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Systematic Review Article

Physiological Roles of Hippo Signaling Pathway and Autophagy in Dementia

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Abstract

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Conclusion: The impairment of the Hippo signaling pathway and autophagy in the dementia process in aging should be considered since it might predict the severity, treatment, and prevention of dementia.

Keywords: Aging, autophagy, brain, dementia, Hippo signaling pathway, neurodegeneration.

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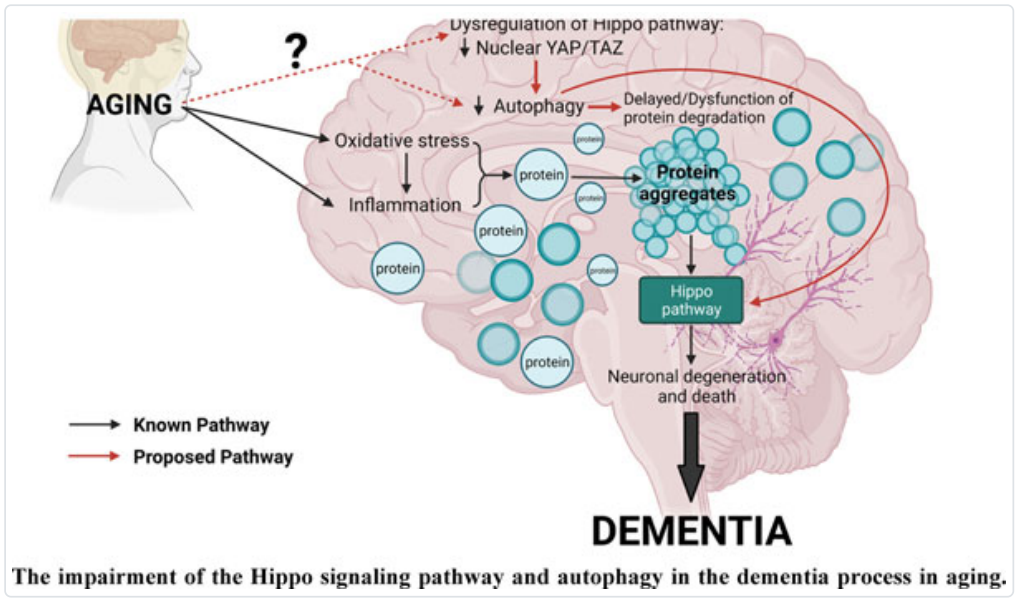

The impairment of the Hippo signaling pathway and autophagy in the dementia process in aging.

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Yenni Limyati et al., Curr Cardiol Rev, 2022

Hippo Signaling: A Stress Response Pathway in Stem Cells
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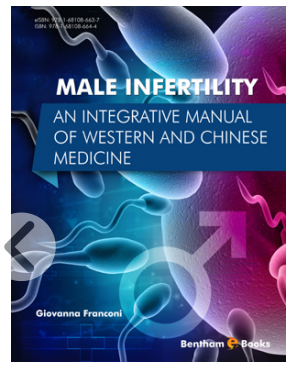

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SYSTEMATIC REVIEW ARTICLE

Physiological Roles of Hippo Signaling Pathway and Autophagy in Dementia

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Abstract: ***Background*:** Dementia is a neurocognitive disorder associated with the aging brain and mainly affects the hippocampus and cerebral cortex. The Hippo signaling pathway and autophagy proteins have been found to be perturbed in the brain affected by dementia processes.

***Objective*:** This systematic review aims to elaborate on the involvement of the Hippo signaling pathway and autophagy in modulating the progression and severity of dementia in aging.

***Methods*:** Searches were conducted on MEDLINE, Google Scholar, Scopus, and Web of Science databases.

***Results*:** The Hippo signaling pathway is dependent upon the transcriptional co-activator YAP/TAZ, which forms complexes with TEAD in the nucleus in order to maintain cell homeostasis. When the expression YAP/TAZ is reduced, transcriptional repression-induced atypical cell death, ballooning cell death, and necrosis will consequently occur in the neurons. Moreover, the autophagic proteins, such as *LC3*, *ATG* proteins, and *Beclin*, are reduced, resulting in the disruption of autophagosome formation and accumulation and the spread of misfolded proteins in the brain suffering from dementia.

***Conclusion*:** The impairment of the Hippo signaling pathway and autophagy in the dementia process in aging should be considered since it might predict the severity, treatment, and prevention of dementia.

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1. INTRODUCTION

Dementia is a term that refers to a group of neurocognitive disorders marked by gradual memory impairment and cognitive and motor deterioration. It is mainly a form of neurodegeneration that typically occurs during and is associated with aging [1, 2]. However, the dementia process is not the norm and does not occur in all aging processes. The loss of executive and memory function and attention, the reduction of grey and white matter volume, and other alterations of activity level in the brain occur in normal aging, but more gradually [3]. The progression of dementia accelerates in some populations with various risk factors, such as cardio-

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vascular diseases. According to the CDC, African Americans and Hispanics have the highest prevalence of dementia among other races or ethnic groups. Alarmingly, the future generations of these groups are predicted to have a threefold increase in risks of dementia in their old age [4].

Moreover, the dementia progression in aging is accelerated in certain diseases, such as Alzheimer's disease, vascular dementia, or Lewy body disease. These diseases affect parts of the brain, albeit manifested in different types and levels of protein changes and gene expression belonging to similar pathways [5, 6]. Consequently, the hippocampus and cerebral cortex, the crucial structures in learning and memory functions, are damaged morphologically and functionally in dementia [2, 7].

The alteration and inactivation of the Hippo signaling pathway in the hippocampus and cerebral cortex have been causally linked to dementia-causing diseases. The reduction of Hippo signaling effectors proteins in the hippocampus and cerebral cortex is associated with the progression and severity of dementia [8, 9]. The Hippo signaling pathway modulates cell growth and death. It has been identified in *Drosophila melanogaster* and mammals [10]. Yes-Association Protein (YAP) and the transcriptional co-activator with PDZ-binding motif (TAZ) are essential components of the Hippo pathway. In *Drosophila*, YAP/TAZ or Yorkie binds to the TEA domain family member 1 (TEAD) transcription factor to regulate cell survival and death. Increased TEAD activity mediated by YAP is linked to cell proliferation and differentiation. An increase in p73 activity and a decrease in TEAD activity, on the other hand, promoted apoptosis and necrosis [10, 11].

The modulation of the Hippo pathway by amyloid precursor protein (APP) and amyloid β peptides has been studied. In agreement with the study by Tanaka *et al.*, intracellular amyloid β (Aβ) accumulation removes YAP from the nucleus in Alzheimer's disease. Reduced levels of nuclear YAP due to activation of the Hippo pathway in cortical neurons stimulate Hippo pathway-dependent necrosis and accumulation of the inflammatory cytokines [9, 11-13]. Therefore, the Hippo signaling pathway appears to be induced by Aβ accumulation in the hippocampus, which promotes neuronal cell death and triggers neurodegeneration [14].

Proteins, such as amyloid β peptides and tau, accumulate in the brain and cause the simultaneous occurrence of microglia activation and neuronal damage. The activation of microglia is initiated by the senescence-associated secretory cytokines and chemokines, such as IFNγ, IL-6, and IL-8, produced by astrocytes that undergo senescence [15, 16]. Aβ accumulation has also been associated with the occurrence of fewer neurons and more microglia [14, 17]. In the hippocampus, the accumulation of Aβ can cause aberrant mitochondrial dynamics and biogenesis defects [18].

According to the research conducted by Chen *et al.* and Manczak *et al.*, autophagy and mitophagy also play a significant role in the progression of dementia. The expression of the autophagy-associated genes, such as *ATG5*, *Beclin1*, and *LC3*, and mitophagy genes *BNIP3L*, *PINK1*, and *BCL2*, increases in the early onset of Alzheimer's disease but decreases in the late onset of disease. The dysregulation of autophagy genes will reduce misfolded protein degradation and consequently promote the accumulation of those proteins, thus increasing the severity of neurodegeneration and dementia [17-19].

The Hippo signaling pathway proteins, YAP/TAZ, play a role in regulating the autophagic flux by controlling the autophagosome and autolysosome. In addition, the autophagic flux maintains the homeostasis of cell proliferation and death by keeping YAP/TAZ at a constant level to prevent them from overpromoting nuclear cell growth [20]. When the Hippo signaling pathway is activated by external stimuli and the co-activator protein YAP/TAZ expression is reduced, the dysregulation of the formation and maturation of intracellular autophagosome and autolysosome occurs. This dysregulation will result in the failure of 'recycling' misfolded or damaged proteins and organelles, and consequently, untimely cell death occurs [11, 14]. To our knowledge, there is no systematic review exploring the relationship between the Hippo signaling pathway and autophagy in neurodegeneration and neuronal death in terms of the progression of dementia. Thus, the present review attempted to discuss the involvement of the Hippo signaling pathway and autophagy in modulating the progression and severity of dementia in aging.

2. MATERIALS AND METHODS

The systematic review was conducted by searching the MEDLINE database, Scopus, Google Scholar, and Web of Science in August 2021. The guiding question was as follows: Are the Hippo pathway and autophagy involved in the process of dementia, and what are the roles of the Hippo pathway and autophagy in the progression of dementia? The search strategy is shown in Supplementary Table **S1**. The search was limited to papers published between 2011 and 2021. We included articles, not limited to *in vitro* studies, animal models, and clinical trials, that describe the outcome of any process of dementia concerning the Hippo pathway and autophagy and any condition influencing the Hippo pathway and autophagy in dementia. This study's exclusion criteria were review articles as they might impart biases and studies that do not explicitly illustrate the role of the Hippo pathway and autophagy in relation to dementia and aging.

The titles and abstracts of the papers that fulfilled the eligibility criteria were evaluated independently by two investigators. If feasible, the full text of the publications was retrieved. Only English-language publications were included. Any disagreements regarding the eligibility of a particular article were resolved through discussion with a third investigator. The papers were then exported to Mendeley. The data were collected from the article, such as methodology, the outcome of the study, and references. The collected data were then tabulated in Microsoft Excel.

