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Unleashing the potential: Exploring the ubiquitin-proteasome system as a potential treatment for Alzheimer's disease

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Abstract. Alzheimer's disease (AD) is a neurological disorder that causes the buildup of amyloid-beta plaques and neurofibrillary tangles in the brain. One key mechanism designed to mitigate the buildup of these misfolded proteins is the ubiquitin-proteasome system (UPS). In healthy individuals, the UPS marks these amyloid-beta plaques and neurofibrillary tangles with ubiquitin markers, facilitating their subsequent degradation by the proteasome complex. The UPS is critical for the degradation of the proteins, and its dysfunction has been observed in AD. In this paper, a potential treatment for diminishing dysfunction of the ubiquitin-proteasome system is composed for Alzheimer's disease individuals. This research paper explores the correlation between impaired UPS and AD, focusing on its role in degrading damaged proteins. The paper also collects evidence suggesting that enhancing the ubiquitin-proteasome system can have a positive impact on clearing amyloid-beta plaques and neurofibrillary tangles. Additionally, potential UPS-based treatments for AD, such as PA28 activators and natural compounds, are investigated.

Keywords: Ubiquitin-Proteasome System, Alzheimer's disease, Endoplasmic Reticulum Stress.

1. Introduction

Alzheimer's disease (AD) is a debilitating neurodegenerative condition marked by gradual cognitive deterioration and memory loss. The pathogenesis of AD is complex and involves the accumulation of abnormal protein aggregates, particularly amyloid-beta plaques, and hyperphosphorylated tau protein neurofibrillary tangles within the brain. These structural abnormalities disrupt neuronal communication, trigger widespread inflammation, and ultimately lead to progressive synapse destructions and neuronal death.

In addition, studies have highlighted the critical role of amyloid precursor protein (APP) metabolism in the pathogenesis of AD. Under normal conditions, APP undergoes sequential proteolytic cleavage by various enzymes, resulting in the production of soluble fragments. In Alzheimer's disease, however, abnormal processing of amyloid precursor protein leads to the accumulation of amyloid-beta peptide, a neurotoxic fragment that aggregates to form insoluble plaques. Defects in the protein degradation

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pathway are thought to contribute to this accumulation in individuals with Alzheimer's disease. These neurotoxic plaques induce endoplasmic reticulum (ER) stress responses in neurons, triggering cell apoptosis and immune inflammation, ultimately leading to neuronal death in individuals with Alzheimer's disease.

Given the progression of APP accumulation in Alzheimer's disease, it is critical to understand the mechanisms involved in plaque degradation. The UPS is a common pathway for the degradation of misfolded proteins in AD. The discovery of the ubiquitin-proteasome pathway, which is widely recognized as a critical mechanism for regulating various cellular processes, involved the collective efforts of many scientists over many years. In 1953, researchers observed that protein degradation requires energy, setting the stage for the subsequent identification of key components, including ubiquitin, E1-3 enzymes, and the 26S proteasome. The intricate details of ubiquitin-mediated protein degradation were revealed in 2004 by Aaron Ciechanover and his colleagues. The UPS pathway primarily regulates the cell cycle, eliminating unnecessary or damaged proteins to ensure proper cellular activities and maintain cellular homeostasis. This pathway involves the coordination of ubiquitin, three enzymes, and a proteasome to achieve protein degradation. Due to its critical role in the cellular lifecycle, the ubiquitin-proteasome pathway received increasing attention recently regarding its involvement in various neurodegenerative diseases, including Parkinson's Diseases and Alzheimer's Diseases.

This review aims to provide a comprehensive overview of UPS involvement in Alzheimer's Disease and its potential as a therapeutic target. Understanding the intricate relationship between the UPS and the pathological processes in AD may open up avenues for the discovery and development of innovative drugs or interventions that restore UPS function and promote the clearance of toxic protein aggregates. In addition, future research directions are proposed to further our understanding of the UPS-AD relationship and facilitate the development of effective treatments.

