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# YAP: A Turning Point for Cognitive Function in AD

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## ABSTRACT

Alzheimer's Disease (AD) is a debilitating neurological condition often associated with gradual cognitive decline and memory impairment. A manner in which Alzheimer's presents itself is by impeding the astrocytic function caused by tau aggregates and amyloid beta plaques, which are thought to play a part in the pathogenesis of AD, leading to dysregulation of neurogenesis. The brain becomes incapable of developing new neurons leading to progressive neuronal loss and cognitive deterioration typical of Alzheimer's disease. However, recent studies have identified Yap as a promising target for new drugs. The development of many organs depends on a transcriptional cofactor known as Yes-associated protein (YAP), which is essential for the normal functioning Hippo pathway. However, its functions concerning brain development remain largely obscure. Furthermore, YAP has been seen to curb astrocytic senescence thereby enhancing neurogenesis required for combating the cognitive disorders accompanying hostile neuronal milieu common with AD. This paper examines one such study conducted wherein YAP was introduced to WT and AD mice and the results are then analyzed through rodent field tests. The results verified the claim that YAP can help curb Astrocytic Senescence and therefore retain and even slightly improve cognitive function. However, it is crucial to note that YAP has potential side effects. Side effects including tumor progression and cell proliferation are observed with YAP-inducing treatments since YAP is also a key player in organ growth and regeneration. Further study is crucial to solidify the position of YAP as a treatment for AD.

## Introduction

Aging is the greatest risk factor in connection with Alzheimer's disease (AD), though little is known about how aging affects the vulnerability of the brain to AD (Bhat et al., 2012). However, it is well-known that factors that worsen AD accelerate the degeneration of different brain functions, extending down to the neural level and affecting neurogenesis. In healthy adults, neurogenesis plays a crucial role in maintaining brain health but declines significantly in Alzheimer's patients. This early decrease in neurogenesis can increase neuronal susceptibility within the hostile environment of the AD brain.

Moreover, Alzheimer's is the largest neurodegenerative disease present across the world which signifies a greater global concern in relation to this disease. According to a UN report, population aging will be an inevitable global phenomenon since by 2050 there will be over twice as many people aged 65 or over globally compared to 761 million in 2021, reaching 1.6 billion by then with the most rapidly growing age cohort being 80 and above. Different factors such as age, age at onset, gender, and familial predisposition are associated with varying rates of disease progression. Understanding how AD progresses as well as the pathomechanisms responsible for its initiation may help us identify and test various treatment options available.

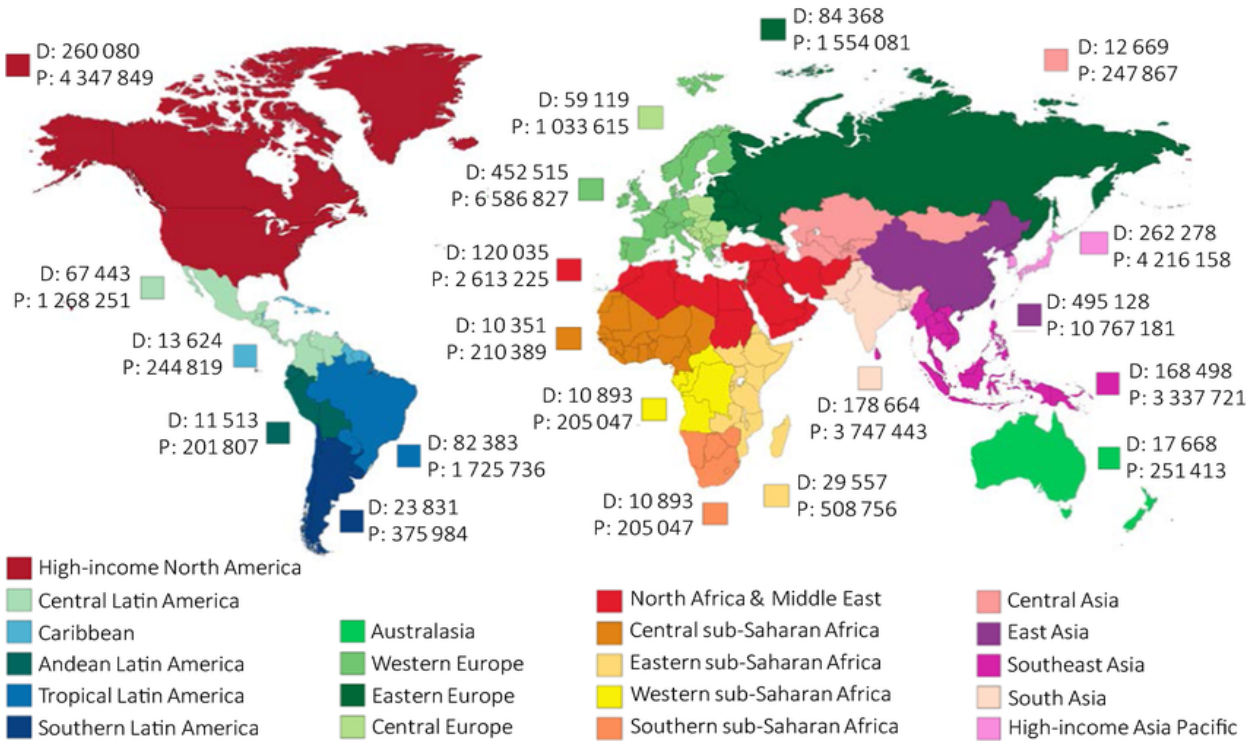


**Figure 1.** Worldwide distribution of Alzheimer's cases by global deaths (D) and prevalence (P)
Source: researchgate.net (2016)
Description: The map shown above is color-coded by region and the prevalence and death number for each region are listed in the map above. The worldwide prevalence and death rate imply the gravity of Alzheimer's across the world.