3. RESULTS AND DISCUSSION

3.1. Characteristics of the Included Studies

A total of 425 scientific articles were retrieved from MEDLINE, Scopus, Google Scholar, and Web of Science (Fig. **1**). The articles were first screened through the titles and abstracts, resulting in sixty articles. Further screening of the full texts was carried out, and nineteen articles were excluded because they did not explore the relationship between

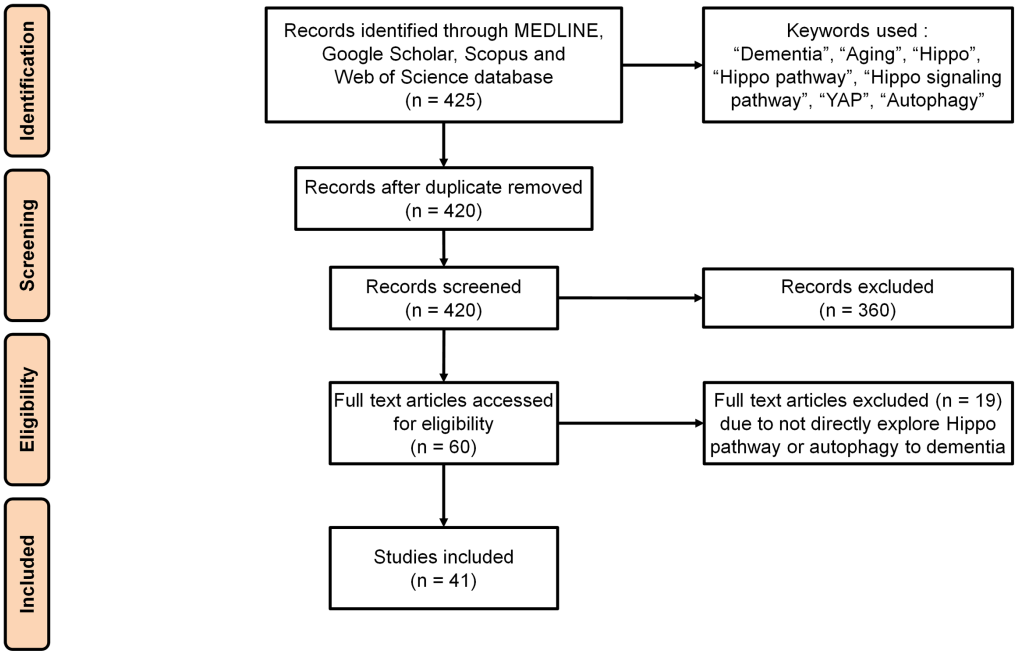

Fig. (1). The screening process of the included studies. Forty-one research articles from 425 articles were included in the systematic review. The screening process was adopted by Page *et al.* [21].

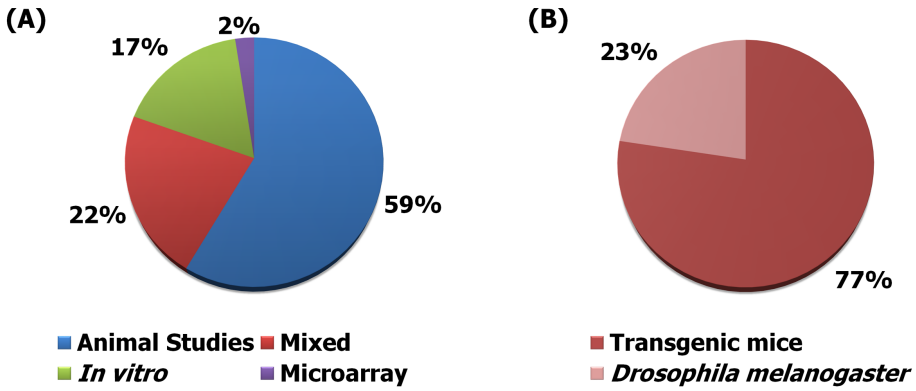

Fig. (2). The characteristics of the study. (**A**) The majority of the studies in the review were animal studies, followed by mixed studies, *in vitro* experiments, and microarray studies; (**B**) The majority of the experimental animals involved in the studies in the review were mammals (transgenic mice) and insects (*Drosophila melanogaster*). (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

the Hippo pathway or autophagy and dementia. As a result, forty-one articles were included in the present systematic review. A summary of the included studies and their findings are shown in Supplementary Table **S2**.

A total of 24 animal studies (59%) were included in this review, followed by 9 (22%) mixed studies (*in vitro* and *in vivo* animal studies), 7 (17%) *in vitro* studies, and 1 (2%) microarray study (Fig. **2**). From the animal and mixed studies, 27 (77%) studies conducted the research using mammals, and 5 (23%) studies using insects.

3.2. Dementia and Hippo Signaling Pathway

The Hippo signaling pathway, often called Salvador/Warts/Hippo (SWH) pathway, was first discovered in *Drosophila melanogaster* and, subsequently, in mammals. The Hippo signaling pathway is a serine/threonine kinase signaling cascade, with the involvement of prostate-derived sterile 20-like kinases/TAO kinases (PSK/TAOK), mammalian Ste20-like kinases 1/2 (MST1/2), large tumor suppressor 1/2 (LATS1/2), and transcriptional co-activator yes association protein (YAP) and its paralog TAZ, as well as TEA domain-containing sequence-specific (TEAD) transcription factors. PSK/TAOK phosphorylates and activates MST1/2 when the Hippo pathway is active, and MST1/2 activation phosphorylates SAV1 and MOB1A/B, consequently promoting the phosphorylation of LTS1/2 (Fig. **3**). The YAP/TAZ transcriptional co-activator is inactivated when LATS1/2 is phosphorylated and activated. When the Hippo pathway is not active, the active proteins of YAP and TAZ bind directly to the nucleus and interact with TEAD, activating several genes involved in cell growth and organ size control [10, 22].

Cell death can occur when the Hippo signaling system is disrupted. The accumulation of Aβ peptide, the product of amyloid precursor protein miscleavage, in the hippocampus

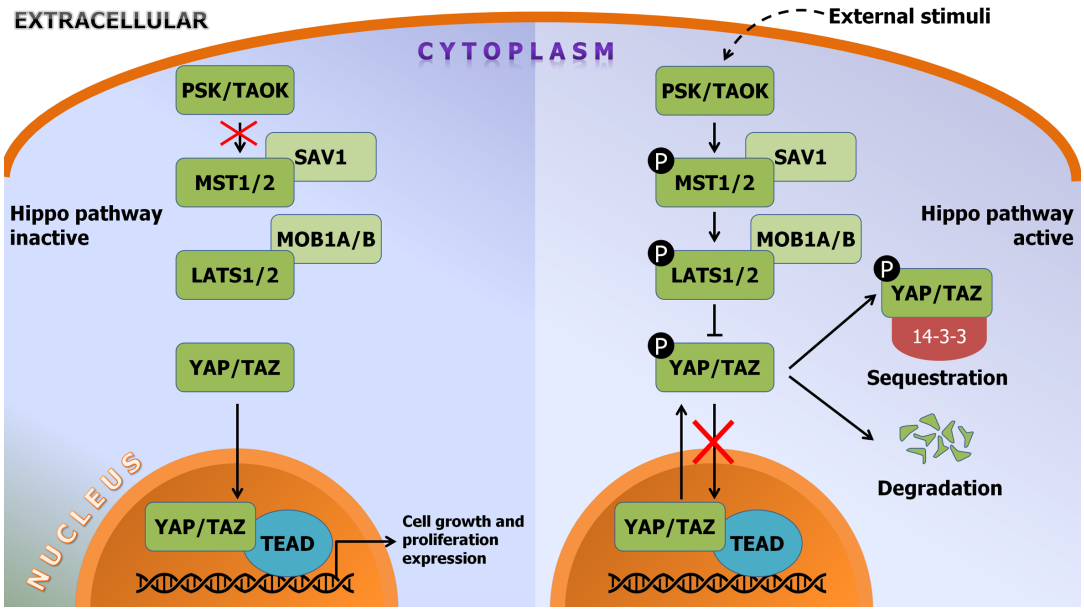

Fig. (3). Hippo signaling pathway. When the Hippo signaling pathway is inactive (left-hand side), PSK/TAOK protein kinases do not activate MST1/2 protein kinases. Therefore, YAP and TAZ can interact with TEAD and bind directly to the nucleus to activate several genes that regulate organ size and cell proliferation. However, when the Hippo signaling pathway is active (right-hand side), external stimuli activate PSK/TAOK protein kinases, and then the kinases phosphorylate and activate MST1/2. The activation of MST1/2, in turn, phosphorylates LATS1/2 and inactivates YAP/TAZ. The inactive form of YAP/TAZ cannot bind to TEAD in the nucleus, causing the sequestration of the YAP/TAZ with 14-3-3 protein or the degradation of YAP/TAZ protein in the cytoplasm. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

and cerebral cortex, as well as the downregulation and activation of the Hippo signaling pathway, are linked to dementia, specifically in Alzheimer's disease [23]. YAP deficiency enhances transcriptional repression-induced atypical cell death (TRIAD), ballooning cell death (BCD), and necrosis in Alzheimer's disease and Huntington's disease, resulting in TEAD suppression [14, 24, 25]. Intracellular Aβ also subsequently activates the Hippo signaling pathway, which in turn induces the JNK signaling pathway, which initiates neuroinflammation and neuronal cell necrosis [11, 12, 14]. YAP expression is found to be down-regulated in a Hippo pathway-dependent manner in the hippocampus astrocytes of aged mice and mice models of Alzheimer's disease. Consequently, at least in the *in vitro* and *in vivo* models, the signaling cascade appears to promote astrocyte senescence [13]. In addition, the core component MST1 appears to provoke neuronal apoptosis *via* regulator Bcl-2. Moreover, the increased level of MST1 activates Bax and inhibits the Bcl-2 expression in cells, thus promoting mitochondrial dysfunction [26]. Furthermore, PSK/TAOK, an upstream regulator of the Hippo pathway, is also involved in the pathogenesis of Alzheimer's disease-related dementia. In cell cultures, tau phosphorylation had been shown to be modulated by the activation of PSK1 and PSK2 in the cortex and the hippocampus. Other kinases stimulated by PSKs, such as JNK, p38, and MARK, have also been found to aggravate tau phosphorylation, and consequently promote neurodegeneration [27].