2. Ubiquitination-Proteasome System (UPS) Pathway

2.1. Activation of Ubiquitin

For ubiquitin to be targeted for degradation, it undergoes an activation process. The initial step involves E1, a multidomain enzyme that plays a crucial role in activating ubiquitin and transferring it to the E2 enzyme. Through the utilization of ATP as an energy source, the active site cysteine residue of E1 attaches ubiquitin's C-terminal carboxyl group through adenylation, resulting in the formation of a complex known as UBE1. Once the C-terminal glycine on ubiquitin starts to form a thioester bond with the cysteine residue in E1, the ubiquitin becomes activated and ready to be transferred to the E2 enzyme.

This process involves significant conformational changes. The first notable rearrangement occurs in the E1 enzyme domain. This change makes the E1 cysteine binding to the adenylation of SUMO moiety and facilitates the reformation of the active site component. As a result, the active site can catalyze the formation of the thioester bond instead of SUMO adenylation [1]. The second significant conformational change arises from the transport of ubiquitin from E1 to the E2 enzyme. Studies have demonstrated that the forming process of the thioester bond between E1 and Nedd8 (a ubiquitin-like molecule) induces a positional change of the Ubiquitin fold domain (UFD) on E1. This conformation enables the subsequent transfer of ubiquitin and facilitates the binding of ubiquitin to E2 [1].

2.2. Marking Proteins for Degradation

After activation by the E1 enzyme, ubiquitin is transferred from E1 to E2, also called ubiquitin-conjugating enzyme. Like E1, E2 possesses a cysteine residue that allows binding with the C-terminal glycine of ubiquitin, forming a thioester bond. E2 plays a vital role in marking proteins for degradation, as it works to facilitate the transfer of ubiquitin to potentially degradable proteins in almost all ubiquitination-mediated processes. Additionally, E2 acts as a chaperone, facilitating the connection between ubiquitin and the E3 enzyme, which serves as a platform for recognition and binding to target proteins. E3 exhibits high specificity in selecting the appropriate E2 for interacting with the substrate. Once the E2 enzyme, along with ubiquitin, is attached to the E3 enzyme, ubiquitin dissociates from E2

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and forms an isopeptide bond with a lysine residue on the target protein. This process is usually repeated multiple times until the formation of polyubiquitination. Research shows that the ubiquitin transferring rate depends on achieving an optimal conformation for the thioester bond, which can be influenced by either E2 and E3 or an interplay between both enzymes. E2 primarily achieves this by binding ubiquitin against an interface on the E2 surface to achieve the optimal position and promote transfer [1]. Additionally, certain E3s can enhance the transfer rate by stabilizing the conformation between the conjugation enzyme and ubiquitin.

2.3. The Final Step of Degradation: the 26S Proteasome

The 26S proteasome serves as the end step in degradation, acting as the actual executor. It is primarily composed of two subunits: the 20S core protease and the 19S regulatory particle. The 20S core is composed of 4 rings, with the inner 2 rings consisting of 7 β subunits that contain protease active sites. The two rings sat outside have seven α subunits. These subunits determinate ubiquitin tags and start the degradating process. As the α subunits recognize the target protein with polyubiquitin, the β subunits become involved in removing the polyubiquitin chain and cleaving the protein into short peptides and amino acids, which can be reused within the cell for synthesis. The removed ubiquitin is also available for reuse in the subsequent targeting of proteins. The 19S regulatory particle is located at the end of the 20S and is responsible for regulating its function. The regulatory particle can open the pore of the α subunits, promote protein unfolding, transport proteins into the 20S core, and release polyubiquitin before degradation [2].

3. Function of Ubiquitination-Proteasome System (UPS) in Alzheimer's disease (AD)

3.1. Detailed Description of Alzheimer's Disease (AD)

Alzheimer's Disease (AD) is a neurodegenerative disease that primarily affects the elderly population. The disease is thought to be characterized by the presence of two abnormal protein aggregates in the brain: amyloid-beta (aβ) plaques and tau tangles. Amyloid-beta plaques are primarily composed of amyloid-beta peptides, which are fragments of amyloid precursor protein (APP). Amyloid Precursor Protein is a larger transmembrane protein expressed in high levels in neurons.

