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Functional analyses of major cancer-related signaling pathways in Alzheimer's disease etiology

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Abstract

Alzheimer's disease (AD) is an aging-related neurodegenerative disease and accounts for majority of human dementia. The hyper-phosphorylated tau-mediated intracellular neurofibrillary tangle and amyloid β -mediated extracellular senile plaque are characterized as major pathological lesions of AD. Different from the dysregulated growth control and ample genetic mutations associated with human cancers, AD displays damage and death of brain neurons in the absence of genomic alterations. Although various biological processes predominately governing tumorigenesis such as inflammation, metabolic alteration, oxidative stress and insulin resistance have been associated with AD genesis, the mechanistic connection of these biological processes and signaling pathways including mTOR, MAPK, SIRT, HIF, and the FOXO pathway controlling aging and the pathological lesions of AD are not well recapitulated. Hence, we performed a thorough review by summarizing the physiological roles of these key cancer-related signaling pathways in AD pathogenesis, comprising of the crosstalk of these pathways with neurofibrillary tangle and senile plaque formation to impact AD phenotypes. Importantly, the pharmaceutical investigations of anti-aging and AD relevant medications have also been highlighted. In summary, in this review, we discuss the potential role that cancer-related signaling pathways may play in governing the pathogenesis of AD, as well as their potential as future targeted strategies to delay or prevent aging-related diseases and combating AD.

Keywords

Alzheimer's disease; aging; tumorigenesis; cell signaling; tau; amyloid

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1. Introduction

1.1 Aging, cancer and neurodegenerative disorders

Aging has generally been referred to as the progress of becoming older, especially when occurring in animals and in particular mammals such as human beings. Biologically, aging is also referred to cells within organism losing the ability to divide (also termed cellular senescence) [1, 2]. Aging represents the accumulation of changes or damage in organs or cells over time, including the increase of DNA damage, mis-folding of proteins, and oxidative stress, which carries the greatest risk of human chronic diseases, including cancer, cardiovascular and neurodegenerative disorders [3–5]. Although the damage-related factors (such as DNA-oxidation) or programmed factors (such as apoptosis) are established as the major contributors of aging [3, 6], the mechanisms governing the aging process have largely remained elusive.

As two of the major diseases associated aging, cancer and neurodegenerative diseases display rather different properties, and in many aspects exhibit an inverse relationship [7]. For instance, genetic alterations including amplification or gain-of-function (GOF) mutations of oncogenes and deletion or loss-of-function (LOF) mutations of tumor suppressors play critical roles in various types of cancer [8, 9]. However, genetic alterations are not common in neurodegenerative disorders, especially in Alzheimer's disease (AD) [10]. Furthermore, tumors display aberrant growth control properties to developing disseminated carcinomatosis, infection or pulmonary embolus ultimately leading to the death of patients [11]. Whereas, the major neurodegenerative diseases are associated with damage or death of neurons, leading to impairment of the patients' movement or mental functioning leading to death [12]. Finally, multiple therapeutic strategies including surgical removal, radio/chemo-therapies, targeted and immune-therapies have been developed to ameliorate or cure cancer patients. In contrast, neurodegenerative disorders, in particular Alzheimer's disease, are currently incurable [13]. To better understand the mechanisms underlying regulation of aging and neurodegenerative diseases, multiple signaling pathways heavily involved and well-studied in tumorigenesis, including FOXO, mTOR, MAPK, insulin resistant, autophagy, inflammation, oxidative stress, and metabolic pathways have now been shown to be associated with neurodegenerative diseases as well, especially in the pathogenesis of Alzheimer's disease, and is the focus of this review.

1.2. Alzheimer's disease (AD)

In 2015, approximately 49 million people were diagnosed with AD worldwide, which is anticipated to increase to 115 million by 2050 [14], in which nearly 15% of people over 65 years old and 50% of people over 85 years old will suffer with AD. This supports the notion that aging is the highest risk factor of AD [14]. However, early-onset AD (under the age of 65) also has been reported occurring in approximately 200,000 Americans due to the inherited mutations [15]. As the major cause of dementia, AD accounts for around 70% of dementia cases with symptoms including difficulty remembering new information, and is characterized as the 6th leading cause of death for all Americans without any efficient treatment strategy [13]. Thus, studies leading to early diagnosis and therapies of AD are urgent in the medical field.

Since 1907, two pathological lesions with abnormal structures and parallel spatial distribution, called senile plaques and neurofibrillary tangles (NFT), are suspected to damage neuronal cells, and have been characterized as the major pathological hallmark of AD [16]. Senile plaques are caused by deposition of a protein fragment called amyloid beta ($A\beta$, 42 and 40 peptides) that build up in the spaces between nerve cells, also referred to “brain amyloidosis”. Specifically, $A\beta$ peptides are released by cleavage of the amyloid precursor protein (APP), to form oligomeric $A\beta$ aggregates, that play a crucial role in disrupting the survival of neuronal cells and are considered a leading cause of AD [17]. Neurofibrillary tangles are twisted fibers of tau protein that build up inside cells. Growing reports demonstrate that hyper-phosphorylation of tau form tangles that could subsequently induce the damage of neuronal structure and function, which is a major intracellular pathology of AD [18]. Thus, the development and regulation of these two lesions have been well studied recently as major hallmarks of AD [19, 20].

1.3. Biomarkers for Alzheimer’s disease

With the difficulty associated with diagnosing AD, identification of biomarkers is necessary for early detection of AD and drug treatment validation. Until now, cognitive assessment is still the primary method for diagnosing AD-induced dementia [21]. Magnetic resonance imaging (MRI) has been developed for the diagnosis of AD, however, the microscopic changes in the brain has been reported to occurring long before the first signs of losing memory [22]. Recently, biomarkers derived from cerebrospinal fluid (CSF) and peripheral blood have been developed for the purpose of early AD symptom detection. Among which, CSF-based biomarkers have been designed for AD detection dependent on the alteration of neuron pathological lesions, including total tau protein (T-tau, reflecting the intensity of neuro axonal degeneration), phosphorylated tau (P-tau, correlating with tangle pathology) and the ratio of $A\beta_{42/40}$ (correlating inversely with the plaque pathology) as previously reported [23, 24].

Although genetic alterations are rare in AD, genetic biomarkers for AD have also been investigated in which mutations of *PSEN1*, *PSEN2* and *APP* have been found to be responsible for a majority of familial early-onset AD cases (1–2% of total AD) [25], and were further validated by the generation of mouse models based on these mutations which lead to the development of AD-like symptoms [26]. Moreover, *APOE $\epsilon 4$* has been characterized as an important genetic risk factor for sporadic AD (98% of total AD), although its alternation is neither necessary nor sufficient for AD pathogenesis [27]. More recently, peripheral plasma proteins have been identified as being associated with AD [28], and blood profile biomarkers derived from lipidomic approaches are may be relevant to the levels of AD [29], in which ten lipid metabolites from plasma could distinguish with 90% accuracy between people remaining cognitively healthy from those appearing cognitively impaired [29].

1.4. Mouse models for Alzheimer’s disease

Due to the current dilemma in elucidating pathophysiology and therapeutic strategies of AD, more robust animal models are therefore urgently needed. Mouse models, which feature highly genetic kinship with the human genome, have been widely regarded as a suitable tool

for AD researches, similar to their role in other disorders, including cancers (Table 1) [30, 31].