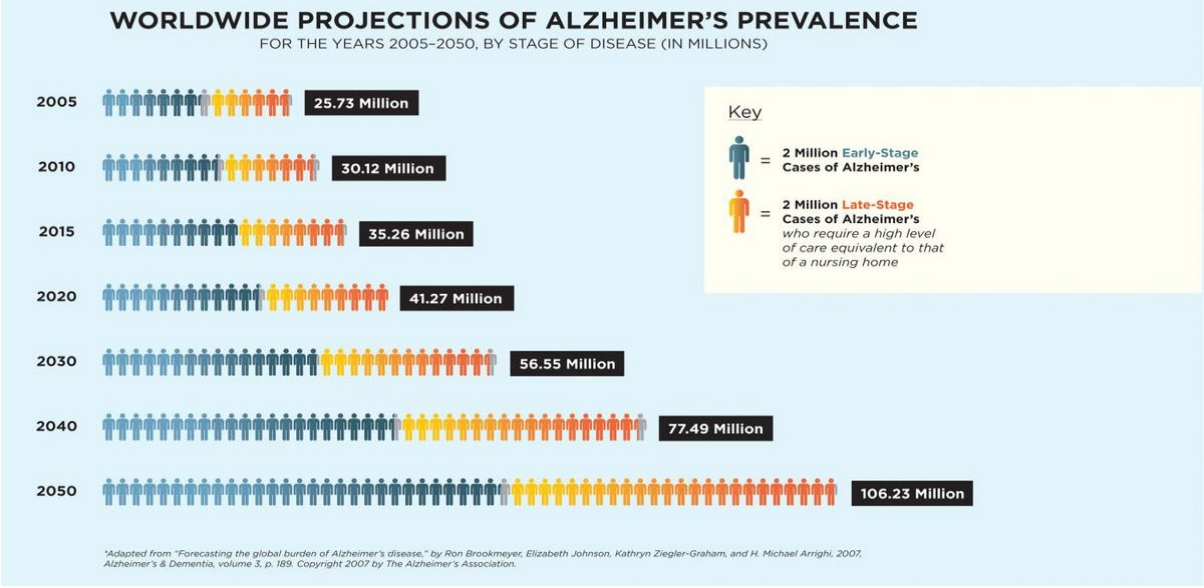


**Figure 2.** Projected worldwide Alzheimer's cases by 2050
Source: UCLA Newsroom (2016)
Description: The projection of worldwide Alzheimer's cases by 2050 are displayed through the chart above. By 2050, an estimated 106.23 million individuals are expected to either already have or be diagnosed with Alzheimer's. With a

number of that magnitude, scientists, researchers, and medical professionals are grappling to find methods to treat this disease or find additional ways for individuals with the disease to maintain their lifestyle.

Approximately 6.5 million Americans aged 65 and older are currently living with Alzheimer's dementia. This number could potentially increase to 13.8 million by 2060 unless there are significant medical breakthroughs to prevent, slow, or cure Alzheimer's disease. Official records indicate that 121,499 people died from Alzheimer's in 2019, the most recent year for which data is available. Alzheimer's disease was listed as the sixth-leading cause of death in the United States in 2019 and became the seventh-leading cause of death in 2020 and 2021, following the emergence of COVID-19 in the top ten causes of death. Alzheimer's remains the fifth-leading cause of death among Americans aged 65 and older. Between 2000 and 2019, while deaths from stroke, heart disease, and HIV decreased, reported deaths from Alzheimer's disease increased by over 145%.

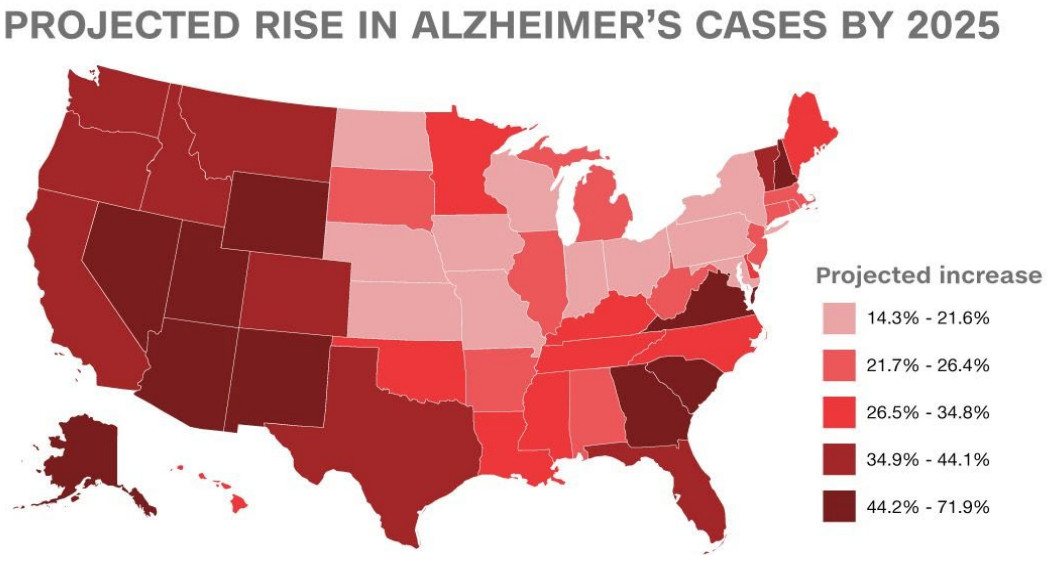


**Figure 3.** Distribution of projected Alzheimer's cases in the United States by 2025.
**Source:** Alzheimer's Association (2017)
**Description:** The map of the United States above showcases the rates and distribution of Alzheimer's in each state along with their projected increase based on color.

Researching cognitive decline in relation to Alzheimer's condition is crucial because of its extensive consequences on public health and wellness, very early medical diagnosis together with healing treatments. Because Alzheimer's is a leading cause of mental deterioration and even dementia later on, it progressively impairs cognitive features such as memory, thinking, and interaction, it drastically influences individuals' lifestyles and places a considerable amount of pressure on caregivers and also medical care systems. Recognizing the systems underlying cognitive decline with respect to AD and also finding potential treatments can not only assist in very early discovery but also much more efficient treatment approaches therefore boosting results for countless people globally.

## Methodology

The study primarily focuses on Alzheimer's Disease and utilizes a mixed-method approach, combining systematic literature review and content analysis to gain a thorough comprehension of the subject matter. A systematic review was conducted first to identify journals, articles, and scholarly works that are related to the topic being discussed and

it involved searching through multiple databases including but not limited to PubMed, JSTOR, and Google Scholar. This helped in narrowing down the boundaries of the investigation through keywords. The next step was selecting primary sources followed by thorough screening for quality purposes where only high-standard peer-reviewed articles were chosen according to pre-set criteria on pertinence and reliability. Secondly, content analysis required a close reading of textual data such as major findings, arguments used by authors, methods applied, and theoretical frameworks as employed in the reviewed papers. By grouping them into categories various literatures reveal patterns present within them hence bringing out issues such as trends or gaps that should be known when studying these topics.