In neurodegenerative diseases, the overexpression of YAP and the inactivation of the Hippo pathway are beneficial in ameliorating neurodegeneration and suppressing the progression of the illness. In the research conducted by Dubey *et al.*, the neurodegeneration of eye disks mediated by mutant huntingtin (Htt) was overcome by Yorkie, the effector protein YAP in *Drosophila melanogaster* [23]. Moreover, the activation of the Hippo pathway and the phosphorylation of MST1/2 and LATS 1/2 can phosphorylate and inactivate YAP by sequestration or degradation in the cytoplasm. The inactivation of the Hippo pathway results in the unphosphorylated YAP, essential for cell longevity as YAP can bind with nuclear TEAD to express the protein. The unphosphorylated YAP helps the cortical neurons from degeneration and cell death, as reported in the study by Mao *et al.*. In the report, YAP/YAPdeltaC and the transcription of YAP and TEAD1 prevented neuronal death by suppressing BCD and TRIAD in primary cortical neurons affected by Htt proteins [25]. Thus, the expression and nuclear transcription of YAP and TEAD are essential in neuronal health and survival from neurodegeneration.

3.3. Dementia and Autophagy

Autophagy is a cellular mechanism in which damaged cell structures are degraded and recycled from the cytoplasm through the lysosomes [28]. There are several forms of autophagy, each with its purposes and processes. Macroautophagy, often generalized as autophagy, is the non-selective process of degrading damaged cell organelles with autophagosome involvement. It starts when *ULK1/2* induces and nucleates the phagophore. Subsequently, the elongation of the phagophore is induced and transformed into an autophagosome (Fig. **4**). The autophagosome would then fuse with the damaged structure or the targeted cargo. The process is regulated by *ATG12-ATG5-ATG16L1*, *ATG9*, *LC3-II*, and *Class III PtdIns3K*. The autophagosome subsequently combines with lysosomes to generate autolysosomes, which degrade the structure/cargo, after which the resulting broken-

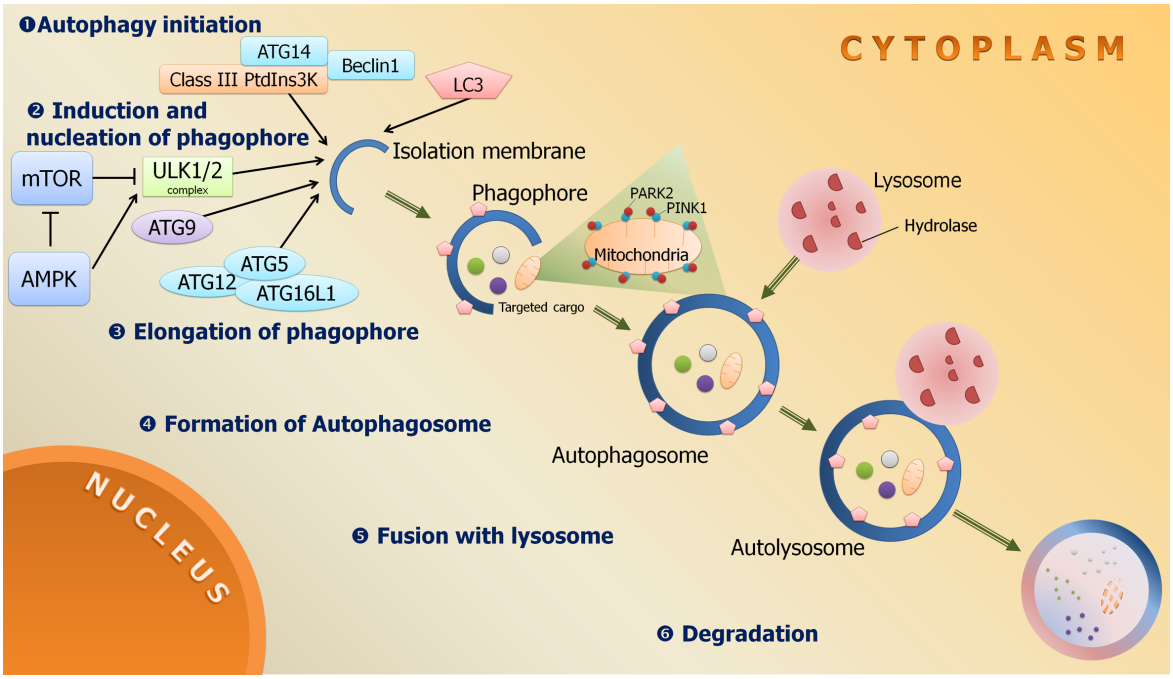

Fig. (4). The typical pathway of autophagy and mitophagy. (**1**) The process of autophagy is initiated by *ULK1/2* protein kinase complex activated by AMPK; (**2**) The phagophore is induced and nucleated by *ULK1/2* and regulated by *ATG9*, *ATG12-ATG5-ATG16L1*, *LC3-II*, and Class III PtdIns3K; (**3**) The elongation of phagophore to the targeted cargo appears after the nucleation of phagophore and later develops into autophagosome; (**4**) The autophagosome fuses with the damaged structure or the targeted cargo; (**5**) The autophagosome then merges with the lysosome to form autolysosomes; (**6**) The formed autolysosome degrades the cargo. The proteins are subsequently transferred back to the cytoplasm. In mitophagy, the dysfunctional or damaged mitochondria on the outer membrane of *PINK1* attach to *PARK2* to stimulate the elongation of phagophore and mitophagy. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

down components are transferred back to the cytoplasm *via* the lysosomal permeases [29, 30].

Microautophagy is a selective degradation process using small parts of the cytoplasm without autophagosome involvement. The cytoplasmic material reaches the lysosome by a lysosomal membrane invagination [31]. A microautophagy process has been known to include the delivery of cytosolic proteins directly into the vesicle of late endosome multivesicular bodies [32].

The other type of autophagy, called chaperone-mediated autophagy, involves the KFERQ motifs in transferring cytosolic proteins into the lysosomal membrane. In this process, KFERQ motifs are linked to the HSPA8/HSC70 and other co-chaperones, which are then delivered to lysosomes *via* the LAMP2A substrate receptor and degraded in the lysosomal lumen [30].

Another type of autophagy is called mitophagy. Mitophagy focuses on mitochondrial breakdown involving BNIP3L/NIX, *PINK1*, and *PARK2* proteins. BCL2 Interacting Protein 3 Like (BNIP3L/NIX) is an autophagy-selective protein found on the mitochondria's outer membrane, which is required for mitochondrial elimination [33, 34]. PTEN-induced putative kinase-1, often known as *PINK1*, is a serine/threonine-protein kinase that sticks to the depolarized mitochondria. *PARK2*, also known as Parkin, is an E3-ubiquitin-protein ligase that binds to *PINK1* and ubiquitinates the mitochondrial outer membrane protein, which subsequently interacts with *LC3* with the assistance of SQSTM1 to initiate the process of mitophagy [35].

Both the BNIP3L-mediated mitophagy and *PINK1-PARK2*-mediated mitophagy have been shown to be critical in cell maturation and the removal of aged or defective mitochondria to support cellular functions. In the maturation of red blood cells, BNIP3L is the mitochondrial outer membrane protein that binds to the microtubule-associated protein 1A/1B-light chain 3 (*LC3*) and gamma-aminobutyric acid receptor-associated protein (GABARAP) on the phagophore to allow the recognition and the subsequent degradation of mitochondria. The removal of damaged mitochondria is assumed to be aided by *PINK1* and *PARK2*. The outer membrane kinase *PINK1* connects to the cytosolic E3 ubiquitin ligase *PARK2* in defective mitochondria, leading to the ubiquitination of *PARK2* mitochondrial proteins and mitophagy [30].

The autophagy processes to clear misfolded or damaged proteins are needed in a healthy human brain to preserve brain functions. Defective autophagy processes have been linked to the pathophysiology of dementia (Fig. **5**). In Alzheimer's disease and other forms of dementia, circulating levels of autophagic markers, including *ATG5*, *ATG7*, *Beclin*, *LC3*, and *NRBF2*, are significantly reduced. The deficiency of these markers leads to the gradual deterioration of brain neurons, which manifests in physiological and behavioral impairments [19, 36-39].

Autophagy has been demonstrated to be inhibited by the aggregation of amyloid precursor protein (APP), Aβ peptide, and tau protein, particularly in the hippocampal neurons [40–43]. When autophagic markers are reduced or depleted, the autophagosome formation is disrupted and consequently

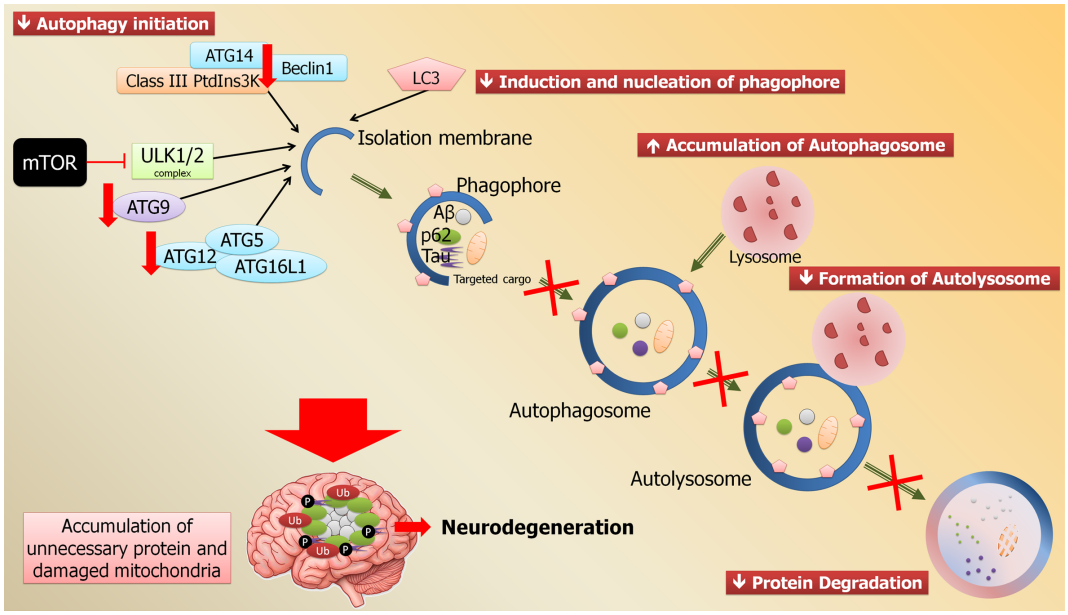

Fig. (5). The autophagy impairment in dementia. In defective autophagy, activated mTOR inhibits the *ULK1/2* protein kinase complex, resulting in the disturbance in the formation of the phagophore. Other autophagic proteins, such as *ATG5*, *ATG7*, *Beclin*, and *LC3*, are depleted in dementia, which results in decreased autophagosome synthesis or accumulation of autophagosomes, decreased autolysosome formation, and reduction of protein degradation. Neurodegeneration and the build-up of damaged proteins can result from the autophagy dysfunction. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

exacerbates the aggregation and spread of Aβ and tau proteins in the brain [37, 44, 45]. Interestingly, in studies conducted by Yu *et al.* (2011), Chen *et al.* (2015), Ma *et al.* (2017), and Villamil Ortiz *et al.* (2021), autophagy was shown to be boosted in the early stages of Alzheimer's disease but deteriorated as the disease progressed [2, 17, 46, 47].