Since Games and colleagues firstly succeeded in constructing AD-transgenic mice [32], multiple generations of AD rodents have been developed on basis of pathological hypotheses and mutation sites, which are often produced using knock-in techniques. As a key hallmark during AD pathogenesis, overloaded amyloid plaques are induced by hyperactivity of *AβPP* gene [25], thus the first generation of AD engineered mice were characterized by activating mutations on certain AβPP sites. Interestingly, these engineered mice displayed aberrant amyloid accumulation at 6 months of age and rapidly suffered from learning and memory impairment [33]. After the immunotherapeutic contribution by those first generation products, more transgenic mice have also been designed and produced, mainly concentrating on *Presenilin (PSEN1)* mutagenesis [34]. PSEN1 is responsible for the catalytic activity of the γ-secretase complex, whose loss-of-function mutations significantly facilitates AD formation [35]. Mice with silencing of *PSEN1* demonstrates a more robust development of AD compared to mono-mutation of AβPP, inducing earlier onset and faster progression of this neurodegenerative disease [34].

Furthermore, as another pathological hallmark of AD, Tau-mediated NFTs were also a focus for the development of an AD mouse model. Pre-tangle and hyper-phosphorylation of tau were observed in the first tau transgenic mouse models with ectopic expression of the longest form of tau in neurons [36]. Moreover, different mutations of Tau including P301L and P301S were generated in transgenic mice to produce aggregation and NFT formation, leading to nerve cell dysfunction and loss *in vivo* [37–39]. Moreover, the generation of compound mice carrying the *PSEN1* mutation, *Tau* mutation and *AβPP* mutations referred to 3xtg-AD mice, were closely recapitulated with human AD pathology: inducing cognitive impairment at 3–4 months, amyloid deposits at 6 months and tau pathology at 12 months, and are recognized as the most extensively studied model for AD [40]. In addition, transgenic mice mutated on several metabolism-related genes such as *APOE* have been developed, in accordance with the evidence that insulin insensitivity and lipid dysfunction contribute to the origin and deterioration of AD [41, 42]. Additionally, the deletion of peptidyl-prolyl cis/trans isomerase *Pin1* in mice also displays an AD-like phenotype by modulating tau phosphorylation and promoting the cleavage of APP [43]. However, despite all these scientific achievements, due to the limits of shorter lifespan of mouse and complicated cause of AD, AD-like mouse models do not fully recapitulate human AD pathology, thus more effort is needed to generation more robust models closely resembling the human pathophysiology of AD.

2. Major cancer-related signaling pathways with links to AD pathogenesis

AD results from a complex interplay of signaling pathways related to aging that affect cellular metabolism, inflammation, DNA repair and stress response, resulting in abnormal protein deposition, mitochondrial dysfunction, and ultimately neuronal death. Given the important role for senile plaques and neurofibrillary tangles in AD genesis, understanding the signaling pathways involved in the formation or accumulation of plaques or tangles is crucial for future development of AD therapies. To this end, in the sections below, we

discuss the recent progresses in understanding of the role of major cancer-related signaling pathways in the aging process, and more specifically AD genesis.

2.1 Autophagy and Alzheimer's disease

2.1.1 Physiological roles of Autophagy—Autophagy is a highly conserved degradation process in eukaryotic cells [44]. Mechanistically, the cellular substrates are engulfed by autophagosomes which then move towards and fuse with lysosomes via the cytoskeleton, which facilitates the degradation of cytoplasmic contents including misfolding proteins (aggrephagy), overloaded peroxisomes (perophagy), pathogenic organisms (xenophagy) and malfunctioned mitochondria (mitophagy) [45]. It is currently acknowledged that a complicated series of signaling cascades contribute to the completion of autophagy. To this end, multiple intracellular proteins that associate with autophagic process are categorized as autophagy-related proteins (ATG) [46].

In most circumstances, energy deprivation initiates the autophagy pathway by stimulating AMPK kinase, which subsequently inhibits mTORC1 [47]. Inhibition of mTORC1 kinase activity triggers the activation of transcription factor EB (TFEB) that promotes transcription of autophagy and lysosome related genes, including Atg5, Atg12 and Atg16 [48]. Through several phosphorylation events, mTORC1 can unleash the kinase activity of the ULK1 complex, which in turns activates its downstream complex Vps34. PI3P, a synthesized product by the Vps34 complex, is largely responsible for the recruitment of ATG12-ATG5-ATG16 trimer at the phagopore [49]. With the help of light chain 3 (LC3), a ubiquitin-like molecule, this trimeric complex is critical for membrane elongation as well as the recognition of cellular macromolecules targeted for degradation [50]. After the autophagosome is completely constructed it will fuse with the lysosome to form an autolysosome and continue to process of macromolecule degradation [45]. Generally, defects in autophagy are associated with increased tumorigenesis. However, autophagy also provides a protective function to limit tumor necrosis and inflammation [51].

2.1.2 Protective roles of Autophagy in AD genesis—Based on the protective role of autophagy in neurophysiology, the current viewpoint is that the aberrant accumulation of tau proteins may, at least in part, may be due to impaired autophagy inside neurons [52]. Multiple researchers have verified that increased activity of the autophagy pathway leads to increased degradation of the tau protein and hence reduced intracellular tau aggregation [53]. Nevertheless, the molecular interaction between autophagy and A β remains controversial. Several labs have reported that elevated autophagy effectively decreases A β content in multiple systems, especially in the early stage of A β accumulation [54, 55]. However, deficiencies in the clearance of autophagic vacuoles may exacerbate the AD phenotype [56]. Thus, autophagic vacuole accumulation in AD brains and in *APP/PS1* transgenic mice have been observed [57, 58]. Interestingly, Boland and colleagues have discovered a surprising phenomenon that A β can also be synthesized from amyloid precursor protein inside the autophagosome, showing a potentially novel interaction between the autophagy pathway and A β plaques formation [59]. Due to the existing inconsistency at present, more in-depth investigations are still needed to clarify the functional role of autophagy on pathological alteration of AD.

Genetic alterations in autophagy and their role in AD have gradually emerged [59]. For example, a loss-of-function mutation in phosphatidylinositol-binding clathrin assembly protein (*PICALM*) could block its protective role on neuronal cell survival, while trigger the pathological production, accumulation and transportation of A β [60]. Furthermore, Moreau and colleagues have described that dysfunctional *PICALM* could significantly silence autophagic pathway in part via blocking the formation of autophagosomes, revealing their underlying correlations [61]. Additionally, results using tissue analysis have confirmed the reduced levels of Beclin-1, an inducer of autophagy signaling in a variety of organisms, have been observed within AD-affected brain regions [62]. Moreover, oxidative stress, hypoxia, and FOXO signaling pathways are all involved in regulating autophagy (Fig. 1), and will be discussed further below. Taken together, despite a lack of molecular characterization, a potential role for autophagy in diminishing the pathogenesis of AD deserves more attention.

2.2 FOXO signaling pathway and Alzheimer's disease

2.2.1 FOXO signaling pathway—Forkhead/winged helix box proteins (FOXA-FOXS) are evolutionarily conserved transcription factors [63], in which FOXO proteins (including FOXO1, FOXO3, FOXO4 and FOXO6) are well established as tumor suppressors in different types of cancer by transcriptionally regulating cohorts of target genes [64]. In detail, FOXO proteins manipulate multiple biological processes including DNA repair, cell cycle arrest, stem cell homeostasis and autophagy by regulating cell cycle proteins (p27, CCND1), pre-apoptosis proteins (BCL6), and autophagy proteins (ATG12) [65]. Due to the crucial roles of FOXO proteins in diverse biological processes, FOXOs are tightly controlled in cells through post-translational modification. Specifically, the kinases Akt, SGK, IKBKB and ERK1/2 could directly phosphorylate and negatively regulate FOXO protein abundance [66], in contrast, JNK and MST1 phosphorylate and positively regulate FOXO protein abundance in stress conditions [67]. Moreover, histone acetyl-transferase p300-mediated acetylation could activate FOXO transcriptional activities [68], which can be counteracted by the deacetylase SIRT1 [69]. More recently, other post-translational modifications including hydroxylation, methylation and ubiquitination have been identified to regulate FOXOs [70–72].