## Alzheimer's Disease

Alzheimer's disease (AD) is a progressive neurodegenerative condition characterized by a gradual decline in cognitive function and memory loss. It is the most common form of dementia, affecting millions of individuals worldwide. Alzheimer's primarily targets regions of the brain responsible for memory, learning, and decision-making. AD is characterized by the presence of amyloid plaques, which are extracellular deposits of beta-amyloid protein, and neurofibrillary tangles, which are intracellular aggregates of hyperphosphorylated tau protein (Lin et al., 2020). These pathological features contribute to synaptic dysfunction, neuronal loss, and brain atrophy, particularly in regions associated with memory and cognition. Chronic neuroinflammation, involving the activation of microglia and astrocytes, exacerbates neuronal damage. Additionally, cerebral amyloid angiopathy, marked by beta-amyloid deposits in brain blood vessel walls, increases the risk of cerebral hemorrhage and cognitive decline. These abnormalities disrupt communication between nerve cells and eventually lead to their death, resulting in the progressive loss of cognitive abilities, behavioral changes, and ultimately, the inability to perform daily tasks independently. Although research has made strides in understanding the underlying mechanisms of Alzheimer's, effective treatments to halt or reverse the disease's progression remain elusive, highlighting the urgent need for further investigation and therapeutic interventions.

Scientists continue to unravel the mysteries that AD presents as definitive changes in the brain may begin a decade or more before symptoms appear. During this very early stage of Alzheimer's, an abnormal buildup of protein that forms amyloid plaques and tau tangles contributes to the beginning of a hostile, toxic neuronal environment. The damage associated with AD initially appears to take place in the Hippocampus and the Entorhinal Cortex, parts of the brain essential in cognitive function and forming memories. Moreover, "as the damage in Alzheimer's is widespread, neurons stop functioning properly and lose their connection with other neurons, resulting in neuronal death. By the final stages of Alzheimer's, brain tissue has shrunk significantly" (NIH National Institute on Aging, 2023). As we notice in the Brain diagram indicated in Figure 1, AD's mark on the brain is evident in the atrophy of the cortex and hippocampus.

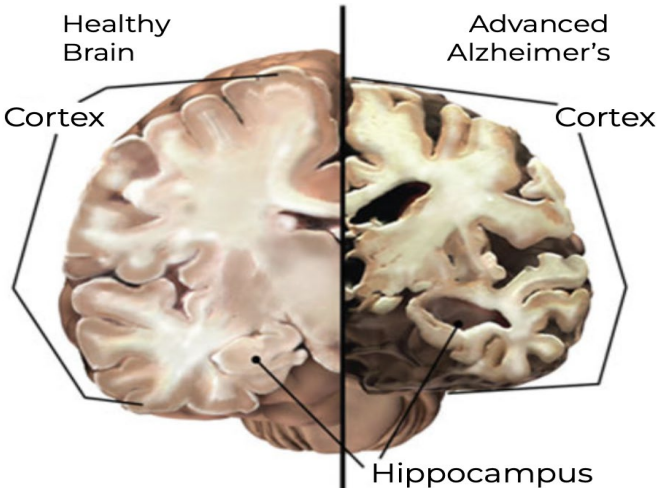

**Figure 4.** Comparison of a Healthy Brain alongside an individual with AD
Source: Alzheimer's Disease Fact Sheet, 2023
Description: A healthy brain is presented alongside a brain with Advanced Alzheimer's indicating the widespread neural and tissue damage characteristic of the condition.

Cognitive dysfunction is of interest to researchers and medical practitioners because late-stage Alzheimer's disease frequently causes dementia. The brain network pattern of early-stage Alzheimer's disease varies from normal aging in early-stage Alzheimer's disease. Developments in Alzheimer's disease have demonstrated that some circuits beyond memory and attention circuits have been altered, including sensory and motor processing circuits. In this respect, disorders like Lewy body dementia and Parkinson's disease dementia show similar cognitive symptoms to behaving, and they share common pathological features with AD. Vascular dementia, on the other hand, has cognitive deficits that are not uniformly distributed across patients. The results from this study underscore the significance of brain network-based biomarkers in distinguishing Alzheimer's-related cognitive decline from the normal aging process, which is likely to be of considerable significance for more accurate and early diagnosis and risk assessment. Given that pathological brain network changes attributable to Alzheimer's were discovered, independent of amyloid plaques, the study introduces a strong potential for characterizing cognitive pathology in Alzheimer's from a new perspective and presuming new therapeutic goals.

Finding an exact source or etiology of Alzheimer's disease is challenging in a variety of ways given this disease's complex and multifaceted nature. The occurrence of Alzheimer's Disease includes a wide range of symptoms, as well as a variety of pathological shifts in the brain, all of which ensure that there is no single source. Furthermore, the approach in which the disease manifests itself might differ from person to person, limiting the inquiry into a singular resource. Smaller-scale, intracerebral processes that underlie the pathology of Alzheimer's, such as amyloid-beta plaques and tau tangles, are complex molecular mechanisms for which very little consensus and understanding currently exist. Hence, extricating the sources of their occurrence is even more intimidating.

To understand this, it is important to note that AD is greatly affected by several factors; which include both genetic, environmental, and lifestyle factors. The relative prevalence or influence of each of these factors and how they work together is difficult to quantify. Genetic factors may also have a role in certain instances where the person may possess a mutation in APP, PSEN1, or PSEN2. However, there is also mutual evidence that disposition or environmental factors can contribute to Alzheimer's onset. It also takes many years or even decades for the diagnosis to be made in symptoms that may not be apparent, therefore, monitoring and tracing the progress of the disease from primary dementia to end-stage dementia is quite difficult. However, at present, there are no clear and effective biomarkers for early detection and diagnosis of Alzheimer's disease. Most individuals are diagnosed only when symptoms of the disease start appearing or when the disease has progressed.