Furthermore, Joshi *et al.* (2015) found that in the late stage of Alzheimer's disease, *p62* and *pAkt/mTOR* kinase activity were enhanced in transgenic mice models, but Bcl-2 levels were considerably lowered. Since the inactivation of Akt/mTOR promotes autophagy, it implies that *p62* and *mTOR* activities inhibit autophagy in dementia [48].

Mitophagy also decreases in dementia and aging. The progression of Alzheimer's disease is exacerbated by, among other factors, the accumulation of defective and dysfunctional mitochondria [49]. The simultaneous rise in *PINK1* levels and reduction in *PARK2* levels are some of the consequences of severe mitochondrial breakdown. In addition, APP and Tau suppress the action of the mitochondrial-targeting *PINK1*/*PARK2* complex, resulting in the failure of mitophagy [50, 51]. The mitophagy impairment appears to be related to the early tau accumulation in the brain [52].

Vascular and Lewy body dementia have different pathophysiology compared to Alzheimer's disease with regards to autophagy regulation. The activation of autophagy-mediated chronic cerebral hypoperfusion exacerbates the degree of dementia in vascular dementia patients. Therefore, in vascular dementia patients, cognitive and motor function decline can be alleviated by inhibiting autophagy [53-55]. There is an ongoing debate about whether autophagy activation or inhibition by synuclein expression causes Lewy body dementia development and severity [56-58].

3.4. Dementia and Aging

The brain functions deteriorate progressively with age, which manifests in cognitive and motor decline. The hallmarks of aging found in brain tissues include DNA oxidative damage and repair defect, epigenetic alterations, telomeric attrition, loss of proteostasis, mitochondrial dysfunction, neuronal senescence, stem cells exhaustion, altered cellular network, and inflammation (Fig. **6**) [59, 60].

The types of neuronal DNA damage in an aging brain are DNA single-strand breaks, double-strand breaks, abasic sites, bulky adducts, base mismatches, insertions, and deletions [60]. Increased Reactive Oxygen Species (ROS) generation and DNA repair failure can be regarded as both a cause and/or a consequence of oxidative-stress-related DNA damage by endogenous ROS. More importantly, the DNA double-strand breaks caused by oxidative stress have been shown to be the most destructive type of DNA damage [61]. This particular damage has been found to be the etiology of dementia and linked to methionine-35, an amino acid responsible for the production of amyloid β and the subsequent plaque formation in Alzheimer's disease [61, 62].

The DNA repair systems, such as homologous combinational repair, non-homologous end-joining repair, and base excess repair (BER), are reduced in dementia, resulting in a decreased ability of cells to remove DNA lesions [61, 63]. BER enzymes, such as APE1 and OGG1, are increased in normal brain tissues but reduced in the frontal cortex of brain tissues suffering from Alzheimer's disease [64].

The poly (ADP-ribose) polymerase-1 (PARP-1) is an essential enzyme in maintaining memory and synaptic plasticity in the brain. The reduction of this enzyme activity and expression has been observed in the hippocampus and the

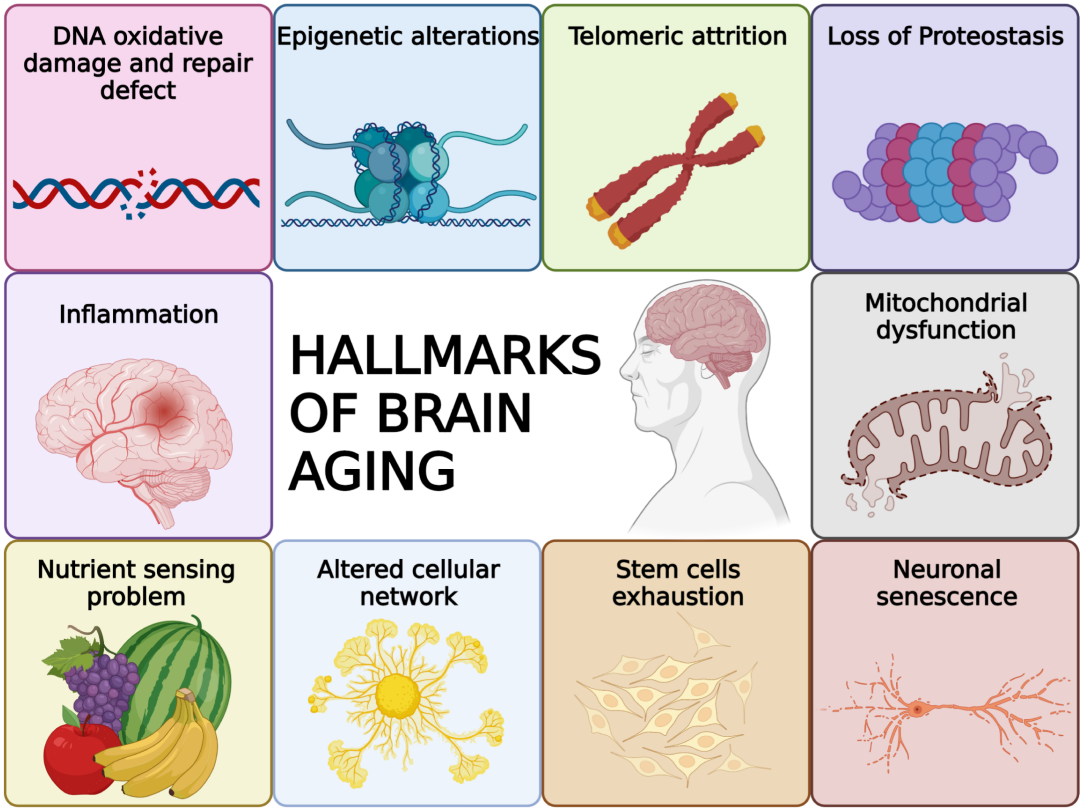

Fig. (6). The hallmarks of brain aging include DNA oxidative damage and repair defect, epigenetic alterations, telomeric attrition, loss of proteostasis, mitochondrial dysfunction, neuronal senescence, stem cells exhaustion, altered cellular network, nutrient sensing problem, and inflammation [59, 60]. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

cerebral cortex of dementia patients, displaying DNA damage, cellular senescence, and inflammation [65, 66].

Some of the hallmarks of aging, such as epigenetic alterations, telomeric attrition, and the loss of proteostasis, have been linked to dementia progression. Memory, learning, and behavior deficits in dementia are strongly associated with epigenetic alterations, such as DNA methylation and histone acetylation. Bradley-Whitman *et al.* (2013) and Coppieters *et al.* (2014) found active DNA methylation of 5-methylcytosine and 5-hydroxymethylcytosine in aging brain tissues, implicating epigenetic changes in the early progression and clinical features of dementia [67, 68]. Furthermore, histone H3 Ser57 and Thr58 dephosphorylation and histone H4K16ac deacetylation have been shown to be associated with dementia neuropathology and progression. The dephosphorylation and deacetylation cause a reduction in neuronal gene transcription by stabilizing the nucleosomes and condensing the chromatin [69, 70].

The severity of dementia-related neurodegenerative disorders, such as vascular dementia, Lewy body dementia, and Alzheimer's disease, has also been associated with telomeric attrition or shortening. Accelerated telomere shortening has been associated with the increased formation of ROS, cellular oxidative damage, and inflammation in patients with high-risk dementia [71-73]. Meanwhile, the loss of proteostasis has been found in the hippocampal neurons of brains in aging mice. Proteostasis failure results in the accumulation of poly-ubiquitin and amyloid, exacerbating cellular senescence and autophagic activity impairment [74-76].

The configuration of mitochondria in the dendrites and axons of neurons is designed to produce ATP for neurotransmission, preservation, and cellular recovery. The proliferation and differentiation of mitochondria in the form of mitochondrial biogenesis are modulated by mitophagy. Mitophagy is crucial in maintaining cell functions and homeostasis to prevent the accumulation of dysfunctional mitochondria [77]. The analyses of mitochondria from brain tissues of patients with cognitive decline demonstrate abnormal fission and morphology, reduced mitochondrial function, diminished mitochondrial membrane potential, and mitophagy dysfunction, which results in the disturbance of ATP production as well as oxidative stress [78-81].

In addition, the amyloid β peptides and tau-containing neurofibrillary tangles have been found to promote cellular senescence, aging, and neurodegeneration. The $A\beta_{42}$ peptides increase intracellular ROS by activating FPR2 in the brain and the downstream ROS-p38 MAPK signaling pathway, inhibiting neurogenesis and triggering astrocyte senescence *in vitro*. These processes upregulate the expression of inflammatory cytokines, such as IL-6, RANTES, IL-8, and ICAM-1. The secretion of IL-6 is promoted by the activation of p38MAPK. IL-6 is considered the central chronic inflammation mediator in aging and dementia. Moreover, the insoluble tau is considered to be causative factor for the senescence of neurons and astrocytes, marked by the elevated levels of $p16^{INK4a}$, the astrocyte marker GFAP, and senescence-associated secretory phenotype [15, 82-84].

Lifestyle changes, such as the control of calorie intake and physical activities, are associated with nutrient-sensing gene expression during aging. Caloric restriction is neuroprotective by reducing the levels of amyloid β and the activation of microglia [85, 86]. Insulin, insulin-like growth factor 1 (IGF-1), mammalian target of rapamycin (mTOR), AMP-activated protein kinase (AMPK), and sirtuins are some of the significant nutrient-sensing pathways and molecules involved in aging. Central insulin resistance, marked by the increased level of IRS-1 $pSer^{616}$ and decreased level of IGF-1, is found in dementia patients and is related to worsening cognitive function [87, 88]. mTOR and AMPK have been found to be involved in dementia pathophysiology. The studies by Caccamo *et al.* (2013) and Zimmerman *et al.* (2013) reveal that the elevation of mTOR and reduction of AMPK activity levels are both associated with learning and memory deficits in dementia [89, 90]. On the other hand, the neuroprotective sirtuins (SIRT1) usually decrease during aging and are significantly reduced in dementia [91].