2.2.2 Protective functions of FOXO in aging and AD genesis—FOXO proteins have attracted attention in the aging field due to the notion that activation of DAF-16, a *C. elegans* FOXO homolog, is obligatory for extending the lifespan of *C. elegans* [73]. Until now, only two genes *FOXO3* and *APEO* have been identified to be associated with attainment of extreme old age [74], thus large efforts have been performed in recent years to explore the upstream regulators or downstream effectors of FOXO3 in the regulation of ageing and lifespan [75]. Consistent with tumor suppressive role of FOXO proteins in repressing tumorigenesis, activation of FOXO could serve as homeostatic regulators in response to stress to protect against the onset of aging-related diseases including AD.

The function of FOXO proteins, has been directly linked to proteostasis (including autophagy, mitophagy) or apoptosis by transcriptionally regulating factors such as ATG12, BCEN1, BNIP3 for autophagy [76, 77], PINK1 for mitophagy [78], the E3 ligases FBXO32 and TRIM63 for proteasome-mediated protein degradation [77], and pro-apoptosis proteins

BBC3, BCL6 and TNF for apoptosis [79]. Through regulating these factors, FOXO can efficiently clear mis-folding proteins or damaged organelles to avoid cellular damage, or clear the damaged cells by apoptosis. Recently, a pivotal role for FOXO4 in senescent cell viability has been revealed, and blocking the interplay of FOXO4 with p53 could induce apoptosis of senescent cells and reverse the effects of aging in mice [80]. More importantly, FOXO also responds to and controls oxidative stress, another major driver of aging and AD, by transcriptionally regulating ROS detoxification enzymes such as CAT, PRDX3, SENP and SOD2 to reduce ROS-induced cellular damage, especially in neuronal cells, to protect neuron cells from aging (Fig. 2) [81]. Additionally, FOXOs functions in promoting stem cell viability by translationally regulating pluripotency maintenance factors such as OCT4 and SOX2 are also shown to promote an anti-aging effect [82]. Thus, activation of FOXO could be a potential strategy to delay aging and diminishing AD genesis.

2.3 mTOR signaling network and Alzheimer's disease

2.3.1 mTOR signaling pathway—The mammalian target of rapamycin (mTOR) signaling pathway is evolutionarily conserved from yeast to mammalian, and integrates a wide range of extracellular stimuli to mediate cellular growth and metabolic homeostasis [83]. As a protein serine/threonine kinase, mTOR incorporates into two structurally and functionally distinct complexes, mTORC1 and mTORC2. Functionally, mTORC1, as a nutrient sensor, responds to the nutrient changes and controls cellular protein, lipid and nuclear acids homeostasis [84]. In contrast, mTORC2 responds to the stimulation of growth factors (IGF, EGF) and phosphorylates downstream AGC family kinases (such as Akt, SGK, PKC) to promote tumorigenesis [85]. Genetically, deletion/loss-of-function mutations of mTOR negative regulators (such as *PTEN*, *NF1* and *TSC1/2*), or amplification/gain-of-function mutations of mTOR positive regulators (such as *EGFR*, *PIK3CA*, *RAS* and *AKT*) occurring in different types of cancer all attribute to abnormal activation of Akt/mTORC1 signaling [83]. It is well documented that the mTOR pathway regulates multiple biological processes, and is implicated in the etiology of numerous pathological conditions including cancer [86], diabetes [87] and neurodegeneration [88]. The predominant function of mTOR complexes in regulating metabolic diseases, such as cancer and diabetes, have been extensively reviewed recently [83]. In this section, we will summarize the recent progress of mTOR signaling pathway in neurodegenerative diseases, especially in Alzheimer's disease.

2.3.2 Role of mTOR pathway in promoting AD genesis—mTOR is a conserved protein kinase that plays a key role in controlling a balance between protein synthesis and degradation [89]. It has been well established that genetic manipulation of mTOR signaling increase the life span of multiple organisms, including *C. elegans* [90] and *M. musculus* [91]. Consistent with these findings, Rapamycin, a well-characterized mTOR specific inhibitor, has also been shown to extend the lifespan of multiple organisms [92–97]. For example, it increases the mean lifespan of male and female mice by 9% and 13%, respectively [98]. Thus, increasing studies highlight the potential strategy to combat AD by targeting mTOR pathway via its anti-aging effects.

It is reported that chronic increase in mTOR activity occurring during aging may facilitate the development of tau pathology. Tau's main function is to promote microtubule assembly

and stabilization [99]. However, hyper-phosphorylated tau could accumulate to form insoluble tau aggregates, leading to neurofibrillary tangles [18], a pathological hallmark of AD. Importantly, mTOR has been found to promote tau phosphorylation directly or indirectly by modulating multiple kinases, including protein kinase A (PKA), glycogen synthase kinase 3 (GSK3) and cyclin-dependent kinase 5 (CDK5) [100]. In addition, mTOR has also been reported to directly phosphorylate and inhibit protein phosphatase 2A (PP2A), the major phosphatase of tau phosphorylation and down-regulated in AD brains [101], to increase tau phosphorylation [102]. Whereas, mTOR, via its downstream targets, such as eukaryotic translation factor 4E (eIF4E) and S6K, increases the translation of tau mRNAs, suggesting that hyperactive mTOR may facilitate tau accumulation [103]. These results together implicate mTOR in promoting an imbalance of tau homeostasis, leading to tau aggregation and formation of neurofibrillary tangles observed in AD genesis (Fig. 3).

As the major substrates of mTORC1, S6K1 and eIF4E are significantly increased in AD brain compared to age-matched control cases, indicating higher mTOR activity in AD [104]. Furthermore, the injecting natural A β oligomers into the hippocampi of normal mice could activate mTOR signaling, indicating that the amyloid precursor protein could directly activate the mTOR pathway [105]. Furthermore, rapamycin could ameliorate A β and tau pathology in the brains of 3xTg-AD mice, a widely used animal model of AD [106]. Mechanistically, reducing mTOR hyperactivity in the brains of the 3xTg-AD mice increase the autophagy marker LC3II and other related proteins [107]. Therefore, Rapamycin has been shown to ameliorate AD-like pathology and cognitive deficits effectively in a broad range of animal models [108].

2.4 MAPK signaling pathway and Alzheimer's disease

2.4.1 MAPK signaling pathway—Mitogen-activated protein kinases (MAPKs) are highly conserved serine/threonine protein kinases among found in a large number of organisms. Members of this kinase superfamily could be directly activated by extracellular stimuli, typically including oxidative stress, growth factors, and pro-inflammatory factors [109, 110]. Following the interaction between extracellular signals and membrane receptors, three levels of kinases in MAPK pathway are needed for intracellular responses. Specifically, MAPK kinase kinase (first hierarchy as MAP3K, including RAF, ASK1, TAK1, MEKK1 and MLK3) phosphorylates MAPK kinase (second hierarchy as MAP2K, including MEK1/2, MKK3/6 and MKK4/7), which subsequently phosphorylates MAPK (third hierarchy, including ERK1/2, p38 and JNK) to induce cellular responses, such as proliferation, invasiveness, differentiation and autophagy [111, 112]. The role of abnormal activation of the MEK/ERK pathway through genetic alterations in cancer has been extensively investigated [113]. Specifically, gain-of-function mutations of *K-Ras* in non-small-cell lung cancer (NSCLC) and pancreatic cancer [114], *EGFR* in NSCLC and glioblastoma [115, 116], and *BRAF* in melanoma [117] all are considered as driver mutations to activate the MEK/ERK pathway, consequently lead to tumorigenesis.