As Alzheimer's begins to make its imprint on the patient's livelihood, activities of daily living and other physical-related activities are set to the back burner. Current management strategies for AD primarily focus on symptomatic relief and include pharmacological treatments targeting neurotransmitter imbalances, as well as non-pharmacological approaches like cognitive stimulation therapy (Spector et al. 2008) and lifestyle modifications (Klodian et al., 2020). Therapeutically, current interventions aim to alleviate symptoms and delay disease progression. Cholinesterase inhibitors and N-methyl-D-aspartate (NMDA) receptor antagonists remain mainstays in managing cognitive symptoms (Shega et al., 2009), albeit with limited efficacy in improving cognitive impairments across related dementias, with ongoing studies investigating their symptomatic and potentially disease-modifying effects. Emerging treatments targeting amyloid and tau pathology, including monoclonal antibodies and small molecule inhibitors, are under rigorous investigation in clinical trials (Congdon et al., 2018). Moreover, non-pharmacological approaches, such as cognitive stimulation and physical exercise, show potential in enhancing cognitive reserve and quality of life for individuals with AD (Meng et al., 2020). Promoting and sustaining this rapid reduction in cognitive function and neurogenesis could potentially mitigate further neuroinflammation and cognitive decline. Therefore, using YAP as a

roadmap in potential Alzheimer's therapy is essential to understand a method in which we can prevent further neurological deficits and impairment.

## Adult Neurogenesis

Adult neurogenesis is one the most considerable forms of brain plasticity in adulthood and there is an increasing body of evidence indicating its' significant role in memory mechanisms within the hippocampus (Casse et al., 2018). Neurogenesis is the process by which new neurons are generated in the brain by neural stem cells (NSCs) and occurs mainly in two regions of the brain: the hippocampus, which is involved in learning and memory, and the olfactory bulb, which is responsible for processing smell. Neurogenesis is a complex process involving the proliferation, migration, and differentiation of neural stem cells into mature neurons which is not crucial but necessary for brain development during embryonic and early postnatal stages and certain forms of learning, memory, and recovery from brain injury or disease in adulthood (Kumar et al., 2019). In the condition of AD, the number and maturation of neurons associated with the hippocampal dentate gyrus and the lateral ventricle of the adult brain declines progressively (Noureddini & Mohammadi et al., 2021), therefore suggesting the relation between the deterioration of neurons and the decline in neurogenesis which contributes to a decline in cognitive function as well; all attributed to AD pathology.

### Relation Between Yap1 and Neurogenesis

In a study at King's College in London, researchers at the Center for Developmental Neurobiology sought to understand the processes supporting neurogenesis in the adult hippocampus. Through the analysis of data from RNA sequencing, researchers found that Yap1 is enhanced in activated NSCs which then prompted a closer look at the role of Yap1 in relation to Neurogenesis and cognitive maintenance (Jurado-Arjona et al., 2023).

### Altered Neurogenesis and AD Progression

Multiple disease-related metabolites (APP) or regulators (PSEN1 of GSK-3β) affect adult hippocampal neurogenesis, therefore, it could be possible that alteration of neurogenesis facilitates the AD pathogeny (Sung et al., 2020). Furthermore, a recent investigation by (Choi et al., 2018), examined the relation between neurogenesis and AD disorder.

Their study findings indicated that substantial suppression of adult hippocampal neurogenesis (AHN) in the early disease phases (six to eight weeks) did not affect the accumulation of Aβ plaques or the severity of gliosis, but it did result in the death of mature neurons and aggravated cognitive dysfunction in later disease stages (five months) in the 5xFAD mice, and this result insinuates that early alterations in neurogenesis do not directly impact Aβ pathology. However, impaired hippocampal neurogenesis during the initial stages of Alzheimer's disease (AD) may heighten the vulnerability of hippocampal neurons, potentially worsening cognitive impairment and neuronal loss during subsequent disease stages, especially in the presence of an unfavorable brain environment (Sung et al 2020).

## Astrocytes

Astrocytes are a type of glial cell found in the central nervous system, primarily in the brain and spinal cord. They are star-shaped cells with numerous processes that extend outward and interact with neurons and blood vessels. Astrocytes play crucial roles in maintaining the health and function of neurons by regulating the chemical environment, providing structural support, and participating in the repair of damaged tissue (Wei et al., 2023). They also modulate synaptic transmission and contribute to the blood-brain barrier, which controls the passage of substances between the bloodstream and the brain. Additionally, recent research suggests that astrocytes are involved in various neurological

functions, including synaptic plasticity, learning, and memory. Synaptic plasticity is the capacity of neurons to adjust the efficacy of their connections, playing a vital role in the neurophysiological development of brain networks and their reorganization following injury.

Astrocytes have a profound impact on Neurogenesis as they are able to control whether aNSCs mature into neurons through membrane-membrane interactions as well as extracellular signaling (Lim & Alvarez-Buylla, 1999). Astrocytes can also influence the formation of synaptic connections and the migration of new neurons (Griffiths et al., 2019).