Furthermore, there is evidence that aging causes alteration in autophagy function and the Hippo pathway. Nutrient sensing and epigenetic alterations are some of the hallmarks of aging, which can affect autophagic flux [92, 93]. As mentioned, mTOR, AMPK, and SIRT1 levels have been associated with aging. SIRT1 can activate AMPK *via* deacetylation of LKB1 kinase, in which the activation of AMPK can phosphorylate forkhead transcription factors (FoxO) proteins. SIRT-1 can also deacetylate FoxO1 and FoxO3 to elevate levels of autophagy-related proteins, such as *BNIP3*, *ULK1/2*, *ATG5*, *ATG7*, *ATG8*, and *LC3*.

Additionally, AMPK can regulate the ULK/mTOR pathway to control autophagy by inhibiting the expression of mTOR and enhancing the expression of the ULK complex. The increased mTOR and reduced AMPK and SIRT1 levels in aging may be related to the altered autophagy function [93, 94]. On the other hand, the nuclear protein YAP/TAZ in the Hippo signaling pathway deteriorates in aging, although the biochemical and molecular mechanisms are not yet precise. The decreased level of YAP can activate p53/p21 expression and lysosomal activity to develop cellular senescence and senescence-associated secretory phenotypes [95]. In neurodegenerative diseases, such as Alzheimer's disease, astrocyte senescence in the hippocampus can occur by YAP deficiency or the suppression of YAP activity due to the activation of the Hippo pathway [13].

In this context, the pathophysiology of the progression of dementia has been linked to physiological changes in aging. The hallmarks of aging will affect several pathways that promote cellular senescence. We propose that the elucidation of the complex relationships between the Hippo signaling pathway and autophagy in dementia is one of the key factors to a better understanding of the progression of dementia in aging.

3.5. Dementia, Hippo Signaling Pathway, and Autophagy

The interaction of the Hippo signaling pathway and autophagy plays an essential role in neurodegeneration. The role of Hippo signaling is to maintain organ and cell homeostasis. Hippo signaling co-activator YAP/TAZ controls autophagy by promoting the formation of autophagosomes and autolysosomes and the degradation of the autophagosome. The knockdown of YAP/TAZ is shown to cause the disturbance of the autophagic flux, with the accumulation of *LC3-II* in the cells and downregulation of Armus, a RAB7-GAP, which assists the autophagosome-lysosome fusion [96]. YAP/TAZ is also found to interact with the F-actin cytoskeleton and myosin-II complex in regulating the autophagy proteins *ATG16L1* and *ATG9*, signaling the formation of autophagosomes. YAP/TAZ collaborates with autophagy to preserve homeostasis in cells by clearing unused or damaging substances [97]. The other components of the Hippo signaling pathway, STK4/MST1 and STK3/MST2, have been considered important in controlling autophagy. The MST1/2 plays a role in phosphorylating *LC3* Thr50 to induce autophagosome and autolysosome formation and increase autophagic flux [98].

It is still unclear whether the activation or the inhibition of autophagy by Hippo pathway inactivation is beneficial for maintaining cell survival or harmful (inducing cell death). The declining level of MST1 can significantly promote autophagic flux. Western blot analysis of motor neuron samples from the $MST1^{-/-}$ group in the spinal cord experiment revealed an increase in *LC3-II* expression and a reduction in p62 expression, demonstrating autophagy to be triggered in response to spinal cord injury [99]. Another study showed that when titanium implants containing spherical silica nanoparticles were placed, the level of YAP rose, and mesenchymal stem cells underwent osteogenic differentiation after autophagy activation, as evidenced by an increase in *LC3-II* following the suppression of Akt/mTOR signaling [100]. Conversely, YAP expression suppresses autophagy to accelerate tumor progression in cancer cells. In the study by Jin *et al.* (2021) on colorectal cancer cells, YAP interacted with TEAD in the nucleus of SW620 cells to generate and bind to the target gene Bcl-2. YAP/Bcl-2 expression inhibited autophagy, which was shown by the decrease in *LC3-II* level in the western blot analysis. Further, the SW620 cell growth was also found to be enhanced as a result [101]. Another study claimed that the downregulation of LATS, an upstream kinase in the Hippo pathway, led to a 2-fold increase in YAP expression. YAP could assist the proliferation of lung cancer cells in lung adenocarcinoma by stimulating Akt/mTOR signaling pathway to inhibit autophagy [102]. Numerous research studies have focused on the relationship between the Hippo pathway and autophagy in several human body systems and cancer cells. Still, relatively few researchers have addressed these topics in the neurological system.

Hypothetically, when the Hippo signaling pathway is activated in the neurons of the brain suffering from neurodegenerative diseases, it causes YAP reduction in the nucleus. Degradation of YAP occurs when it enters the cytoplasm. The reduction of YAP then lowers the autophagic flux, causing the cell's inability to mark misfolded and damaged protein to be degraded in autophagy, leading to protein accumulation and aggregation in neurons (Fig. **7**). The accumulation and aggregation of proteins directly induce BCD and TRIAD to initiate the necrosis and apoptosis of neurons [11, 25]. The accumulation of misfolded proteins in neurons can activate Hippo signaling and the JNK signaling pathways. The interaction between the activated Hippo signaling and JNK signaling pathways indirectly induces neurodegeneration through the promotion of apoptotic neuronal death [14, 103].

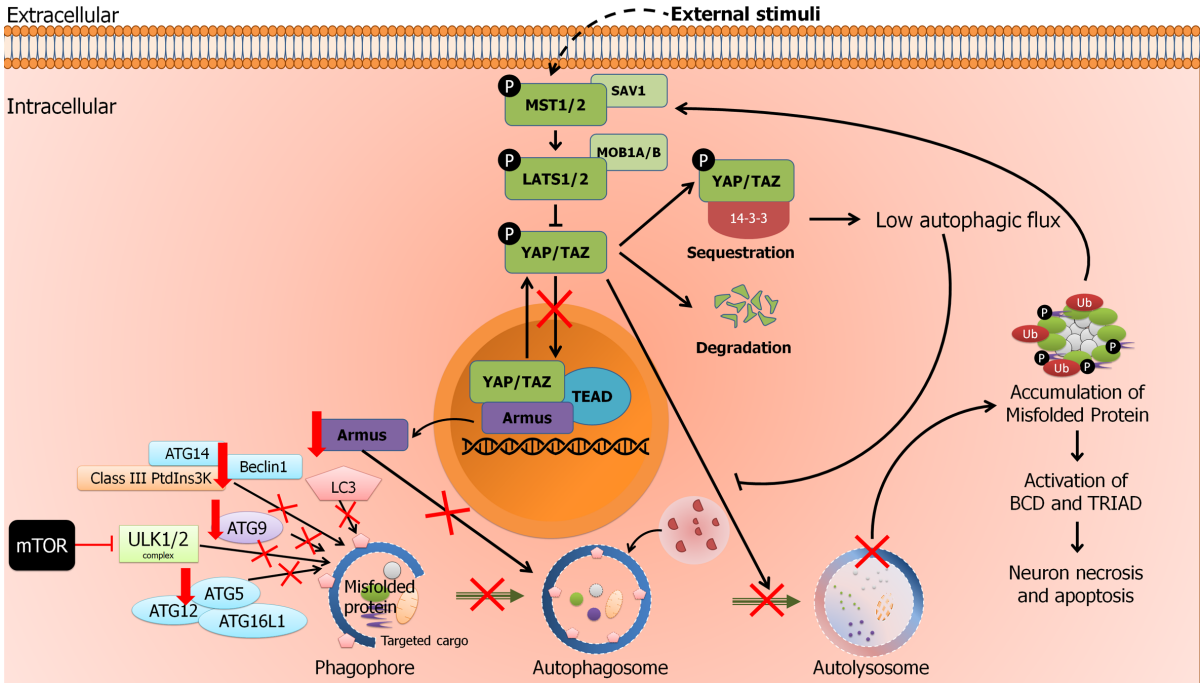

Fig. (7). The YAP/TAZ knockdown affects autophagy, causing neuron necrosis and apoptosis. A reduction in the autophagy protein and activation of the Hippo signaling pathway can inhibit the development of autophagosomes and autolysosomes in the neuron, leading to the sequestration of YAP/TAZ and 14-3-3 protein as well as the downregulation of Armus synthesis from the nucleus. These are two ways in which the inactivated version of YAP/TAZ can change the autophagy flux. Due to the buildup of misfolded protein brought on by the disruption of the autophagic flux, BCD and TRIAD-induced neuron necrosis and apoptosis can subsequently develop. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

CONCLUSION

This review provides information on the roles of the Hippo signaling pathway and autophagy in the development of dementia in aging. The Hippo signaling pathway and autophagy alterations play a major role in the progression of dementia as demonstrated in animal, *in vitro*, *in vivo*, and microarray studies. The Hippo signaling pathway is dependent on the transcriptional co-activator YAP/TAZ, which connects with TEAD in the nucleus to maintain cell homeostasis. When YAP/TAZ is reduced, TRIAD, BCD, and necrosis will occur in the neurons. Moreover, the autophagic proteins, such as *LC3*, *ATG* proteins, and *Beclin*, are reduced in dementia, resulting in the disruption of autophagosome formation and accumulation and spread of misfolded proteins in the brain.

Although the relationship between the Hippo signaling pathway and autophagy in dementia is not clear, it has been shown that when Hippo signaling co-activator YAP/TAZ is reduced in neurons, the autophagic flux is decreased, causing misfolded proteins to accumulate in the brain leading to neurodegeneration. Further research should be carried out to determine the specific relationships between the Hippo signaling pathway and autophagy in dementia, as they are clearly essential in the progression of dementia.

The studies that describe the contribution of the Hippo signaling pathway and autophagy to dementia in aging are limited. To date, there is no available article on the relationship between the Hippo signaling pathway and autophagy in dementia involved in aging. Although articles that discuss the relationship between the Hippo signaling pathway and autophagy are available, no specific theory or evidence has been found to describe this relationship in the aging brain. From the results, we found that the disturbance of the Hippo signaling pathway and autophagy could affect the progression of dementia. We believe this systematic review can pave the way for new research on the relationship between Hippo signaling pathway and autophagy in the brain, especially with respect to dementia in aging. By understanding these relationships, new treatment and/or prevention strategies could be developed by targeting the Hippo pathway and autophagy in aging-related dementia.

LIST OF ABBREVIATIONS

YAP	=	Yes-Association Protein
TAZ	=	Transcriptional Co-activator with PDZ-Binding Motif
APP	=	Amyloid Precursor Protein
Aβ	=	Amyloid β
TRIAD	=	Transcriptional Repression-Induced Atypical Cell Death
BCD	=	Ballooning Cell Death

CONSENT FOR PUBLICATION

Not applicable.