2.4.2 Role of MAPK in promoting AD genesis—The regulatory role that MAPK signaling has played on AD pathogenesis is currently unclear. First, oxidative stress is regarded as a vital factor that deteriorates neuronal survival when A β is aberrantly

accumulated [118]. Results have shown that p38, a tier 3 kinase in the MAPK pathway, is capable of mediating this specific response, which ultimately leads to hyper-phosphorylation and aggregation of the tau protein [119]. Second, neuro-inflammation provoked by A β drives cell death of preliminarily affected neurons have high concentrations of tau aggregates and A β production, driving a vicious circle. Similarly, p38 contributes as an intermediate inflammatory responses induced by IL-1 β , IL-6 and TNF- α , the suppression of which could greatly diminish neural apoptosis and cognitive impairment of rodent models [120, 121]. Finally, due to the overloaded A β in neuronal regions, mitochondrial dysregulation is commonly observed in early-phase AD, which may induce neural apoptosis and thus exacerbate memory defects in AD models.

Studies on its mechanism of action have suggested that ERK is the central kinase as well as signal transducer of this pathway, depletion of which successfully reverses the morphological and functional abnormality of mitochondria in AD-affected cells [111, 122]. Moreover, in terms of the regulation of synaptic dysfunction, activation of the JNK axis accounts for the aggravation of synaptic impairment in AD cells. Likewise, pharmaceutical inhibition of JNK can significantly restore the damaged synapses and loss of synaptic proteins [123]. These results demonstrating the role of the MAPK pathway in AD suggest that MAPKs could be targeted for novel treatments in the future, although details of the mechanisms remain partially unclear.

2.4.3 MAPK inhibitors and AD—Due to the close correlation between MAPK pathway and AD pathogenesis, researchers and pharmacists have paid more attention on potentially therapeutic role of MAPK inhibitors against AD. Firstly invented in 1995, PD98059 is a typical molecule among MAPK inhibitor family. It displays significant effects against aberrant formation and secretion of A β [124, 125], thus blocking the pathological inflammation and subsequent neuronal death [126]. Besides, other specific inhibitors of MAPK such as SB202190 and U-0126 demonstrate similar anti-AD efficacy, mainly lowering the inflammatory tendency as well as A β accumulation in sick neurons [127–129]. Recently, investigations have reported that novel inhibitors (SB239063 and MW01-2-069A-SRM) have shown great anti-ischemic and anti-hypoxia impacts, both could contribute to the amelioration of AD pathogenesis in rodent models [130–132]. These results together hint the value of MAPK-targeted strategy among AD patients, although clinical evidences remain lacking in current situation.

2.5 Insulin resistance and Alzheimer's disease

2.5.1 Mechanisms of insulin resistance—Insulin, an exocrine hormone secreted by pancreatic beta cells, plays core roles in modulating cell metabolism under physiological conditions. Insulin binds to the insulin receptor (IR) on plasma membrane which then auto-phosphorylates and acts as a tyrosine kinase of its downstream insulin receptor substrate 1 (IRS1) [133]. Immediately, the phosphorylated IRS1 triggers a cascade of phosphorylation events on intracellular proteins such as PI3K/Akt, mTOR and S6K to expand the biological response. Eventually, this signaling culminates in the translocation of insulin-dependent glucose transporter 4 (GLUT4) towards the plasma membrane so that the glucose uptake and

energy production could be enhanced. Liver, skeletal muscle and adipose tissue are main targets of insulin action [134, 135].

When the IR loses binding affinity to its ligand, higher concentration of peripheral insulin is therefore required to maintain the normal translocation of GLUT4 and uptake of glucose, which is functionally defined as insulin resistance [136]. Currently, the causes of insulin resistance remain largely unclear, while multiple internal abnormalities seem to contribute to, including the loss-of-function mutation of *IR*, transduction impairment by obesity-related inflammation and toxic effects of metabolites by overloaded fatty acid or glucose. All these possible mechanisms could destroy the structure or activity of pathway molecules, hence inducing signaling insensitivity [137]. Patients with insulin resistance often suffer from hyperinsulinemia, hyperglycemia, hyperuricemia and dysfunctional lipid metabolism, which may evolve into metabolic disorders such as type 2 diabetes mellitus (T2DM), polycystic ovary syndrome (PCOS) and atherosclerosis [138, 139].

2.5.2 Role of insulin resistance in promoting AD genesis—*DAF-2* (homologues of *IR* in mammalian) mutations [73] or CHIP-mediated degradation of *DAF-2* [140] in *C. elegans*, could significantly extend *C. elegans* lifespan by activating FOXO signaling pathway. Furthermore, numerous studies have identified a close correlation between insulin resistance and A β plaques [141]. Normally, the activation of the insulin pathway strengthens the degrading process of excessive A β and thus effectively avoids the formation of extracellular A β plaques. However, when insulin insensitivity occurs in neuronal cells, the functionality of γ -secretase could also be stimulated, which promotes the cleavage of APP into A β [142, 143]. Additionally, due to the secondary hyperinsulinemia by insulin non-responsiveness, the expression of insulin-degrading enzyme (IDE) is greatly suppressed, which physiologically functions as a potent scavenger of A β in brain cells [144]. Meanwhile, *in vivo* evidence has also shown that A β could deteriorate insulin resistance by decreasing the density of membrane IRs as well as restricting IRS-1 activity via an inhibitory phosphorylation on its serine residue [143]. This feed-forward loop outlines the vital connection between insulin resistance and A β [145]. Several *in vitro* studies have shown that A β can activate the PI3K/Akt pathway as well (Fig. 3) [146].

The relationship between tau tangles and insulin insensitivity have also been recently reported. GSK3 β , functionally down-regulates Akt-mediated phosphorylation after insulin stimulation [147], is therefore activated in the setting of insulin resistance. Moreover, GSK3 is the main kinase targeting the tau protein, whose aberrant activation significantly promotes phosphorylation on intracellular tau [148]. Meanwhile, insulin resistance has a negative impact on PP2A, which is normally an indispensable tau phosphatase under physiological conditions [143]. These mechanisms jointly explain the potential interplay between insulin resistance and tau protein aggregation, revealing that insulin resistance may be regarded as an important contributor of the pathogenesis of AD (Fig. 3).

2.6 SIRT1 signaling pathway and Alzheimer's disease

2.6.1 Physiology of SIRT1 signaling—Sirtuins are NAD⁺-dependent deacetylase in mammalian cells, functionally serving as a post-translational modifier of histone and non-

histone substrates in order to regulate gene expression. There are seven orthologous members among the Sirtuin family, defined as SIRT1-SIRT7 [149]. Each of them features different enzymatic properties and subcellular localizations, in which SIRT1 was the first identified subtype among mammalian Sirtuins, which locates either in nucleus or cytoplasm of multiple tissues and exerts deacetylase activity on multiple target proteins [150].

