de Strooper, B. (2012). The mechanism of γ-Secretase dysfunction in familial Alzheimer disease. The EMBO Journal, 31(10), 2261–2274. https://doi.org/10.1038/emboj.2012.79

[11] Wu, L., Rosa-Neto, P., Hsiung, G. Y. R., Sadovnick, A. D., Masellis, M., Black, S. E., Jia, J., & Gauthier, S. (2012). Early-Onset Familial Alzheimer's Disease (EOFAD). Canadian Journal of Neurological Sciences / Journal Canadien Des Sciences Neurologiques, 39(4), 436–445. https://doi.org/10.1017/s0317167100013949

[12] Kamenetz, F., Tomita, T., Hsieh, H., Seabrook, G., Borchelt, D., Iwatsubo, T., Sisodia, S., & Malinow, R. (2003). APP Processing and Synaptic Function. Neuron, 37(6), 925–937. https://doi.org/10.1016/s0896-6273(03)00124-7

[13] Näslund, J. (2000). Correlation Between Elevated Levels of Amyloid β-Peptide in the Brain and Cognitive Decline. JAMA, 283(12), 1571. https://doi.org/10.1001/jama.283.12.1571

[14] Paglini, G., Peris, L., Mascotti, F., Quiroga, S., & Caceres, A. (2000). Tau Protein Function in Axonal Formation. Neurochemical Research, 25(1), 37–42. https://doi.org/10.1023/a:1007531230651

[15] Mitchison, T., & Kirschner, M. (1988). Cytoskeletal dynamics and nerve growth. Neuron, 1(9), 761–772. https://doi.org/10.1016/0896-6273(88)90124-9

[16] Grundke-Iqbal, I., Iqbal, K., Quinlan, M., Tung, Y. C., Zaidi, M. S., & Wisniewski, H. M. (1986). Microtubule-associated protein tau. A component of Alzheimer paired helical filaments. Journal of Biological Chemistry, 261(13), 6084–6089. https://doi.org/10.1016/s0021-9258(17)38495-8

[17] Mandelkow, E. M. (1995). Hyperphosphorylation of tau in PHF. Neurobiology of Aging, 16(3), 374. https://doi.org/10.1016/0197-4580(95)00029-e

[18] Medeiros, R., Baglietto-Vargas, D., & LaFerla, F. M. (2010). The Role of Tau in Alzheimer's Disease and Related Disorders. CNS Neuroscience & Therapeutics, 17(5), 514–524. https://doi.org/10.1111/j.1755-5949.2010.00177.x

[19] Liu, L., Drouet, V., Wu, J. W., Witter, M. P., Small, S. A., Clelland, C., & Duff, K. (2012). Trans-Synaptic Spread of Tau Pathology In Vivo. PLoS ONE, 7(2), e31302. https://doi.org/10.1371/journal.pone.0031302

[20] Lee, V. M. Y., Goedert, M., & Trojanowski, J. Q. (2001). Neurodegenerative Tauopathies. Annual Review of Neuroscience, 24(1), 1121–1159. https://doi.org/10.1146/annurev.neuro.24.1.1121

[21] Buée, L., Bussière, T., Buée-Scherrer, V., Delacourte, A., & Hof, P. R. (2000). Tau protein isoforms, phosphorylation and role in neurodegenerative disorders11These authors contributed equally to this work. Brain Research Reviews, 33(1), 95–130. https://doi.org/10.1016/s0165-0173(00)00019-9

[22] Spillantini, M. G., Bird, T. D., & Ghetti, B. (2006). Frontotemporal Dementia and Parkinsonism Linked to Chromosome 17: A New Group of Tauopathies. Brain Pathology, 8(2), 387–402. https://doi.org/10.1111/j.1750-3639.1998.tb00162.x

[23] Geschwind, D. H. (2003). Tau Phosphorylation, Tangles, and Neurodegeneration. Neuron, 40(3), 457–460. https://doi.org/10.1016/s0896-6273(03)00681-0

[24] Fath, T., Eidenmüller, J., & Brandt, R. (2002). Tau-Mediated Cytotoxicity in a Pseudohyperphosphorylation Model of Alzheimer's Disease. The Journal of Neuroscience, 22(22), 9733–9741. https://doi.org/10.1523/jneurosci.22-22-09733.2002

[25] Ittner, A., Chua, S. W., Bertz, J., Volkerling, A., van der Hoven, J., Gladbach, A., Przybyla, M., Bi, M., van Hummel, A., Stevens, C. H., Ippati, S., Suh, L. S., Macmillan, A., Sutherland, G., Kril, J. J., Silva, A. P. G., Mackay, J. P., Poljak, A., Delerue, F., . . . Ittner, L. M. (2016). Site-specific phosphorylation of tau inhibits amyloid-β toxicity in Alzheimer's mice. Science, 354(6314), 904–908. https://doi.org/10.1126/science.aah6205

[26] Melov, S., Adlard, P. A., Morten, K., Johnson, F., Golden, T. R., Hinerfeld, D., Schilling, B., Mavros, C., Masters, C. L., Volitakis, I., Li, Q. X., Laughton, K., Hubbard, A., Cherny, R. A., Gibson, B., & Bush, A. I. (2007). Mitochondrial Oxidative Stress Causes Hyperphosphorylation of Tau. PLoS ONE, 2(6), e536. https://doi.org/10.1371/journal.pone.0000536