Under normal conditions, APP undergoes internalization in clathrin-coated pits, leading to its processing by proteases such as BACE1 and γ-secretase. This processing generates amyloid-beta peptides as by-products [3]. Studies have shown that the chemical conformation and micelle-like structure of amyloid-beta peptides can promote their spontaneous aggregation into larger and more stable amyloid-beta plaques [4-6].

Amyloid-beta plaques induce cell apoptosis through the unfolded protein response (UPR) and trigger inflammation in the brain. The rapid aggregation of misfolded amyloid-beta plaques significantly increases ER stress in neuron cells, resulting in a lethal UPR instead of a protective one [7]. This lethal unfolded protein response pathway leads to cell apoptosis. Furthermore, amyloid-beta plaques can cause synaptic loss and disrupt the cytoskeleton [7].

In addition to amyloid-beta plaques, amyloid-beta peptides can also induce hyperphosphorylation of tau proteins, causing the formation of neurofibrillary tangles. Hyperphosphorylated tau proteins lose their ability to bind to microtubules, causing them to disband from the microtubule structure and aggregate into neurofibrillary tangles [8]. These tangles, similar to amyloid-beta plaques, increase ER stress in neuron cells, triggering UPR, cell apoptosis, and immune inflammation. Although amyloid-beta plaques and tau protein tangles have different protein components and conformations, they both contribute to the neurodegenerative process in AD through the same mechanism, further impairing neuronal function and survival [8, 9].

In healthy individuals, APP is processed and cleared from the brain through UPR-triggered Ubiquitination-Proteasome System degradation and cellular autophagy. However, in Alzheimer's Disease, there exists an imbalance between the production and clearance of aβ peptides, resulting their

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massive accumulation into amyloid-beta plaques and resulting in neurotoxicity. It is believed that dysfunction in the Ubiquitination-Proteasome System is one of the reasons for this imbalance.

3.2. Molecular Pathway of Ubiquitination-Proteasome System (UPS) in the Early Stage of Alzheimer's Disease (AD)

The Ubiquitination-Proteasome System functions to mark misfolded amyloid-beta peptides using ubiquitin and triggers the degradation pathway through the proteasome. In healthy individuals, when the Ubiquitination marking and Proteasome degradation work properly, ER stress induced by misfolded amyloid-beta peptides is maintained within an acceptable range, triggering a protective Misfolded Protein response that leads to the total degradation of amyloid-beta peptides. However, in individuals with Alzheimer's disease, the activity of the proteasome is inhibited [10, 11].

E2-25K/Hip-2 is an unusual enzyme in the Ubiquitination-Proteasome System. It works as an E2-ubiquitin conjugating enzyme and can ubiquitinate its substrates without the need for an E3 ubiquitin ligase. Examination of individuals with Alzheimer's disease has revealed a decrease in the concentration of E2-25K/Hip-2, which is associated with decreased inhibition of the proteasome and reduced neurotoxicity of amyloid-beta plaques [11]. Studies suggest that the substrates of E2-25K/Hip-2 are a ubiquitin-like protein called NEDD8 and a false-translated protein called UBB+1. Ubiquitinated NEDD8 and UBB+1 decrease proteasome activity, but the exact mechanism by which they achieve this is still unknown.

Evidence also indicates that NEDD8 and UBB+1 can decrease the levels of two factors involved in the degradation of Amyloid Precursor Protein, namely (CTF)-PS1 and (CTF)-PS2. A decrease in (CTF)-PS1 and (CTF)-PS2 leads to increased production of amyloid-beta peptides while degrading APP. This process is subject to positive feedback, resulting in an imbalance between the Ubiquitination-Proteasome System and amyloid-beta plaque formation that worsens over time. In individuals with AD, higher than usual concentrations of E2-25K/Hip-2 lead to a natural inability to degrade amyloid-beta peptides [10]. As more amyloid-beta peptides are formed, they are unable to be degraded in a timely manner, leading to increased ER stress that triggers a lethal UPR (cell apoptosis) instead of a protective UPR (Ubiquitination-Proteasome System degradation). The shift to a lethal UPR further inhibits the protective UPR, exacerbating the inability to degrade these peptides [12].