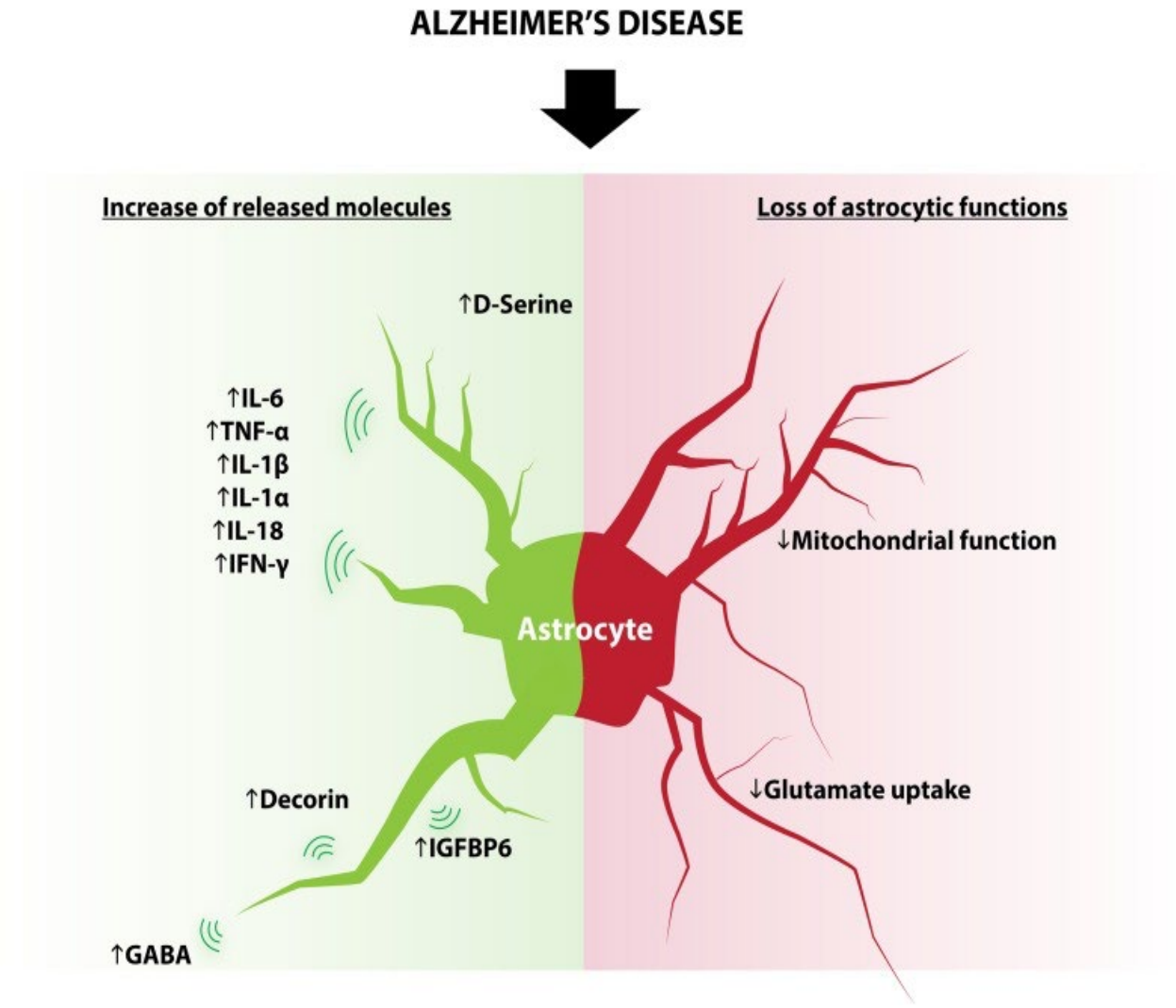


**Figure 5.** Changes in Astrocytic Function due to AD
Source: Cassé et al., 2018
Description: Changes in astrocytes occur in Alzheimer's disease (AD), affecting various functions crucial for adult neurogenesis. These alterations involve heightened levels of d-serine, IL-6, TNF-α, IL-1β, IL1-α, IL-18, IFN-γ, decorin, IGFBP6, and GABA, along with diminished glutamate reuptake and compromised mitochondrial function.

Astrocytes exhibit an intensified sensitivity to oxidative stress and trigger the initiation of a senescence pathway when exposed to various stress factors (Bhat et al., 2012). In a study conducted by researchers at Drexel University in the United States, brain tissue samples from older individuals and patients with AD were examined for the

presence of senescent astrocytes using p16(INK4a) and matrix metalloproteinase-1 (MMP-1) expression, both of which can indicate senescence. The results indicated increased metalloproteinase MMP-1 correlated with p16(INK4a) which was also consistent with the senescent nature of the p16(INK4a)-positive astrocytes (Bhat et al., 2012). Through this study, researchers found that senescent astrocytes release several inflammatory cytokines and could potentially connect advanced age with a heightened risk of sporadic Alzheimer's disease (Bhat et al., 2012).

However, the overarching effects of atrophy of astrocytes are not limited to AD itself; emerging evidence suggests that early stages of neurodegenerative processes are being linked to the premature deterioration of astroglia which then causes imbalances in synaptic connectivity, neurotransmitter homeostasis, and neuronal death due to increased excitotoxicity (Verkhratsky et al., 2010).

## Relation Between Astrocytes and AD Progression

Astrocytes carry out many essential functions in the neurological setting due to which their dysfunction connects them to several neurological disorders including AD (Griffiths, B. et al 2019), and these astroglial cells are actively engaged in the progression and outcome of pathological changes in the nervous system. However, new findings suggest that senescent astrocytes play a crucial role in instigating and advancing the development of Alzheimer's disease (AD) (Han et al., 2020).

As previously discussed in the factors of Alzheimer's disease, the heightened cleavage of amyloid precursor protein (APP) by beta and gamma secretases (as opposed to alpha-secretase, which typically cleaves APP into a non-toxic form that the body can eliminate) leads to the formation of abnormal beta-amyloid plaques. Under normal circumstances, astrocytes become reactive when they are exposed to these amyloid plaques. This sets a cascade into motion in which the astrocytes release proteases and other substances in order to degrade and clear the amyloid plaques from the CNS (Wei et al. 2023). However, the pathological aggregation of the amyloid plaques associated with the pathogenesis of AD causes astrocytes to deteriorate. This deterioration process happens in the locus coeruleus, where astrocytes carry out essential functions such as glycogen metabolism, synapse maintenance, and calcium signaling (Wei et al., 2023).

Senescent astrocytes can exhibit certain characteristics such as an enlarged and flattened composition along with the formation of vacuole-like structures (vacuolated), increased levels of senescence-associated β-galactosidase activity, leading to cell cycle arrest, and an elevation in the expression of proteins like p16, p53, and p21, coupled with a decrease in Lamin B1. Furthermore, these astrocytes exhibit the presence of a senescence-associated secretory phenotype (SASP) (Han et al., 2020).

Furthermore, as the brain is particularly sensitive to aging, premature astrocytic senescence occurs in which astrocytes acquire neurotoxic functions, which then contribute to the decline of neuronal survival and performance. This contributes to the loss of neurogenesis and cognitive function associated with AD.

## Astrocytic Senescence in Relation to Cognitive Function

One point that has been iterated is the cruciality of aging in relation to neurodegenerative disorders, and this aging can be attributed to environmental stressors which over time accumulate and burden cellular defense systems. When this damage has progressed far enough, cellular defense systems enter what is known as replicative senescence. Aggregation of senescent cells in tissues and organs influences the pathogenesis of disease as well as drives the aging process and age-related diseases (Childs et al., 2015). In turn, these senescent astrocytes can then contribute to Astrocytic senescence in several ways such as reduced support for neuronal function, increased inflammatory signaling, dysregulated neurotrophic factor secretion, and impaired clearance of toxic molecules.

Under normal conditions, Astrocytes provide support for neurons by regulating neurotransmitter levels, maintaining the blood-brain barrier, and clearing metabolic waste products, but senescent astrocytes become less effective in these supportive functions, leading to impaired neuronal signaling and synaptic dysfunction.