So far, calorie restriction is the most recognized initiator of SIRT1 signaling, together with NAD⁺ biosynthesis and small molecule Sirtuin activators (STACs), which partially contribute to SIRT1 activation under certain circumstances [150, 151]. SIRT1 pathway is involved in many physiological processes to maintain cellular homeostasis and stress resistance. For instance, SIRT1 is able to suppress the NF- κ B pathway to dampen systemic inflammation induced by energy deficiency [152]. Similarly, through activating PGC1 α , SIRT1 is involved in regulating mitochondrial biogenesis, fatty acid oxidation and glucose production to increase intracellular energy [150, 153]. These results suggest a widespread involvement of SIRT1 in cell physiology, especially in metabolic homeostasis. Apart from its regulatory role in cell metabolism, researchers have paid more attention on SIRT1 participation in neural behavior. Studies of SIRT1 deficient mouse models at the histological level has revealed a role in the development of the central nervous system, including axonal elongation, synaptic plasticity and hypothalamic formation, which primarily has a protective impact on neural health and survival [149, 154, 155].

2.6.2 Protective roles for SIRT1 signaling in AD genesis—According to current literature, SIRT1 is believed to have a protective impact against AD by ameliorating its pathological hallmarks in rodent models [149]. Evidence suggest that limited calorie intake could significantly lower the risk and severity of AD, while further studies have discovered that this beneficial effect is largely attributed to SIRT1 activation [156]. Based on pharmacological analysis, resveratrol reverses AD progression largely due to the activation of SIRT1 and its downstream substrate PGC1 α [157]. In-depth investigations have elucidated that different activities of the SIRT1 pathway could affect the formation of both tau tangles and A β plaques in the central nervous system. SIRT1 regulates ROCK1 or inflammation to attenuate the accumulation of A β [158, 159]. In addition, SIRT1 deacetylates FOXOs and p53 to modulate apoptosis and thereby antagonizing the aging process (Fig. 4) [160, 161]. p300, a histone acetyltransferase, is able to acetylate tau and block its degradation, leading to an enrichment of tau and increase propensity to form intracellular tangles [162]. However, this process appears to be reversed by SIRT1 deacetylation of tau, which exhibits a pro-degrading effect of tau [162]. However, SIRT1 protects neural cells from the effects of A β plaques [163]. Taken all into account, SIRT1 activation may be a promising therapeutic target for treating AD patients.

2.7 Hypoxia/HIF signaling and Alzheimer's disease

2.7.1 Hypoxia/HIF signaling—Hypoxia occurs in physiological (strenuous physical exercise) or pathological (stroke, ischemia, solid tumors) conditions with the feature of lacking oxygen (less 1%) [164]. The major molecular sensor of oxygen is the prolyl hydroxylases (PHD), which are inactivated in hypoxic conditions, and in turn impairs prolyl hydroxylation of various cellular substrates, including hypoxia-induced factor alpha (HIF α)

and serine/threonine kinase Akt [165, 166]. It is well-established that hydroxylated HIF α is recognized and polyubiquitinated by the tumor suppressor protein pVHL and undergoes proteasome-dependent degradation [167, 168]. Consequently, accumulation of HIF α under hypoxic or *VHL* deficient conditions such as clear cell renal carcinomas (ccRCCs) leads to its incorporation with HIF1 β to form HIF α/β heterodimers which transcriptionally regulating a large number of genes in response to the pathophysiological oxygen deprivation [167].

Among the multiple biological functions of HIF, angiogenesis is the most critical response of cells to oxygen deprivation by elevation of HIF substrates including VEGF, EPO and VEGFR [169]. This response contributes to the formation and maintenance of stem cell and regenerating cells as well as cell survival in the center of solid tumors [170]. Consistent with this function, HIF α is demonstrated as an oncoprotein in triple-negative breast cancers, and its inhibitors have been developed to conquer accumulating HIF-induced tumor growth [171]. In contrast, HIF1 α is considered a tumor suppressor in glioblastoma and ccRCC, in which knockdown *HIF1 α* could efficiently decrease glioblastoma or ccRCC growth [172, 173].

2.7.2 Hypoxia/HIF signaling pathways in AD genesis—Due to the fact that aging impairs oxygen delivery by weakening cardiovascular system and central neurons are highly sensitive to oxygen supply, aging-induced reduction in oxygen supply has been strongly linked to neurodegenerative diseases, especially to AD [174]. Hypoxia not only contributes to the plaque formation, but also increases the memory deficit in an AD transgenic mouse model [175]. Compelling evidence also shows that short periods of hypoxia can potentiate A β -induced expression of pro-inflammatory markers, such as Cyclooxygenase-2 (COX-2) and Presenilin 1 (PS1), thus accelerating the neuro-inflammation characterized in AD brains [176]. In addition, prolonged hypoxia-upregulated Ca²⁺ channels are required for A β formation [177]. Furthermore, multiple signaling pathways including the angiogenesis pathway [178], Akt/mTOR pathway [179], oxidative stress pathway [180], metabolic pathways [181] could all be modulated by hypoxia or the HIF pathway heavily involved in AD genesis (Fig. 5).

Hypoxia/HIF upregulates multiple-biological processes, in which angiogenesis is the most important response of cells to hypoxia [169]. Multiple independent studies have demonstrated that the vessels isolated from the brain of AD patients [178] or transgenic AD mice [178] display accumulating HIF α and angiogenic proteins, such as angiopoietin-2. Moreover, the HIF substrate EPO is necessary and sufficient to prevent A β -induced apoptosis in neurodegenerative disease via activating the downstream NF- κ B pathway [182]. In keeping with this notion, treatment of neuron degeneration by intra-cerebroventricular delivery of VEGF benefits patients [183], highlighting that improvement of cerebral perfusion may combat AD genesis. Importantly, HIF is reported to transcriptionally induce the expression of APP cleavage enzyme 1 (BACE1) [184], a major CSF biomarker for AD detection, and contributes to A β production. Thus, hypoxia treatment markedly increased A β deposition and neurotic plaque formation in Swedish mutant APP transgenic mice [184].

On the other hand, as a major substrate of HIF signaling, two major brain glucose transporters, GLUT1 and GLUT3, were observed to have decreased expression in the AD brain [185]. Furthermore, the decrease of GLUT1 and GLUT3 protein abundance is also negatively correlated with the hyper-phosphorylation of tau and an increased density of NFTs [186]. HIF also induces the phosphorylation of Tau by modulating GSK3 β , mTOR and CDK5, which would be further discussed below [186, 187]. Another AD event linked to HIF is the oxidative stress-induced accumulation of A β [188], which is discussed in the following section. Together, it appears that aging-induced hypoxia may attenuate neuroprotective pathways and lead to increased susceptibility to AD genesis (Fig. 5).

2.8 Oxidative stress and Alzheimer's disease

2.8.1 Oxidative stress—Oxidative stress reflects an imbalance between the generation and clearance of reactive oxygen species (ROS) [189]. Biologically, ROS is formed as a natural byproduct of metabolism and has important roles in cell signaling and homeostasis. However, excessive production of ROS during environmental stress (such as UV or heat exposure) or defective mitochondria, can induce significant damage to cell components, including DNA, proteins and lipids [190]. Moreover, oxidative stress can also disturb multiple cellular signaling, including NF- κ B, HIF and STAT3 pathways, leading to expression of proteins that control inflammation, cellular transformation, survival and metastasis [191–193]. In contrast, the antioxidant system, including enzymes (such as catalase, superoxide dismutase) and non-enzymatic antioxidants (such as chelating agents) protects against the damaging effects of ROS, thereby exhibiting anti-tumor and anti-inflammation activity [194].