4. Potential Therapeutic Strategies Targeting the UPS for AD

4.1. Potential Therapeutic Strategies Targeting the UPS for AD in Prevention

As discussed earlier, the accumulation of amyloid-beta (aβ) plaques and tau tangles contributes to the neurotoxicity in Alzheimer's disease (AD). The imbalance between the Ubiquitination-Proteasome System (UPS) protein degradation and the formation of these protein aggregates results in their rapid accumulation. To prevent their accumulation, one potential direction is to focus on enhancing UPS-mediated protein degradation.

Individuals with Alzheimer's disease have lower Proteasome activity compared to normal individuals [13, 14]. This reduced activity hampers the degradation of amyloid-beta (aβ) peptides, leading to the formation of amyloid-beta (aβ) plaques. Therefore, a possible treatment strategy is to increase Proteasome activity in individuals with AD, allowing for the normal degradation of amyloid-beta (aβ) peptides through the UPS [15-17]. This would prevent the formation of amyloid-beta (aβ) plaques and subsequently hinder the formation of tau tangles and the ER stress in neuronal cells.

There are various approaches to achieving this goal, one of which is using pharmacological agents known as proteasome activators [16-19]. These compounds can modulate the activity of the proteasome by binding to specific sites and promoting its catalytic function. For example, PA28 activators, including small molecules, have shown potential in enhancing proteasome activity and improving the degradation of misfolded proteins in other disease models such as diabetes [20]. Some studies have also demonstrated the effect of PA28 usage in AD models, showing a decrease in amyloid-beta (aβ) plaque concentration [21]. Thus, it is reasonable to consider PA28 a potential modulator of Proteasome activity

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in individuals with AD. Furthermore, studies involving overexpression of PA28α and PA28β, the two peptides composing PA28, have shown increased PA28 expression, resulting in decreased ER stress due to enhanced Proteasome activity [22-24]. This suggests that the increased activity of PA28 could enhance the clearance of amyloid-beta (aβ) peptides and tau tangles through the Proteasome, mitigating their accumulation and subsequent neurotoxicity.

Another strategy to enhance proteasome activity involves using natural compounds with proteasome-stimulating properties. Curcumin, a polyphenolic compound found in turmeric, has shown proteasome-stimulating effects in low concentrations (≥1 μM and ≤10 μM) [25]. Studies have demonstrated that curcumin can enhance proteasome activity in animal models of AD under these low-concentration conditions. Considering the difficulties in reaching high concentrations of curcumin through diet, maintaining a low concentration of curcumin through dietary intake could potentially decrease neurotoxicity in individuals with AD, making curcumin a promising candidate for future AD medication.

Similarly, resveratrol, a natural polyphenol found in grapes and berries, has been reported to promote the clearance of amyloid-beta (aβ) peptides and tau tangles, offering potential therapeutic benefits for AD prevention [26]. Studies have shown that resveratrol increases the activity of the Proteasome and enhances the degradation of amyloid-beta (aβ) peptides [27]. The underlying mechanisms by which curcumin and resveratrol achieve these effects are still not fully understood and warrant further investigation as potential research directions. By enhancing UPS-mediated protein degradation through proteasome activators or natural compounds, it may be possible to prevent the accumulation of amyloid-beta (aβ) plaques and tau tangles, ultimately mitigating the neurotoxicity associated with AD.

5. Conclusion

Dysfunctional UPS contributes to the pathogenesis of AD by promoting the accumulation of amyloid-beta peptides. Targeting the UPS with proteasome activators or natural compounds may offer potential therapeutic benefits by promoting the clearance of toxic protein aggregates. Understanding the UPS-AD relationship is critical for developing effective treatments for AD. Further research in this area is essential to explore the full potential of UPS-based interventions in AD therapy.