Senescent cells, including astrocytes, can release inflammatory molecules such as cytokines, chemokines, and reactive oxygen species as part of the senescence-associated secretory phenotype (SASP) (Csipo et al., 2020). This chronic low-level inflammation can contribute to neuroinflammation, which has been implicated in various neurodegenerative disorders, including Alzheimer's disease. Neuroinflammation can further exacerbate synaptic dysfunction and neuronal damage, ultimately impairing cognitive function. Additionally, changes in mitochondria within astrocytes in Alzheimer's disease (AD) also disrupt adult neurogenesis, aggravating symptoms of the disease.
Because senescent astrocytes have a reduced capacity to clear toxic molecules efficiently, leading to their accumulation in the brain and subsequent neuronal toxicity and cognitive impairment, looking into clearing the toxic aggregates or any therapeutic intervention that prevents this astrocytic senescence would aid in combating cognitive decline.

## YAP Protein

YAP1, alternatively known as YAP or YAP65, is a transcription coregulator which facilitates the transcription of genes associated with cellular proliferation. Research indicates that YAP has the capability to hinder the senescence process in different cell types, including glioblastoma cells (Xu et al., 2020). In D-galactose-induced senescent glioblastoma cells, a down-regulation of YAP expression is present; conversely, enhancing YAP expression partially alleviates glioblastoma cell senescence, underscoring the involvement of YAP in the regulation of cellular senescence (Xu et al., 2020).

Recently, our research has revealed that YAP experiences down-regulation and inactivation in senescent astrocytes, not only within cultured senescent astrocytes but also in hippocampal astrocytes of aging mice and mice models of Alzheimer's disease (AD), in a manner dependent on the Hippo pathway. This underscores the involvement of YAP in astrocytic senescence (Xu et al., 2021).

The Hippo pathway is a fundamental cellular regulatory network that moderates organ size, apoptosis, and cell proliferation. By regulating YAP (Yes-associated protein) and TAZ (transcriptional coactivator with PDZ-binding motif), thus ensuring tissue homeostasis and cancer prevention by means of controlling transcriptional co-activators. Therefore, the Hippo pathway when activated phosphorylates YAP/TAZ resulting in their retention within the cytoplasm for subsequent degradation, thereby inhibiting them from driving gene expression through promoting survival as well as growth of cells. Thus, if there is any dysregulation of this pathway leads to uncontrolled division of cells and tumorigenesis, which makes it an essential field of research in regenerative medicine and cancer biology.

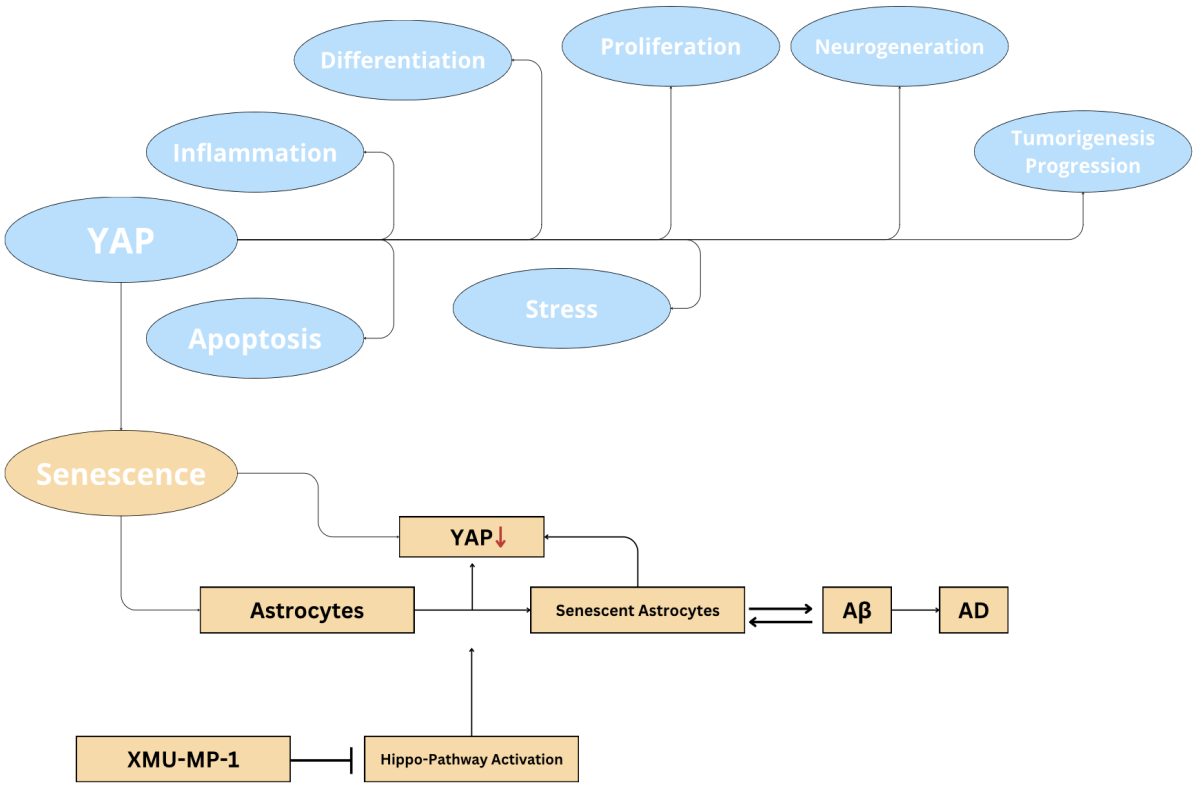


**Figure 6.** Functions of YAP and the specific breakdown of YAP and its role in senescence
Source: Tejasvi Kondury, 2024
Description: YAP1 is involved in downregulation of astrocytic senescence associated with AD. Inhibition and/or downregulation of YAP promotes senescence of astrocytes and may increase deposition of Aβ, which in turn, aggravates senescence of astrocytes, which then contributes to the pathogenesis of aging-related brain diseases such as AD.

In previous studies, the inhibition of YAP has been shown to promote the senescence of IMR-90 cells through downregulation of CDK6- a cyclin-dependent kinase (Xie et al. 2013). Therefore, (Xu et al 2021) tested whether YAP prevents the senescence of astrocytes through the same method of CDK6 signaling. When comparing the expression of YAP and CDK6 in the hippocampus of old and young mice, the YAP and CDK6 levels were notably decrease in the old mice and more so, the protein levels of YAP and CDK6 were decreased in the AD model mice, signifying that YAP-CDK6 signaling is reduced in the old mice and AD model mice.