STANDARDS OF REPORTING

PRISMA guidelines and methodology were followed.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise

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SUPPLEMENTARY MATERIAL

Supplementary material is available on the publisher's website along with the published article.

REFERENCES

[1] Mota C, Taipa R, das Neves SP, *et al.* Structural and molecular correlates of cognitive aging in the rat. Sci Rep 2019; 9(1): 2005. http://dx.doi.org/10.1038/s41598-019-39645-w PMID: 30765864

[2] Yu Y, Feng L, Li J, *et al.* The alteration of autophagy and apoptosis in the hippocampus of rats with natural aging-dependent cognitive deficits. Behav Brain Res 2017; 334: 155-62. http://dx.doi.org/10.1016/j.bbr.2017.07.003 PMID: 28688896

[3] Toepper M. Dissociating normal aging from Alzheimer's disease: A view from cognitive neuroscience. J Alzheimers Dis 2017; 57(2): 331-52. http://dx.doi.org/10.3233/JAD-161099 PMID: 28269778

[4] Matthews KA, Xu W, Gaglioti AH, *et al.* Racial and ethnic estimates of Alzheimer's disease and related dementias in the United States (2015–2060) in adults aged ≥ 65 years. Alzheimers Dement 2019; 15(1): 17-24. http://dx.doi.org/10.1016/j.jalz.2018.06.3063 PMID: 30243772

[5] Podcasy JL, Epperson CN. Considering sex and gender in Alzheimer disease and other dementias. Dialogues Clin Neurosci 2016; 18(4): 437-46. http://dx.doi.org/10.31887/DCNS.2016.18.4/cepperson PMID: 28179815

[6] Silva MVF, Loures CMG, Alves LCV, de Souza LC, Borges KBG, Carvalho MG. Alzheimer's disease: Risk factors and potentially protective measures. J Biomed Sci 2019; 26(1): 33. http://dx.doi.org/10.1186/s12929-019-0524-y PMID: 31072403

[7] Long Z, Chen J, Zhao Y, *et al.* Dynamic changes of autophagic flux induced by Abeta in the brain of postmortem Alzheimer's disease patients, animal models and cell models. Aging (Albany NY) 2020; 12(11): 10912-30. http://dx.doi.org/10.18632/aging.103305 PMID: 32535554

[8] Xu J, Patassini S, Rustogi N, *et al.* Regional protein expression in human Alzheimer's brain correlates with disease severity. Commun Biol 2019; 2(1): 43. http://dx.doi.org/10.1038/s42003-018-0254-9 PMID: 30729181

[9] Xu M, Zhang DF, Luo R, *et al.* A systematic integrated analysis of brain expression profiles reveals YAP1 and other prioritized hub genes as important upstream regulators in Alzheimer's disease. Alzheimers Dement 2018; 14(2): 215-29. http://dx.doi.org/10.1016/j.jalz.2017.08.012 PMID: 28923553

[10] Meng Z, Moroishi T, Guan KL. Mechanisms of Hippo pathway regulation. Genes Dev 2016; 30(1): 1-17. http://dx.doi.org/10.1101/gad.274027.115 PMID: 26728553

[11] Tanaka H, Homma H, Fujita K, *et al.* YAP-dependent necrosis occurs in early stages of Alzheimer's disease and regulates mouse model pathology. Nat Commun 2020; 11(1): 507. http://dx.doi.org/10.1038/s41467-020-14353-6 PMID: 31980612

[12] Qing J, Liu X, Wu Q, *et al.* Hippo/YAP pathway plays a critical role in effect of GDNF against Aβ-induced inflammation in microglial cells. DNA Cell Biol 2020; 39(6): 1064-71. http://dx.doi.org/10.1089/dna.2019.5308 PMID: 32255663

[13] Xu X, Shen X, Wang J, *et al.* YAP prevents premature senescence of astrocytes and cognitive decline of Alzheimer's disease through regulating CDK6 signaling. Aging Cell 2021; 20(9): e13465. http://dx.doi.org/10.1111/acel.13465 PMID: 34415667

[14] Irwin M, Tare M, Singh A, *et al.* A positive feedback loop of hippo- and c-jun-amino-terminal kinase signaling pathways regulates amyloid-beta-mediated neurodegeneration. Front Cell Dev Biol 2020; 8: 117. http://dx.doi.org/10.3389/fcell.2020.00117 PMID: 32232042

[15] Bhat R, Crowe EP, Bitto A, *et al.* Astrocyte senescence as a component of Alzheimer's disease. PLoS One 2012; 7(9): e45069. http://dx.doi.org/10.1371/journal.pone.0045069 PMID: 22984612

[16] Han X, Zhang T, Liu H, Mi Y, Gou X. Astrocyte senescence and Alzheimer's disease: A review. Front Aging Neurosci 2020; 12: 148. http://dx.doi.org/10.3389/fnagi.2020.00148 PMID: 32581763

[17] Chen ML, Hong CG, Yue T, *et al.* Inhibition of miR-331-3p and miR-9-5p ameliorates Alzheimer's disease by enhancing autophagy. Theranostics 2021; 11(5): 2395-409. http://dx.doi.org/10.7150/thno.47408 PMID: 33500732

[18] Manczak M, Kandimalla R, Yin X, Reddy PH. Hippocampal mutant APP and amyloid beta-induced cognitive decline, dendritic spine loss, defective autophagy, mitophagy and mitochondrial abnormalities in a mouse model of Alzheimer's disease. Hum Mol Genet 2018; 27(8): 1332-42. http://dx.doi.org/10.1093/hmg/ddy042 PMID: 29408999

[19] Reddy PH, Yin X, Manczak M, *et al.* Mutant APP and amyloid beta-induced defective autophagy, mitophagy, mitochondrial structural and functional changes and synaptic damage in hippocampal neurons from Alzheimer's disease. Hum Mol Genet 2018; 27(14): 2502-16. http://dx.doi.org/10.1093/hmg/ddy154 PMID: 29701781

[20] Wang D, He J, Huang B, Liu S, Zhu H, Xu T. Emerging role of the Hippo pathway in autophagy. Cell Death Dis 2020; 11(10): 880. http://dx.doi.org/10.1038/s41419-020-03069-6 PMID: 33082313

[21] Page MJ, McKenzie JE, Bossuyt PM, *et al.* The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ 2021; 372: n71. http://dx.doi.org/10.1136/bmj.n71 PMID: 33782057

[22] Singh A, Gogia N, Chimata AV, Deshpande P, Singh A. Hippo signaling: Bridging the gap between cancer and neurodegenerative disorders. Neural Regen Res 2021; 16(4): 643-52. http://dx.doi.org/10.4103/1673-5374.295273 PMID: 33063715

[23] Dubey SK, Tapadia MG. Yorkie regulates neurodegeneration through canonical pathway and innate immune response. Mol Neurobiol 2018; 55(2): 1193-207. http://dx.doi.org/10.1007/s12035-017-0388-7 PMID: 28102471

[24] Mueller KA, Glajch KE, Huizenga MN, *et al.* Hippo signaling pathway dysregulation in human Huntington's disease brain and neuronal stem cells. Sci Rep 2018; 8(1): 11355. http://dx.doi.org/10.1038/s41598-018-29319-4 PMID: 30054496

[25] Mao Y, Chen X, Xu M, *et al.* Targeting TEAD/YAP-transcription-dependent necrosis, TRIAD, ameliorates Huntington's disease pathology. Hum Mol Genet 2016; 25(21): ddw303. http://dx.doi.org/10.1093/hmg/ddw303 PMID: 28171658

[26] Khan M, Rutten BPF, Kim MO. MST1 regulates neuronal cell death via JNK/casp3 signaling pathway in HFD mouse brain and HT22 cells. Int J Mol Sci 2019; 20(10): 2504. http://dx.doi.org/10.3390/ijms20102504 PMID: 31117242

[27] Tavares IA, Touma D, Lynham S, *et al.* Prostate-derived sterile 20-like kinases (PSKs/TAOKs) phosphorylate tau protein and are activated in tangle-bearing neurons in Alzheimer disease. J Biol Chem 2013; 288(21): 15418-29. http://dx.doi.org/10.1074/jbc.M112.448183 PMID: 23585562

[28] de Duve C. The lysosome concept. In: de Duve AVS, Cameron MP, Eds. Novartis Foundation Symposia. Chichester, UK: John Wiley & Sons, Ltd. 1963; pp. 1-35. http://dx.doi.org/10.1002/9780470715314.ch1

[29] Masaki R, Yamamoto A, Tashiro Y. Cytochrome P-450 and NADPH-cytochrome P-450 reductase are degraded in the autolysosomes in rat liver. J Cell Biol 1987; 104(5): 1207-15. http://dx.doi.org/10.1083/jcb.104.5.1207 PMID: 3106362

[30] Parzych KR, Klionsky DJ. An overview of autophagy: Morphology, mechanism, and regulation. Antioxid Redox Signal 2014; 20(3): 460-73. http://dx.doi.org/10.1089/ars.2013.5371 PMID: 23725295

[31] Marzella L, Ahlberg J, Glaumann H. Autophagy, heterophagy, microautophagy and crinophagy as the means for intracellular degradation. Virchows Arch B Cell Pathol Incl Mol Pathol 1981; 36(1): 219-34. http://dx.doi.org/10.1007/BF02912068 PMID: 6116336

[32] Sahu R, Kaushik S, Clement CC, *et al.* Microautophagy of cytosolic proteins by late endosomes. Dev Cell 2011; 20(1): 131-9. http://dx.doi.org/10.1016/j.devcel.2010.12.003 PMID: 21238931

[33] Novak I, Kirkin V, McEwan DG, *et al.* Nix is a selective autophagy receptor for mitochondrial clearance. EMBO Rep 2010; 11(1): 45-51. http://dx.doi.org/10.1038/embor.2009.256 PMID: 20010802

[34] Gao F, Chen D, Si J, *et al.* The mitochondrial protein BNIP3L is the substrate of PARK2 and mediates mitophagy in PINK1/PARK2 pathway. Hum Mol Genet 2015; 24(9): 2528-38. http://dx.doi.org/10.1093/hmg/ddv017 PMID: 25612572

[35] Trempe JF, Fon EA. Structure and function of parkin, PINK1, and DJ-1, the three musketeers of neuroprotection. Front Neurol 2013; 4: 38. http://dx.doi.org/10.3389/fneur.2013.00038 PMID: 23626584