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References

[1] Kleiger, G., & Mayor, T. (2014). Perilous journey: A tour of the Ubiquitin–Proteasome System. Trends in Cell Biology, 24(6), 352–359. https://doi.org/10.1016/j.tcb.2013.12.003

[2] Marshall, R. S., & Vierstra, R. D. (2019). Dynamic Regulation of the 26S proteasome: From synthesis to degradation. Frontiers in Molecular Biosciences, 6. https://doi.org/10.3389/fmolb.2019.00040

[3] 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

[4] Chiorcea-Paquim, A.-M., & Oliveira-Brett, A. M. (2022). Amyloid beta peptides electrochemistry: A review. Current Opinion in Electrochemistry, 31, 100837. https://doi.org/10.1016/j.coelec.2021.100837

[5] Millucci, L., Ghezzi, L., Bernardini, G., & Santucci, A. (2010). Conformations and Biological Activities of Amyloid Beta Peptide 25-35. Current Protein & Peptide Science, 11(1), 54–67. https://doi.org/10.2174/138920310790274626

[6] Morel, B., Carrasco, M. P., Jurado, S., Marco, C., & Conejero-Lara, F. (2018). Dynamic micellar oligomers of amyloid beta peptides play a crucial role in their aggregation mechanisms. Physical Chemistry Chemical Physics, 20(31), 20597–20614. https://doi.org/10.1039/C8CP02685H

[7] Fonseca, A. C. R. G., Ferreiro, E., Oliveira, C. R., Cardoso, S. M., & Pereira, C. F. (2013). Activation of the endoplasmic reticulum stress response by the amyloid-beta 1–40 peptide in brain endothelial cells. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease, 1832(12), 2191–2203. https://doi.org/10.1016/j.bbadis.2013.08.007

[8] Binder, L. I., Guillozet-Bongaarts, A. L., Garcia-Sierra, F., & Berry, R. W. (2005). Tau, tangles, and Alzheimer's disease. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease, 1739(2–3), 216–223. https://doi.org/10.1016/j.bbadis.2004.08.014

[9] Ho, Y.-S., Yang, X., Lau, J. C.-F., Hung, C. H.-L., Wuwongse, S., Zhang, Q., Wang, J., Baum, L., So, K.-F., & Chang, R. C.-C. (2012). Endoplasmic Reticulum Stress Induces Tau Pathology and Forms a Vicious Cycle: Implication in Alzheimer's Disease Pathogenesis. Journal of Alzheimer's Disease, 28(4), 839–854. https://doi.org/10.3233/JAD-2011-111037

[10] Lee, M. J., Lee, J. H., & Rubinsztein, D. C. (2013). Tau degradation: The ubiquitin–proteasome system versus the autophagy-lysosome system. Progress in Neurobiology, 105, 49–59. https://doi.org/10.1016/j.pneurobio.2013.03.001

[11] Song, S., & Jung, Y.-K. (2004). Alzheimer's disease meets the ubiquitin–proteasome system. Trends in Molecular Medicine, 10(11), 565–570. https://doi.org/10.1016/j.molmed.2004.09.005

[12] Liu, B., Zhu, Y., Zhou, J., Wei, Y., Long, C., Chen, M., Ling, Y., Ge, J., & Zhuo, Y. (2014). Endoplasmic reticulum stress promotes amyloid-beta peptides production in RGC-5 cells. Cell Stress and Chaperones, 19(6), 827–835. https://doi.org/10.1007/s12192-014-0506-7

[13] Cecarini, V., Ding, Q., & Keller, J. N. (2007). Oxidative inactivation of the proteasome in Alzheimer's disease. Free Radical Research, 41(6), 673–680. https://doi.org/10.1080/10715760701286159

[14] Keller, J. N., Hanni, K. B., & Markesbery, W. R. (2001). Impaired Proteasome Function in Alzheimer's Disease. Journal of Neurochemistry, 75(1), 436–439. https://doi.org/10.1046/j.1471-4159.2000.0750436.x

[15] Al Mamun, A., Uddin, Md. S., Kabir, Md. T., Khanum, S., Sarwar, Md. S., Mathew, B., Rauf, A., Ahmed, M., & Ashraf, G. M. (2020). Exploring the Promise of Targeting Ubiquitin-Proteasome System to Combat Alzheimer's Disease. Neurotoxicity Research, 38(1), 8–17. https://doi.org/10.1007/s12640-020-00185-1

[16] Bianchi, C., Alvarez-Castelao, B., Sebastián-Serrano, Á., Di Lauro, C., Soria-Tobar, L., Nicke, A., Engel, T., & Díaz-Hernández, M. (2023). P2X7 receptor inhibition ameliorates ubiquitin–proteasome system dysfunction associated with Alzheimer's disease. Alzheimer's Research & Therapy, 15(1), 105. https://doi.org/10.1186/s13195-023-01258-x