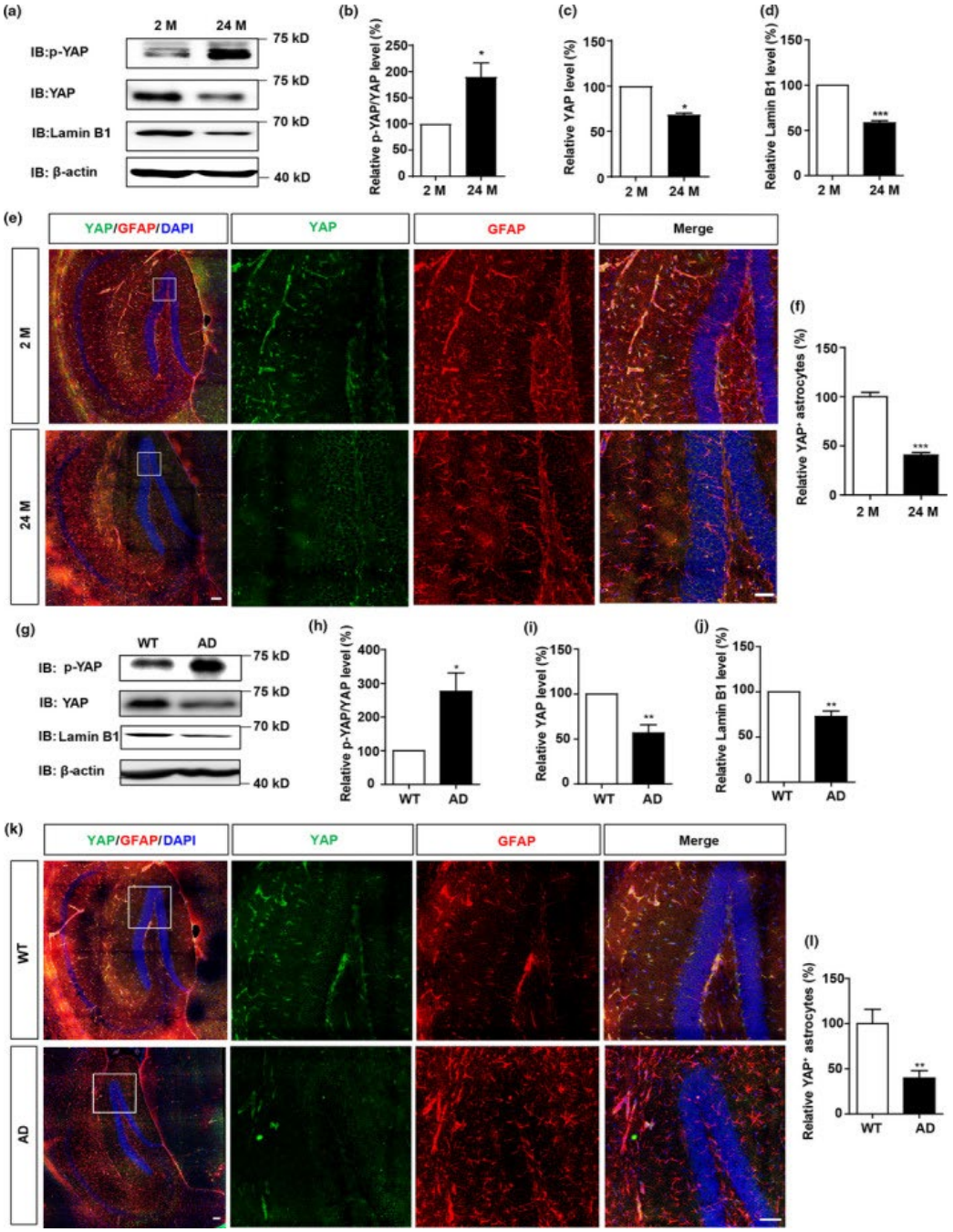


**Figure 7.** Western Blot Analysis and Double Immunostainting conducted on hippocampal tissue samples of WT and AD mice

Source: Xu et al., 2021

Description: In the study done by (Xu et al 2021), analysis of hippocampal tissue samples of aged mice and AD model mice displayed lower and even inactive levels of YAP, p-YAP, and Lamin B1 in hippocampal astrocytes.