[36] Castellazzi M, Patergnani S, Donadio M, *et al.* Autophagy and mitophagy biomarkers are reduced in sera of patients with Alzheimer's disease and mild cognitive impairment. Sci Rep 2019; 9(1): 20009. http://dx.doi.org/10.1038/s41598-019-56614-5 PMID: 31882960

[37] Inoue K, Rispoli J, Kaphzan H, *et al.* Macroautophagy deficiency mediates age-dependent neurodegeneration through a phospho-tau pathway. Mol Neurodegener 2012; 7(1): 48. http://dx.doi.org/10.1186/1750-1326-7-48 PMID: 22998728

[38] Omata Y, Lim YM, Akao Y, Tsuda L. Age-induced reduction of autophagy-related gene expression is associated with onset of Alzheimer's disease. Am J Neurodegener Dis 2014; 3(3): 134-42. PMID: 25628964

[39] Lachance V, Wang Q, Sweet E, *et al.* Autophagy protein NRBF2 has reduced expression in Alzheimer's brains and modulates memory and amyloid-beta homeostasis in mice. Mol Neurodegener 2019; 14(1): 43. http://dx.doi.org/10.1186/s13024-019-0342-4 PMID: 31775806

[40] Tsakiri EN, Gumeni S, Manola MS, Trougakos IP. Amyloid toxicity in a Drosophila Alzheimer's model is ameliorated by autophagy activation. Neurobiol Aging 2021; 105: 137-47. http://dx.doi.org/10.1016/j.neurobiolaging.2021.04.017 PMID: 34062489

[41] Pomilio C, Pavia P, Gorojod RM, *et al.* Glial alterations from early to late stages in a model of Alzheimer's disease: Evidence of autophagy involvement in Aβ internalization. Hippocampus 2016; 26(2): 194-210. http://dx.doi.org/10.1002/hipo.22503 PMID: 26235241

[42] Pomilio C, Gorojod RM, Riudavets M, *et al.* Microglial autophagy is impaired by prolonged exposure to β-amyloid peptides: Evidence from experimental models and Alzheimer's disease patients. Geroscience 2020; 42(2): 613-32. http://dx.doi.org/10.1007/s11357-020-00161-9 PMID: 31975051

[43] Ling D, Salvaterra PM. Brain aging and Aβ1-42 neurotoxicity converge via deterioration in autophagy-lysosomal system: A conditional Drosophila model linking Alzheimer's neurodegeneration with aging. Acta Neuropathol 2011; 121(2): 183-91. http://dx.doi.org/10.1007/s00401-010-0772-0 PMID: 21076961

[44] Xu Y, Propson NE, Du S, Xiong W, Zheng H. Autophagy deficiency modulates microglial lipid homeostasis and aggravates tau pathology and spreading. Proc Natl Acad Sci USA 2021; 118(27): e2023418118. http://dx.doi.org/10.1073/pnas.2023418118 PMID: 34187889

[45] Carvalho C, Santos MS, Oliveira CR, Moreira PI. Alzheimer's disease and type 2 diabetes-related alterations in brain mitochondria, autophagy and synaptic markers. Biochim Biophys Acta Mol Basis Dis 2015; 1852(8): 1665-75. http://dx.doi.org/10.1016/j.bbadis.2015.05.001 PMID: 25960150

[46] Ma Q, Qiang J, Gu P, Wang Y, Geng Y, Wang M. Age-related autophagy alterations in the brain of senescence accelerated mouse prone 8 (SAMP8) mice. Exp Gerontol 2011; 46(7): 533-41. http://dx.doi.org/10.1016/j.exger.2011.02.006 PMID: 21385605

[47] Villamil-Ortiz JG, Cardona-Gomez GP. Comparative analysis of autophagy and tauopathy related markers in cerebral ischemia and Alzheimer's disease animal models. Front Aging Neurosci 2015; 7: 84. PMID: 26042033

[48] Joshi G, Gan KA, Johnson DA, Johnson JA. Increased Alzheimer's disease–like pathology in the APP/ PS1ΔE9 mouse model lacking Nrf2 through modulation of autophagy. Neurobiol Aging 2015; 36(2): 664-79. http://dx.doi.org/10.1016/j.neurobiolaging.2014.09.004 PMID: 25316599

[49] Fang EF, Hou Y, Palikaras K, *et al.* Mitophagy inhibits amyloid-β and tau pathology and reverses cognitive deficits in models of Alzheimer's disease. Nat Neurosci 2019; 22(3): 401-12. http://dx.doi.org/10.1038/s41593-018-0332-9 PMID: 30742114

[50] Martín-Maestro P, Gargini R, García E, Simón D, Avila J, García-Escudero V. Mitophagy failure in app and tau overexpression model of Alzheimer's disease. J Alzheimers Dis 2019; 70(2): 525-40. http://dx.doi.org/10.3233/JAD-190086 PMID: 31256128

[51] Lonskaya I, Shekoyan AR, Hebron ML, Desforges N, Algarzae NK, Moussa CEH. Diminished parkin solubility and co-localization with intraneuronal amyloid-β are associated with autophagic defects in Alzheimer's disease. J Alzheimers Dis 2012; 33(1): 231-47. http://dx.doi.org/10.3233/JAD-2012-121141 PMID: 22954671

[52] Hou X, Watzlawik JO, Cook C, *et al.* Mitophagy alterations in Alzheimer's disease are associated with granulovacuolar degeneration and early tau pathology. Alzheimers Dement 2021; 17(3): 417-30. http://dx.doi.org/10.1002/alz.12198 PMID: 33090691

[53] Liu B, Tang J, Zhang J, Li S, Yuan M, Wang R. Autophagy activation aggravates neuronal injury in the hippocampus of vascular dementia rats. Neural Regen Res 2014; 9(13): 1288-96. http://dx.doi.org/10.4103/1673-5374.137576 PMID: 25221581

[54] Liu B, Liu J, Zhang J, Mao W, Li S. Effects of autophagy on synaptic-plasticity-related protein expression in the hippocampus CA1 of a rat model of vascular dementia. Neurosci Lett 2019; 707(73): 134312. http://dx.doi.org/10.1016/j.neulet.2019.134312 PMID: 31163225

[55] Xu J, Qi Q, Lv P, Dong Y, Jiang X, Liu Z. Oxiracetam ameliorates cognitive deficits in vascular dementia rats by regulating the expression of neuronal apoptosis/autophagy-related genes associated with the activation of the Akt/mTOR signaling pathway. Braz J Med Biol Res 2019; 52(11): e8371. http://dx.doi.org/10.1590/1414-431x20198371 PMID: 31721903

[56] Tanji K, Mori F, Kakita A, Takahashi H, Wakabayashi K. Alteration of autophagosomal proteins (LC3, GABARAP and GATE-16) in Lewy body disease. Neurobiol Dis 2011; 43(3): 690-7. http://dx.doi.org/10.1016/j.nbd.2011.05.022 PMID: 21684337

[57] Evans T, Kok WL, Cowan K, Hefford M, Anichtchik O. Accumulation of beta-synuclein in cortical neurons is associated with autophagy attenuation in the brains of dementia with Lewy body patients. Brain Res 2018; 1681: 1-13. http://dx.doi.org/10.1016/j.brainres.2017.12.026 PMID: 29278715

[58] Miki Y, Tanji K, Mori F, *et al.* Autophagy mediators (FOXO1, SESN3 and TSC2) in Lewy body disease and aging. Neurosci Lett 2018; 684: 35-41. http://dx.doi.org/10.1016/j.neulet.2018.06.052 PMID: 29966750

[59] Mattson MP, Arumugam TV. Hallmarks of brain aging: Adaptive and pathological modification by metabolic states. Cell Metab 2018; 27(6): 1176-99. http://dx.doi.org/10.1016/j.cmet.2018.05.011 PMID: 29874566

[60] López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. Cell 2013; 153(6): 1194-217. http://dx.doi.org/10.1016/j.cell.2013.05.039 PMID: 23746838

[61] Kwiatkowski D, Czarny P, Toma M, *et al.* Associations between DNA damage, DNA base excision repair gene variability and Alz-

heimer's disease risk. Dement Geriatr Cogn Disord 2016; 41(3-4): 152-71.
http://dx.doi.org/10.1159/000443953 PMID: 27011006

[62] Pao PC, Patnaik D, Watson LA, *et al.* HDAC1 modulates OGG1-initiated oxidative DNA damage repair in the aging brain and Alzheimer's disease. Nat Commun 2020; 11(1): 2484.
http://dx.doi.org/10.1038/s41467-020-16361-y PMID: 32424276

[63] Yu H, Harrison FE, Xia F. Altered DNA repair; an early pathogenic pathway in Alzheimer's disease and obesity. Sci Rep 2018; 8(1): 5600.
http://dx.doi.org/10.1038/s41598-018-23644-4 PMID: 29618789

[64] Lillenes MS, Rabano A, Støen M, *et al.* Altered DNA base excision repair profile in brain tissue and blood in Alzheimer's disease. Mol Brain 2016; 9(1): 61.
http://dx.doi.org/10.1186/s13041-016-0237-z PMID: 27234294

[65] Regier M, Liang J, Choi A, Verma K, Libien J, Hernández AI. Evidence for decreased nucleolar PARP-1 as an early marker of cognitive impairment. Neural Plast 2019; 2019: 4383258.
http://dx.doi.org/10.1155/2019/4383258 PMID: 31827497

[66] Zeng J, Libien J, Shaik F, Wolk J, Hernández AI. Nucleolar PARP-1 expression is decreased in Alzheimer's disease: Consequences for epigenetic regulation of rDNA and cognition. Neural Plast 2016; 2016: 8987928.
http://dx.doi.org/10.1155/2016/8987928 PMID: 27034851

[67] Bradley-Whitman MA, Lovell MA. Epigenetic changes in the progression of Alzheimer's disease. Mech Ageing Dev 2013; 134(10): 486-95.
http://dx.doi.org/10.1016/j.mad.2013.08.005 PMID: 24012631

[68] Coppieters N, Dieriks BV, Lill C, Faull RLM, Curtis MA, Dragunow M. Global changes in DNA methylation and hydroxymethylation in Alzheimer's disease human brain. Neurobiol Aging 2014; 35(6): 1334-44.
http://dx.doi.org/10.1016/j.neurobiolaging.2013.11.031 PMID: 24387984