As a double-edged sword, ROS is beneficial to kill pathogens in the context of the immune system [195]. However, as discussed above, excessive oxidative stress may damage cellular components. As one of the main causes of DNA mutations, excessive ROS has been implicated in age-related diseases, including cancer and neurodegenerative diseases [196]. Unexpectedly, modest levels of oxidative stress are required for the survival of cancer cells, whereas excessive levels would kill them by inducing cellular apoptosis [197]. Mechanistically, oxidative stress directly activates MAPK kinases including ERK1/2, p38, and JNK, or inactivation of phosphatases that regulate these proteins to control tumor cell proliferation [198]. Moreover, ROS has also been reported to activate Akt by inhibiting phosphatase and tensin homolog on chromosome ten (PTEN), contributing to cell survival [199]. In contrast, Akt has been reported to downregulate antioxidant defenses and promote tumor cell survival [200]. More interestingly, increased production of ROS in the human stomach by *Helicobacter pylori* infection is important for gastric cancer development [201]. Hence, oxidative stress is profoundly involved in regulating tumorigenesis.

2.8.2 Role of oxidative stress in promoting AD genesis—Oxidative stress has been shown to increase with age in the brain, where oxidative damage is a major contributor to functional decline [202]. Consistent with this notion, lacking specific antioxidant enzymes (such as SOD) show a shortened lifespan in invertebrate models [203]. Conversely, deletion of mitochondrial *SOD2* can extend lifespan in *C. elegans* or mice models [203, 204]. More

importantly, oxidative damage is also recognized as an early event in AD genesis even prior to A β deposition [205, 206].

Increasing evidence demonstrates that ROS or other free radicals in the AD brain are largely derived from mitochondrial dysfunction [207], A β -mediated processes [208], transition metal accumulation [209] and genetic alterations (*Presenilin* mutations) [210]. Both neurons containing NFT and AD brains with extensive A β deposits show very lower levels of 8-hydroxyguanosine (8OHG), a marker of oxidative damage [205, 211]. A β has been shown to produce H₂O₂ in cultured neuronal cells [212]. Further, *in vitro* A β -mediated neuronal damage seems to be a direct result of ROS, and the associated damage can be partially reversed by administration of antioxidants such as vitamin E [213]. Thus, antioxidant treatments have displayed some efficacy for human patients, in particular vitamin E has been utilized for the treatment of AD [214]. In addition, increased oxidative modification to proteins such as A β in AD result in increased protein mis-folding and impaired degradation [215]. Expression of the AD-associated APP mutation in cultured cells results in increased susceptibility to exogenous oxidative stress, and triggers apoptosis. It is also noted that oxidative stress-mediated disruption in mitochondrial respiration and mitochondrial damage are largely related to AD and other neurodegenerative diseases.

Redox-active iron and copper are increased in both NFT and A β deposits [216, 217], and the redox activity in AD lesions is inhibited by exposure to copper or iron chelators [218], indicating that accumulation of iron/copper is a major source of the production of ROS. Thus, the recent usage of chelating agents for AD therapy has been suggested, and metal chelators have been shown to prevent plaque formation in AD mouse models that express mutated *APP* [219]. Moreover, oxidative stress is also the major cause of glial inflammation and apoptosis. As such, the APP mutation in cultured cells results in increased susceptibility to exogenous oxidative stress [220]. Oxidative stress also plays a role in the ischemic cascade due to oxygen reperfusion injury following hypoxia. For example, peroxidized lipids and proteins are accumulated in the brains of Alzheimer's patients [221]. All these findings suggest a critical role for oxidative stress in promoting AD and highlight the potential for antioxidants including Vitamin E and metal chelators as potential drugs for combating AD (Fig. 6).

2.9 Metabolism and Alzheimer's disease

2.9.1 Physiology of Metabolism—Metabolism is defined as enzyme-catalyzed chemical reactions within living organisms, including the production or consumption of energy (calories) and macromolecules (proteins, lipids and nucleic acids), and the elimination of the toxic wastes [222]. Metabolism is largely divided into two groups, catabolism (degrading molecules) and anabolism (synthesizing cellular macromolecules). The metabolic core pathways such as glycolysis, respiration, tricarboxylic acid (TCA) and urea cycles (Krebs) have been extensively exploited within the last 3 decades [222]. The regulation of metabolic pathways by cellular signaling including the growth factor-induced PI3K/Akt/mTOR pathway, which promotes anabolism and suppresses catabolism [223], and the energy deprivation-activated AMPK pathway which limits growth in energetically unfavorable states, have been well-investigated recently [224]. Conceivably, the imbalance of metabolism

induced by abnormal chemical reactions or dysregulation in cell-signaling pathways, genetically or environmentally, can influence the establishment of metabolic syndromes and diseases, such as obesity, diabetes, circulatory disorders, cancer, and neurodegenerative diseases [225].

Metabolic intermediators such as ATP, Acetyl-CoA, α -ketoglutarate (α -KG) and S-adenosyl methionine (SAM) all play critical roles in the post-translational modifications of various proteins such as phosphorylation, acetylation, hydroxylation and methylation respectively, to exert tremendous influence on a majority of cell signaling pathways [226]. Cancer cells have long been noted to preferentially metabolize glucose through glycolysis, known as a Warburg effect [227], and this discovery has been translated into the sensitive methods to image tumors such as PET-CT [228]. Genetic mutations occurring in key metabolic enzymes such as NADP⁺-dependent isocitrate dehydrogenase (IDH1/2) evoke new functions to generate oncointermediates (R-2HG) to induce glioblastoma [173], and mutation in pyruvate dehydrogenase (PDH) consumes greater levels of glucose and secretes high levels of lactate than normal tissue [229]. Moreover, the deficiency of glucose-6-phosphatase (*G6Pase*) is a high risk factor for hepatocellular adenomas [230]. Interestingly, the abnormal gut microbiota, living in the human digestive system, recently appear to play an important role in metabolic disorders [231].

2.9.2 AD is a metabolic disease—The dysregulation of mitochondria, the site of the TCA cycle and respiration, effects energy levels and is a key mechanism promoting neurodegeneration, especially for AD genesis [232]. For instance, disrupting mitochondrial electron transport chain activity increases tau phosphorylation [233]. Whereas, amyloid (A β) disrupts electron transport chain and cytochrome oxidase function [234]. Clinically, neurons derived from AD show a phenotype of increased mitochondrial degradation, leading to decreased energy production and a reduction in normal cognitive function [235], suggesting that both events (dysregulation of mitochondrial and A β) may occur early in the disease process prior to the observation of any symptoms of cognitive impairment. Interestingly, cytochrome oxidase, a core enzyme for mitochondrial metabolism, possibly triggers the early pathological events [236]. Furthermore, the generation of ROS, a byproduct of normal metabolism, has been tightly involved in AD genesis [237] (Fig. 6). In addition, SIRT proteins located in both the nucleus and the mitochondrial deacetylates protein targets including histones and metabolic enzymes, and serve as the key factors linking caloric restriction to longevity (Fig. 4) [238].

Recently, a reduction in caloric intake, referred as calorie restriction, has been shown to slow the progress of age-related disorders in mice and monkeys [239–242]. As an energy sensor, the metabolic AMP-activated protein kinase (AMPK) tightly controls cellular response to energy shortage [243]. The function and regulation of AMPK in cancer has been thoroughly reviewed recently [244]. Given that AMPK is the major regulator of glucose uptake, AMPK may have a significant role in the prevention of AD pathology. Previous studies show that not only is AMPK a direct tau kinase [245], but also abnormally activated in tangle-bearing neurons of AD [246]. Furthermore, AMPK can repress amyloid genesis in neurons, and is activated in response to A β exposure [247]. AMPK is also a potential activator of autophagy

which appears to be suppressed in AD, in addition to other pathways involved in AMPK and AD that have been extensively reviewed recently [248].