[27] Busciglio, J., Lorenzo, A., Yeh, J., & Yankner, B. A. (1995). β-Amyloid fibrils induce tau phosphorylation and loss of microtubule binding. Neuron, 14(4), 879–888. https://doi.org/10.1016/0896-6273(95)90232-5

[28] Sun, X. Y., Wei, Y. P., Xiong, Y., Wang, X. C., Xie, A. J., Wang, X. L., Yang, Y., Wang, Q., Lu, Y. M., Liu, R., & Wang, J. Z. (2012). Synaptic Released Zinc Promotes Tau Hyperphosphorylation by Inhibition of Protein Phosphatase 2A (PP2A). Journal of Biological Chemistry, 287(14), 11174–11182. https://doi.org/10.1074/jbc.m111.309070

[29] Garwood, C. J., Pooler, A. M., Atherton, J., Hanger, D. P., & Noble, W. (2011). Astrocytes are important mediators of Aβ-induced neurotoxicity and tau phosphorylation in primary culture. Cell Death & Disease, 2(6), e167. https://doi.org/10.1038/cddis.2011.50

[30] Rosenmann, H., Blum, D., Kayed, R., & Ittner, L. M. (2012). Tau Protein: Function and Pathology. International Journal of Alzheimer's Disease, 2012, 1–2. https://doi.org/10.1155/2012/707482

[31] Makin, S. (2018). The amyloid hypothesis on trial. Nature, 559(7715), S4–S7. https://doi.org/10.1038/d41586-018-05719-4

[32] Modrego, P., & Lobo, A. (2019). A good marker does not mean a good target for clinical trials in Alzheimer's disease: the amyloid hypothesis questioned. Neurodegenerative Disease Management, 9(3), 119–121. https://doi.org/10.2217/nmt-2019-0006

[33] Fagan, A. M., Xiong, C., Jasielec, M. S., Bateman, R. J., Goate, A. M., Benzinger, T. L. S., Ghetti, B., Martins, R. N., Masters, C. L., Mayeux, R., Ringman, J. M., Rossor, M. N., Salloway, S., Schofield, P. R., Sperling, R. A., Marcus, D., Cairns, N. J., Buckles, V. D., Ladenson, J. H., . . . Holtzman, D. M. (2014). Longitudinal Change in CSF Biomarkers in Autosomal-Dominant Alzheimer's Disease. Science Translational Medicine, 6(226). https://doi.org/10.1126/scitranslmed.3007901

[34] Castello, M. A., & Soriano, S. (2014). On the origin of Alzheimer's disease. Trials and tribulations of the amyloid hypothesis. Ageing Research Reviews, 13, 10–12. https://doi.org/10.1016/j.arr.2013.10.001

[35] Sturchio, A., Dwivedi, A. K., Young, C. B., Malm, T., Marsili, L., Sharma, J. S., Mahajan, A., Hill, E. J., Andaloussi, S. E., Poston, K. L., Manfredsson, F. P., Schneider, L. S., Ezzat, K., & Espay, A. J. (2021). High cerebrospinal amyloid-β 42 is associated with normal cognition in individuals with brain amyloidosis. EClinicalMedicine, 38, 100988. https://doi.org/10.1016/j.eclinm.2021.100988

[36] Davis, D. G., Schmitt, F. A., Wekstein, D. R., & Markesbery, W. R. (1999). Alzheimer Neuropathologic Alterations in Aged Cognitively Normal Subjects. Journal of Neuropathology and Experimental Neurology, 58(4), 376–388. https://doi.org/10.1097/00005072-199904000-00008

[37] Gómez -Isla, T., Hollister, R., West, H., Mui, S., Growdon, J. H., Petersen, R. C., Parisi, J. E., & Hyman, B. T. (1997). Neuronal loss correlates with but exceeds neurofibrillary tangles in Alzheimer's disease. Annals of Neurology, 41(1), 17–24. https://doi.org/10.1002/ana.410410106

[38] 41.Sevigny, J., Chiao, P., Bussière, T., Weinreb, P. H., Williams, L., Maier, M., Dunstan, R., Salloway, S., Chen, T., Ling, Y., O'Gorman, J., Qian, F., Arastu, M., Li, M., Chollate, S., Brennan, M. S., Quintero-Monzon, O., Scannevin, R. H., Arnold, H. M., . . . Sandrock, A. (2016). The antibody aducanumab reduces Aβ plaques in Alzheimer's disease. Nature, 537(7618), 50–56. https://doi.org/10.1038/nature19323

[39] Lovestone, S., Boada, M., Dubois, B., Hüll, M., Rinne, J. O., Huppertz, H. J., Calero, M., Andrés, M. V., Gómez -Carrillo, B., León, T., & del Ser, T. (2015). A Phase II Trial of Tideglusib in Alzheimer's Disease. Journal of Alzheimer's Disease, 45(1), 75–88. https://doi.org/10.3233/jad-141959

[40] Lin, L., Huang, Q. X., Yang, S. S., Chu, J., Wang, J. Z., & Tian, Q. (2013). Melatonin in Alzheimer's Disease. International Journal of Molecular Sciences, 14(7), 14575–14593. https://doi.org/10.3390/ijms140714575.