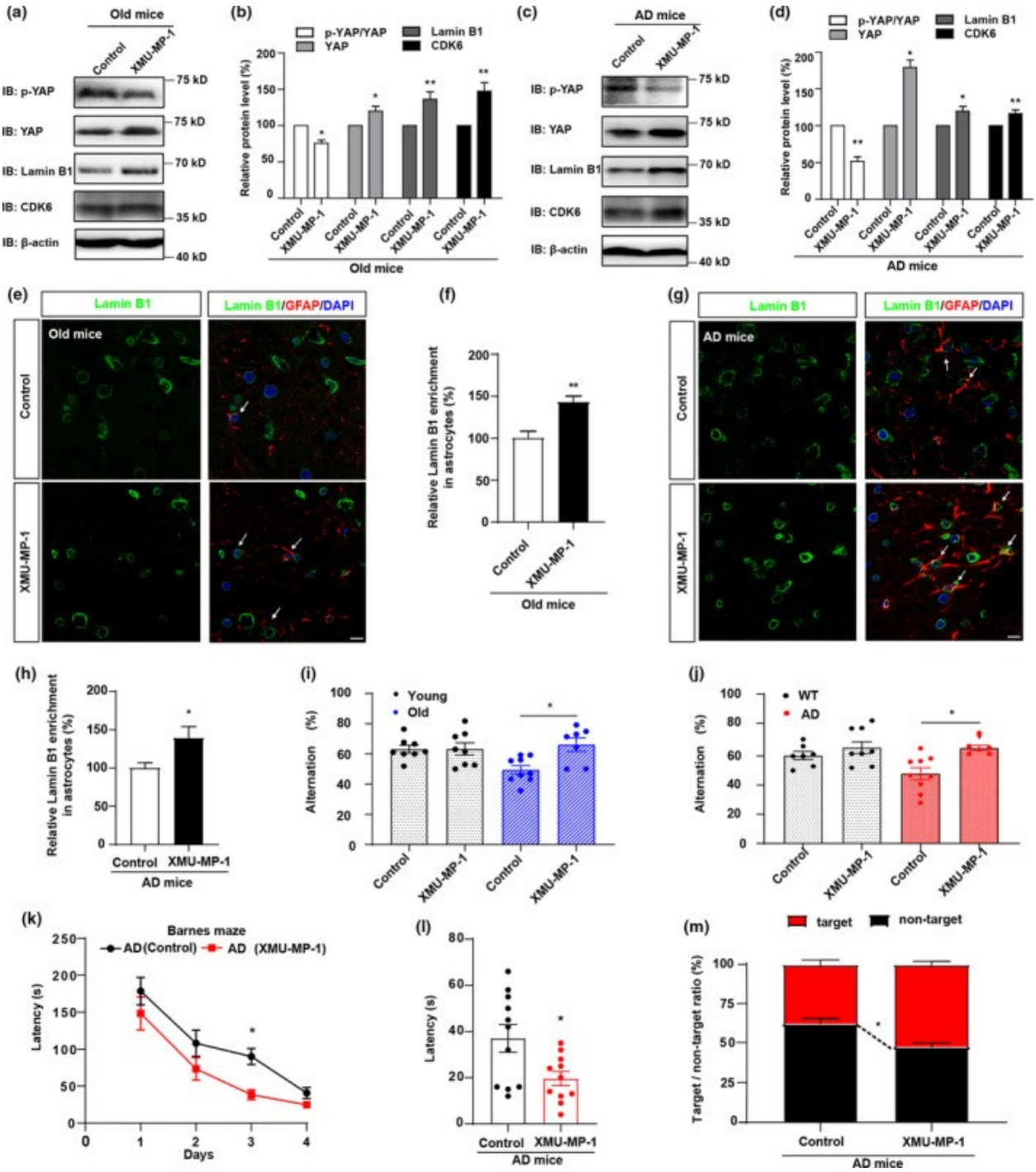


**Figure 8.** Results of Western Blot Analysis, Double-Immunostaining Analysis, Barnes Maze Test, and the Y-maze Test indicating effects of the XMU-MP-1 treatment.

Source: Xu et al. 2021

Description: Activation of YAP by XMU-MP-1 in AD model mice and even aged mice showed significant improvement in cognitive function as demonstrated in the results from the Barnes Maze Test and Y-Maze test.

(Xu et al., 2021) also investigated whether slowing down the senescence of astrocytes was able to enhance the cognitive function of the aged mice and AD model mice where YAP-CDK6 signaling was previously shown to be reduced. The Y-maze test, a behavioral test for measuring the disposition of the rodents in new environments indicated a considerable increase in the number of alternations – successive entries into each branch of the Y-maze without repeating any – by XMU-MP-1 treatment, which increases YAP1 activation (Mitchell et al., 2020). This increase in alternations was shown in the AD model mice and aged mice but not the young mice as displayed in diagrams I-J of Figure 6, from which we can infer that the stimulation of YAP in astrocytes improves the cognitive function and memory capacity in the AD model mice and old mice (Xu et al., 2021). Furthermore, the Barnes maze test – a dry-land-based rodent behavioral paradigm used to evaluate spatial learning and memory – performed in AD model mice indicated that cognitive function was enhanced in the AD model mice by the XMU-MP-1 treatment as the AD model mice reached the target exit quicker as well as the correct target as shown in k-m of figure 6 (Xu et al., 2021).

These studies suggest that stimulation or activation of YAP-CDK6 signaling by XMU-MP-1 has an effect on astrocytic senescence by delaying it and consequently demonstrating an improvement in the cognitive function of aged and AD model mice (Xu et al., 2021) which would provide us with further knowledge and aim to delay aging-related senescence and neurodegenerative disorders such as AD (Xu et al., 2020).

## Conclusion

Ultimately, AD poses a challenge to neurology since it is responsible for millions of people with severe outcomes like cognitive decline and memory loss. The connection between neurogenesis, astrocytic function, and the pathogenesis of this malady adds complexity to this condition. Latest studies have indicated that Yes-associated protein (YAP) plays a significant role in preventing the senescence of astrocytes and promoting neurogenesis within the harsh neuronal environment characteristic of AD. Based on its participation in the Hippo pathway, YAP may be used as a therapeutic target for the maintenance of cognitive functions and alleviation of neurodegeneration during AD. However, YAP activation seems capable of retarding astrocytic senescence and improving preclinical models' cognitive outcomes; more research needs to be done to understand how YAP is regulated by various mechanisms at different stages of AD. Furthermore, bench-to-bedside translation of YAP-based therapies has some obstacles including potential adverse effects/side effects as well as effective delivery methods. Nevertheless, using YAP as a therapeutic approach is a remarkable breakthrough toward revealing the basis for understanding and treating AD in future diseases. Further study along with advancements in gene therapy and targeted drug delivery, holds promise for the development of novel therapeutic strategies to combat the devastating effects of AD and improve the quality of life for millions affected by this debilitating condition.

## Limitations

Although YAP shows great promise in combating AD, subsequent studies and research are needed before any therapeutic claims are made. Dysregulation or overexpression of YAP has been associated with several pathological conditions and diseases, including cancer. The side effects of aberrant YAP activity can vary depending on the context and affected tissues but may include uncontrolled cell proliferation, tumor formation, metastasis, and resistance to therapy. Additionally, excessive YAP activation can disrupt normal tissue architecture and homeostasis, leading to organ dysfunction or developmental abnormalities. Therefore, understanding the precise regulation of YAP and its downstream signaling pathways is essential for developing targeted therapies to mitigate its adverse effects while harnessing its beneficial roles in tissue repair and regeneration.

Moreover, another significant concern that comes with this proposal is the mode of treatment: gene therapy. While gene therapy holds great promise for treating a wide range of genetic disorders and other diseases, several potential challenges and limitations can be considered as its letdowns. One significant concern is the immune response

triggered by the delivery vector used to introduce the therapeutic gene into the body. Adverse immune reactions can lead to inflammation, tissue damage, and even rejection of the modified cells, limiting the effectiveness of the treatment. Another challenge is the difficulty in achieving long-term and stable expression of the therapeutic gene. The transient nature of some gene therapy approaches may require repeated administrations to maintain therapeutic benefits. Additionally, the potential for off-target effects, where the therapeutic gene is inadvertently inserted into the wrong location in the genome, raises safety concerns. Furthermore, the high cost of gene therapy treatments poses a significant barrier to access for many patients, limiting its widespread adoption. Despite these challenges, ongoing research and technological advancements continue to address these limitations, offering hope for the continued improvement and broader application of gene therapy in the future.

## Acknowledgment

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