[69] Anderson KW, Mast N, Pikuleva IA, Turko IV. Histone H3 Ser57 and Thr58 phosphorylation in the brain of 5XFAD mice. FEBS Open Bio 2015; 5(1): 550-6.
http://dx.doi.org/10.1016/j.fob.2015.06.009 PMID: 26199864

[70] Nativio R, Donahue G, Berson A, *et al.* Publisher correction: Dysregulation of the epigenetic landscape of normal aging in Alzheimer's disease. Nat Neurosci 2018; 21(7): 1018.
http://dx.doi.org/10.1038/s41593-018-0124-2 PMID: 29556027

[71] Fani L, Hilal S, Sedaghat S, *et al.* Telomere length and the risk of Alzheimer's disease: The rotterdam study. J Alzheimers Dis 2020; 73(2): 707-14.
http://dx.doi.org/10.3233/JAD-190759 PMID: 31839608

[72] Liu M, Huo YR, Wang J, *et al.* Telomere shortening in alzheimer's disease patients. Ann Clin Lab Sci 2016; 46(3): 260-5.
PMID: 27312549

[73] Hackenhaar FS, Josefsson M, Adolfsson AN, *et al.* Short leukocyte telomeres predict 25-year Alzheimer's disease incidence in non-APOE ε4-carriers. Alzheimers Res Ther 2021; 13(1): 130.
http://dx.doi.org/10.1186/s13195-021-00871-y PMID: 33397495

[74] Ishikawa S, Ishikawa F. Proteostasis failure and cellular senescence in long-term cultured postmitotic rat neurons. Aging Cell 2020; 19(1): e13071.
http://dx.doi.org/10.1111/acel.13071 PMID: 31762159

[75] Kundra R, Ciryam P, Morimoto RI, Dobson CM, Vendruscolo M. Protein homeostasis of a metastable subproteome associated with Alzheimer's disease. Proc Natl Acad Sci USA 2017; 114(28): E5703-11.
http://dx.doi.org/10.1073/pnas.1618417114 PMID: 28652376

[76] Manavalan A, Mishra M, Feng L, Sze SK, Akatsu H, Heese K. Brain site-specific proteome changes in aging-related dementia. Exp Mol Med 2013; 45(9): e39.
http://dx.doi.org/10.1038/emm.2013.76 PMID: 24008896

[77] Ma K, Chen G, Li W, Kepp O, Zhu Y, Chen Q. Mitophagy, mitochondrial homeostasis, and cell fate. Front Cell Dev Biol 2020; 8: 467.
http://dx.doi.org/10.3389/fcell.2020.00467 PMID: 32671064

[78] Apaijai N, Sriwichaiin S, Phrommintikul A, *et al.* Cognitive impairment is associated with mitochondrial dysfunction in peripheral blood mononuclear cells of elderly population. Sci Rep 2020; 10(1): 21400.
http://dx.doi.org/10.1038/s41598-020-78551-4 PMID: 33293556

[79] Morozov YM, Datta D, Paspalas CD, Arnsten AFT. Ultrastructural evidence for impaired mitochondrial fission in the aged rhesus monkey dorsolateral prefrontal cortex. Neurobiol Aging 2017; 51: 9-18.
http://dx.doi.org/10.1016/j.neurobiolaging.2016.12.001 PMID: 28027494

[80] Pollard AK, Craig EL, Chakrabarti L. Mitochondrial complex 1 activity measured by spectrophotometry is reduced across all brain regions in ageing and more specifically in neurodegeneration. PLoS One 2016; 11(6): e0157405.
http://dx.doi.org/10.1371/journal.pone.0157405 PMID: 27333203

[81] Lores-Arnaiz S, Lombardi P, Karadayian AG, Orgambide F, Cicerchia D, Bustamante J. Brain cortex mitochondrial bioenergetics in synaptosomes and non-synaptic mitochondria during aging. Neurochem Res 2016; 41(1-2): 353-63.
http://dx.doi.org/10.1007/s11064-015-1817-5 PMID: 26818758

[82] He N, Jin W-L, Lok K-H, Wang Y, Yin M, Wang Z-J. Amyloid-β1–42 oligomer accelerates senescence in adult hippocampal neural stem/progenitor cells via formylpeptide receptor 2. Cell Death Dis 2013; 4(11): e924-4.
http://dx.doi.org/10.1038/cddis.2013.437 PMID: 24263098

[83] Musi N, Valentine JM, Sickora KR, *et al.* Tau protein aggregation is associated with cellular senescence in the brain. Aging Cell 2018; 17(6): e12840.
http://dx.doi.org/10.1111/acel.12840 PMID: 30126037

[84] Gaikwad S, Puangmalai N, Bittar A, *et al.* Tau oligomer induced HMGB1 release contributes to cellular senescence and neuropathology linked to Alzheimer's disease and frontotemporal dementia. Cell Rep 2021; 36(3): 109419.
http://dx.doi.org/10.1016/j.celrep.2021.109419 PMID: 34289368

[85] Dhurandhar EJ, Allison DB, van Groen T, Kadish I. Hunger in the absence of caloric restriction improves cognition and attenuates Alzheimer's disease pathology in a mouse model. PLoS One 2013; 8(4): e60437.
http://dx.doi.org/10.1371/journal.pone.0060437 PMID: 23565247

[86] Cox LM, Schafer MJ, Sohn J, *et al.* Calorie restriction slows age-related microbiota changes in an Alzheimer's disease model in female mice. Sci Rep 2019; 9(1): 17904.
http://dx.doi.org/10.1038/s41598-019-54187-x PMID: 31784610

[87] Westwood AJ, Beiser A, DeCarli C, *et al.* Insulin-like growth factor-1 and risk of Alzheimer dementia and brain atrophy. Neurology 2014; 82(18): 1613-9.
http://dx.doi.org/10.1212/WNL.0000000000000382 PMID: 24706014

[88] Denver P, English A, McClean PL. Inflammation, insulin signaling and cognitive function in aged APP/PS1 mice. Brain Behav Immun 2018; 70: 423-34.
http://dx.doi.org/10.1016/j.bbi.2018.03.032 PMID: 29604345

[89] Caccamo A, Magrì A, Medina DX, *et al.* mTOR regulates tau phosphorylation and degradation: Implications for Alzheimer's disease and other tauopathies. Aging Cell 2013; 12(3): 370-80.
http://dx.doi.org/10.1111/acel.12057 PMID: 23425014

[90] Zimmermann HR, Yang W, Kasica NP, *et al.* Brain-specific repression of AMPKα1 alleviates pathophysiology in Alzheimer's model mice. J Clin Invest 2020; 130(7): 3511-27.
http://dx.doi.org/10.1172/JCI133982 PMID: 32213711

[91] Kumar R, Chaterjee P, Sharma PK, *et al.* Sirtuin1: A promising serum protein marker for early detection of Alzheimer's disease. PLoS One 2013; 8(4): e61560.
http://dx.doi.org/10.1371/journal.pone.0061560 PMID: 23613875

[92] Wong SQ, Kumar AV, Mills J, Lapierre LR. Autophagy in aging and longevity. Hum Genet 2020; 139(3): 277-90.
http://dx.doi.org/10.1007/s00439-019-02031-7 PMID: 31144030

[93] Lapierre LR, Kumsta C, Sandri M, Ballabio A, Hansen M. Transcriptional and epigenetic regulation of autophagy in aging. Autophagy 2015; 11(6): 867-80.
http://dx.doi.org/10.1080/15548627.2015.1034410 PMID: 25836756

[94] Salminen A, Kaarniranta K. AMP-activated protein kinase (AMPK) controls the aging process *via* an integrated signaling network. Ageing Res Rev 2012; 11(2): 230-41.
http://dx.doi.org/10.1016/j.arr.2011.12.005 PMID: 22186033

[95] Yeung YT, Guerrero-Castilla A, Cano M, Muñoz MF, Ayala A, Argüelles S. Dysregulation of the Hippo pathway signaling in aging and cancer. Pharmacol Res 2019; 143: 151-65. http://dx.doi.org/10.1016/j.phrs.2019.03.018 PMID: 30910741

[96] Totaro A, Zhuang Q, Panciera T, *et al.* Cell phenotypic plasticity requires autophagic flux driven by YAP/TAZ mechanotransduction. Proc Natl Acad Sci USA 2019; 116(36): 17848-57. http://dx.doi.org/10.1073/pnas.1908228116 PMID: 31416916

[97] Pavel M, Renna M, Park SJ, *et al.* Contact inhibition controls cell survival and proliferation *via* YAP/TAZ-autophagy axis. Nat Commun 2018; 9(1): 2961. http://dx.doi.org/10.1038/s41467-018-05388-x PMID: 30054475

[98] Wilkinson DS, Jariwala JS, Anderson E, *et al.* Phosphorylation of LC3 by the Hippo kinases STK3/STK4 is essential for autophagy. Mol Cell 2015; 57(1): 55-68. http://dx.doi.org/10.1016/j.molcel.2014.11.019 PMID: 25544559

[99] Zhang M, Tao W, Yuan Z, Liu Y. Mst-1 deficiency promotes post-traumatic spinal motor neuron survival *via* enhancement of autophagy flux. J Neurochem 2017; 143(2): 244-56. http://dx.doi.org/10.1111/jnc.14154 PMID: 28833175

[100] Chen M, Hu Y, Hou Y, *et al.* Osteogenesis regulation of mesenchymal stem cells *via* autophagy induced by silica-itanium composite surfaces with different mechanical moduli. J Mater Chem B Mater Biol Med 2020; 8(40): 9314-24. http://dx.doi.org/10.1039/D0TB01412E PMID: 32966545

[101] Jin L, Chen Y, Cheng D, *et al.* YAP inhibits autophagy and promotes progression of colorectal cancer *via* upregulating Bcl-2 expression. Cell Death Dis 2021; 12(5): 457. http://dx.doi.org/10.1038/s41419-021-03722-8 PMID: 33963173

[102] Xu W, Zhang M, Li Y, *et al.* YAP manipulates proliferation *via* PTEN/AKT/mTOR-mediated autophagy in lung adenocarcinomas. Cancer Cell Int 2021; 21(1): 30. http://dx.doi.org/10.1186/s12935-020-01688-9 PMID: 33413409

[103] Gogia N, Sarkar A, Mehta AS, *et al.* Inactivation of Hippo and cJun-N-terminal kinase (JNK) signaling mitigate FUS mediated neurodegeneration *in vivo*. Neurobiol Dis 2020; 140: 104837. http://dx.doi.org/10.1016/j.nbd.2020.104837 PMID: 32199908