[17] Mishto, M., Bellavista, E., Santoro, A., & Franceschi, C. (2007). Proteasome Modulation in Brain: A New Target for Anti-Aging Drugs? Central Nervous System Agents in Medicinal Chemistry, 7(4), 236–240. https://doi.org/10.2174/187152407783220832

[18] Gadhave, K., Bolshette, N., Ahire, A., Pardeshi, R., Thakur, K., Trandafir, C., Istrate, A., Ahmed, S., Lahkar, M., Muresanu, D. F., & Balea, M. (2016). The ubiquitin proteasomal system: A potential target for the management of Alzheimer's disease. Journal of Cellular and Molecular Medicine, 20(7), 1392–1407. https://doi.org/10.1111/jcmm.12817

[19] Mladenovic Djordjevic, A. N., Kapetanou, M., Loncarevic-Vasiljkovic, N., Todorovic, S., Athanasopoulou, S., Jovic, M., Prvulovic, M., Taoufik, E., Matsas, R., Kanazir, S., & Gonos, E. S. (2021). Pharmacological intervention in a transgenic mouse model improves Alzheimer's-associated pathological phenotype: Involvement of proteasome activation. Free Radical Biology and Medicine, 162, 88–103. https://doi.org/10.1016/j.freeradbiomed.2020.11.038

[20] Wu, D., Wang, Y., Zhou, Y., Gao, H., & Zhao, B. (2023). Inhibition of the Proteasome Regulator PA28 Aggravates Oxidized Protein Overload in the Diabetic Rat Brain. Cellular and Molecular Neurobiology. https://doi.org/10.1007/s10571-023-01322-y

[21] Aso, E., Lomoio, S., López-González, I., Joda, L., Carmona, M., Fernández-Yagüe, N., Moreno, J., Juvés, S., Pujol, A., Pamplona, R., Portero-Otin, M., Martín, V., Díaz, M., & Ferrer, I. (2012). Amyloid Generation and Dysfunctional Immunoproteasome Activation with Disease Progression in Animal Model of Familial Alzheimer's Disease: Amyloid Generation and UPS in FAD Mice. Brain Pathology, 22(5), 636–653. https://doi.org/10.1111/j.1750-3639.2011.00560.x

[22] Li, J., Powell, S. R., & Wang, X. (2011). Enhancement of proteasome function by PA28α overexpression protects against oxidative stress. The FASEB Journal, 25(3), 883–893. https://doi.org/10.1096/fj.10-160895

[23] Li, N., Lerea, K. M., & Etlinger, J. D. (1996). Phosphorylation of the Proteasome Activator PA28 Is Required for Proteasome Activation. Biochemical and Biophysical Research Communications, 225(3), 855–860. https://doi.org/10.1006/bbrc.1996.1263

[24] Song, X., Mott, J. D., Von Kampen, J., Pramanik, B., Tanaka, K., Slaughter, C. A., & DeMartino, G. N. (1996). A Model for the Quaternary Structure of the Proteasome Activator PA28. Journal of Biological Chemistry, 271(42), 26410–26417. https://doi.org/10.1074/jbc.271.42.26410

[25] Goozee, K. G., Shah, T. M., Sohrabi, H. R., Rainey-Smith, S. R., Brown, B., Verdile, G., & Martins, R. N. (2016). Examining the potential clinical value of curcumin in the prevention and diagnosis of Alzheimer's disease. British Journal of Nutrition, 115(3), 449–465. https://doi.org/10.1017/S0007114515004687

[26] Anekonda, T. S. (2006). Resveratrol—A boon for treating Alzheimer's disease? Brain Research Reviews, 52(2), 316–326. https://doi.org/10.1016/j.brainresrev.2006.04.004

[27] Marambaud, P., Zhao, H., & Davies, P. (2005). Resveratrol Promotes Clearance of Alzheimer's Disease Amyloid-β Peptides. Journal of Biological Chemistry, 280(45), 37377–37382. https://doi.org/10.1074/jbc.M508246200