AMPK functions to suppress or delay the appearance AD pathology as a neuroprotective factor potentially through increasing autophagy or reducing metabolic stress, oxidative stress, and inflammation via regulating proteins such as ULK1, SIRT1, FOXO and PGC1 α (Fig. 7) [248]. In support of this finding, the activator of AMPK, metformin, an anti-diabetic drug used to treat type 2 diabetes, has been used to reduce blood glucose and cholesterol to restrict AD in AMPK-dependent and independent manners. For instance, metformin activates PP2A to reduce tau phosphorylation [102] and increases lysosomal compartments in microglial cells to clear A β and inhibit plaque formation [249]. However, it has also been reported that metformin could induce production of A β via transcriptional upregulation of *BACE1* [247], which possibly limits the benefit of metformin in AD treatment and warrants further investigation.

2.10 Inflammation and Alzheimer's disease

2.10.1 Inflammation—As a protective response of body tissues to harmful stimuli (such as infections), inflammation is a complex biological process to eliminate the cell injury, clear necrotic cells and repair damaged tissues by recruitment of immune cells and molecular mediators to the site of damage [250]. In this process, acute inflammation is a short-term process to remove the injurious stimulus, whereas inflammation can become a chronic process to continuously erode the surrounding tissues if the damaged tissue is not well-repaired during the acute response. Chronic inflammation is well-established to promote cancers progression by orchestrating the microenvironment around tumors, and contributing to cellular proliferation, survival, and migration by the secretion of chemokines or cytokines [251, 252]. On the other hand, immune cells re-educated in tumors, termed tumor associated macrophage (TAM), may exhibit tumor promoting as well as anti-tumor functions [253].

Cell signaling pathways, such as IKK/NF- κ B, JAK/STAT and TBK1/IRF, play key roles in inflammation and mediate critical effects of inflammatory stimuli on cancer cells, and are directly or indirectly activated in tumors [254–256]. Interestingly, FOXO3a is recognized to influence immune cell lifespan, proliferation, differentiation and maturation, and down-regulation of FOXO3a could extend the lifespan of T cells [257], whereas increased FOXO3a transcriptional activity results in the loss of memory B cells via TRAIL-mediated apoptosis [258]. Recently, immunotherapeutic strategies have been developed for cancer intervention, including the discovery of immune checkpoint PD1/PD-L1 as the potential target to activate the host immune system as a way of combating tumors [259].

2.10.2 Role of inflammation in promoting AD genesis—Neuro-inflammation is characterized as a pathological hallmark of AD and one of the major triggers of neurodegeneration [260]. Recently, compelling evidence indicate that A β deposition in AD is associated with a local inflammatory response, and analysis of the transcriptomic data from AD brain tissues reveals a direct link between an inflammation/microglial-enriched network with AD [261]. Thus, the amyloid cascade-inflammatory hypothesis arises to show

that A β aggregation could induce an inflammatory response by triggering the activity of microglia, which has been identified as a key primary event of AD pathology [262]. On the other hand, the tangles may also stimulate chronic inflammation to clear the debris induced by activated microglia and astrocytes, stressed neurons, and A β plaques [263].

As the first line of defense against invading pathogens (such as microbial infection) or other types of brain tissue injury, activated microglia and astrocytes induces A β accumulation, which has been reported in both patients and animal models of AD [264], coupled with an increase of specific chemokines and cytokines [265]. Furthermore, activated microglia may reduce A β deposits by increasing its phagocytosis, clearance, and degradation [266]. Moreover, A β is not only a TLR4 ligand, but also interacts with other microglial receptors, resulting in TLR signaling dysfunction and inflammation [267]. On the other hand, chemokines such as TNF α may enhance APP and A β 42 peptide production [268]. Importantly, A β is able to activate the NF- κ B pathway which is a central signaling pathway for cytokine production [269]. At the same time, A β may directly bind to the surface of microglial cells for the activation of MAPK/ERK pathways and induce pro-inflammatory genes including cytokines and chemokines [270].

Accumulating evidence has revealed that deficits in tau function also affect neuronal functions of microglia, such as binding of CX3CL1 to its receptor in microglia (CX3CR1) to down regulate microglia functionality [271, 272]. Moreover, deficiency of CX3CR1 in microglia enhances tau neuronal pathology via activation of the p38 pathway by secreted cytokines [272]. It has been suggested that cytokines and chemokines (such as IL6, TNF α and TGF β) involved in inflammation are upregulated in brains of AD patients [273, 274]. These pro-inflammatory cytokines (such as TGF- β) could influence A β formation by transcriptional upregulation of *BACE1* mRNA, protein and enzymatic activity [275].

Due to the important roles of inflammation in AD genesis, nonsteroidal anti-inflammatory drugs (NSAIDs) have been investigated in the treatment of AD, but the result is still controversial [274, 276, 277]. Additionally, it was observed that nasal vaccination in mice was able to decrease A β and activate microglia, but the clinical trial in humans was discontinued due to the arise of symptoms of acute meningoencephalitis [278–280].

2.11 Other pathways and Alzheimer's disease

2.11.1 miRNA and AD—MiRNAs consist of small conserved non-coding RNAs (usually 15–25 nucleotides) post-transcriptional gene modifiers that target and suppress the translational process of mRNA. Owing to their widespread distribution from prokaryotic to mammalian cells, it is not difficult to comprehend their extensive roles in maintaining cellular physiology and internal homeostasis [281]. With respect to the central nervous system, developmental researchers have identified that miRNAs are inevitable regulators during neurogenesis and maturity phase. Moreover, further *in vivo* data have verified the modulatory role of miRNAs in aging and neurodegenerative diseases [282].

A broad spectrum of miRNAs have been identified to be involved in AD pathogenesis [283]. For instance, up-regulated miR-34 is detected in AD-affected cells, which represses the degradation of tau and causes memory impairment through SIRT1 inhibition [284, 285].

Whereas, down-regulation of miR-29a in AD notably induces the expression of its downstream target *BACE1*, which accelerates the cleavage from APP to A β [286, 287]. Moreover, several elevated miRNAs such as miR-9, miR-155, miR-146a stimulate neuro-inflammation around brain cells, which is a widely recognized mechanism for AD genesis [282]. In summary, broad connections between AD and miRNAs suggest their great potential as therapeutic targets in future clinical application.

2.11.2 LncRNA and AD—Similar to miRNAs, long non-coding RNAs are also a cluster of regulatory non-coding RNAs however with longer nucleotide length (usually more than 200) [288]. LncRNAs are systematically distributed throughout the biological world, from the prokaryotic organisms to primates and humans [289]. In mammals, lncRNAs adjust gene expression at different phases, frequently participating in epigenetic (such as DNA methylation) and post-transcriptional (such as mRNA degradation) modifications [290]. In consideration of its widespread role in maintaining physiological balance, researchers thus have paid particular attention to its pathological role disease and consequently discovered that lncRNAs contribute to the progression of certain disorders such as stroke, malignancy and autoimmune illness [291, 292].

Furthermore, a critical role of lncRNAs in the pathogenesis of AD is becoming more apparent. *BACE1*, a core promoter of APP cleavage leading to the formation of A β aggregates, is abnormally activated in AD-affected brain cells due to regulation by its antisense RNA called *BACE1-AS*. Depleting this lncRNA in rodent models leads to a reduction in A β and its plaques thereby improving memory capacity in AD mouse models [293, 294]. Another dysregulated lncRNA found to closely associate with AD is brain cytoplasmic RNA 1 (*BCYRN1*). Expression of *BCYRN1* is dramatically inhibited in AD-affected brain regions, especially in Brodmann's 9 area. Loss of *BCYRN1* results in impairment of protein synthesis in dendrites and easily aggravates the synaptodendritic dysfunction in AD [290, 295]. In addition, Sox2 overlapping transcript (*Sox2OT*), an antisense RNA of Sox2, is redundantly expressed in AD which strongly reduces Sox2 activity and thus decreases its protective effects on neurogenesis [296]. Finally, GDNF antisense RNA (*GDNF-AS*) and 17A are also involved in the development of AD despite different expression levels and regulatory targets [290]. Although lncRNAs are newly identified regulatory elements and thus their roles in the mechanisms leading to AD, their clinical worthiness in AD therapy remains promising.

2.11.3 Epigenetic alterations and AD—Epigenetics, a term originating from the 1940s, has already become an indispensable branch of biological genetics and genomic research [297]. Currently, epigenetics has been broadly recognized as relating to structural alterations of chromatin, which changes the phenotypic traits of organisms without affecting their genotype [298]. There are multiple modifications to chromatin that drive epigenetic regulation on target genes, among which DNA methylation and histone modifications are two primary contributors. In terms of DNA methylation, DNA methyltransferases (DNMTs) are responsible for the transfer of an additional methyl group to cytosine sites [299]. Functionally, high level of DNA methylation often indicates suppressed status of gene expression. On the other hand, phenotypic impacts by histone modifications (including

acetylation and methylation) vary under different situations, displaying a complex bi-directional regulation system [300, 301].

According to the definition of epigenetics, it is quite easy to predict that epigenetic mechanisms regulate various physiological and pathological outcomes, including the pathogenesis of AD. Regarding DNA methylation status, studies have revealed that global hypo-methylation of genomic DNA has been observed in most AD samples [302, 303]. Individually, the methylation level of several genes, such as *ANK1* and *BIN1*, are likewise decreased in AD-affected regions which eventually contributes to the aberrant aggregation of tau protein and A β plaques [304, 305]. The role of histone modifications, especially histone acetylation, in AD development is increasingly becoming clarified. Nevertheless, unlike DNA methylation, global histone acetylation does not largely change in AD cells, although expression level of histone deacetylase 2 (HDAC2) is greatly enhanced [306]. Further discoveries have demonstrated that changes in histone acetylation levels within the promoters of at particular genes in AD, such as *ARC* and *CDK5* [307]. Unfortunately, in spite of genome-wide analysis and results of epigenetic changes in AD, there role for epigenetic changes as a causative factor in AD remains largely unclear.

2.11.4 Pin1 and AD—Pin1, a member of peptidyl-prolyl cis/trans isomerase family (PPIase), specifically isomerizes the phosphor-Ser/Thr-Pro (pSer/Thr-Pro) motif in proteins in order to adjust their folding structures [308]. The N-terminal (WW domain contained) of Pin1 is critical for the recognition of pSer/Thr-Pro peptides while the C-terminal (PPIase domain contained) plays the catalytic role of isomerization. Since a majority of phosphorylating events during cellular signaling locate on serine or threonine residues, it is relatively comprehensible that pSer/Thr-Pro isomerization by Pin1 may play a role in multiple physiological or pathological processes [309]. For example, increased expression of Pin1 has been detected in lung, prostate and breast cancer cells, which also acts as an unfavorable indicator of clinical prognosis. Further mechanistic studies have shown that through stabilization of the G1/S cell cycle phase regulator cyclin D1, Pin1 could promote proliferation of retinoblastoma cells. Besides, the etiological relevance between Pin1 and autoimmune disorders has also been proven, displaying its wide-ranging mediation in pathological manners [310, 311].

As a research focus, the correlation between Pin1 and AD has gradually emerged. Histological analysis has revealed strong expression of Pin1 in neurons. Additional analysis has revealed that Pin1 may influence the pathological accumulation of both tau and A β [312]. First, the presence of Pin1 in murine neurons corrects the mis-folding of tau and subsequently facilitates the re-binding of tau protein with microtubule [313]. This is an important explanation underlying why Pin1 helps to avoid the aberrant aggregates of intracellular tau tangles and its level is greatly restricted in AD-affected cells. Second, concerning the formation of A β plaques, APP is found to be the direct substrate of Pin1 in neural cells, whose isomerization slows down the cleavage and transformation into A β [314]. Moreover, based on the above-mentioned role for GSK3 β in AD, Pin1 interacts with the Thr330-Pro motif of GSK3 β inhibiting its function and reducing the production of tau tangles and A β plaques [312, 314]. More interestingly, *Pin1* knockout mice display an AD-like phenotype [43]. All these results suggest a strong potential for targeting Pin1 in AD.

3. Discussion and perspective

What disappoints AD clinicians and researchers most may be that current regimens could only slow down the progression rate of AD instead of reversing the ultimate consequence. These unsatisfactory effects force people to pay attention on more targeted and etiology-oriented strategies [315]. Due to the notion that aging has been acknowledged as one of the major risk factors of AD pathogenesis [316], anti-aging drugs have become a promising therapeutic strategy against AD, which mainly occurs among the elderly population and features senescent phenotypes of affected neurons (Fig. 8). So far, among all possible candidates, rapamycin and resveratrol are two representatives that have been relatively well investigated and mechanistically deciphered [317]. Rapamycin, an inhibitor of mTOR in mammals, could positively influence the longevity among rodent models compared to untreated counterparts. Histological studies have observed that due to the administration of rapamycin, the degradation of cellular organelles and metabolic rate is successfully inhibited amid AD-affected or susceptible cells [318]. This attenuation hallmark of neuronal senescence not only benefits the cognitive and memory capability, but also increases the life expectancy among pathological rats. Furthermore, this mechanism is compatible with current hypothesis that oxygen stress is one of the main causes of cellular senescence [319].

Resveratrol, a naturally occurring polyphenol found, has been recognized as an effective drug against aging-related dysfunction and AD [320]. An increase in Sirtuin activity contributes to the anti-aging effect of resveratrol, which enhances autophagy and reduces peroxidative reactions to prevent the accumulation of harmful metabolites (Fig. 4). Ultimately, all these anti-aging activities in neural cells end up with the less production of tau and A β molecules, effectively inhibiting the pathological expansion of AD regions [321]. Consistent with *in vitro* reports, resveratrol also demonstrates curative effects among AD mice with defective cognition and memory, implying a great clinical potential in reversing AD related damages [322]. Although rapamycin, resveratrol or any other anti-aging agents are still in preclinical phase, we believe that an aging targeted strategy is definitely worth therapeutic expectations for AD patients.

Since formation of extracellular A β plaques is one of the major pathological hallmarks of AD, anti-plaque drugs have been widely considered and designed. Furthermore, because over-production and decreased clearance of A β jointly account for A β surplus, anti-plaque drugs are accordingly classified with corresponding mechanisms [323]. Concerning A β production, BACE1 as well as γ -secretase have been identified as two pivotal enzymes to boost the amount of A β , thus their inhibitors showing great potential as therapeutic targets. Verubecestat (MK-8931) and Lanabecestat (AZD3293) are two representative BACE1 inhibitors under clinical trials. Although phase I and phase II data present exciting benefits on AD models, the preliminary results of phase III trial have failed to meet clinical significance for Verubecestat [324, 325]. Nevertheless, the other oral BACE1 inhibitor Lanabecestat has recently gained support from FDA to further expand its phase III trial, following the data analysis based on early results [326]. On the other hand, PF-03084014, a γ -secretase inhibitor found curative in solid and hematological malignancies, remains in preclinical stage for AD field [327, 328]. At present, immunotherapy is believed to have the ability to clear the redundant A β by specific antigen-antibody reactions, irrespective of

active or passive mechanisms [329]. However, this hypothesis is not fully verified by clinical trials, since neither vaccination injection (active immunotherapy) or immunoglobulins (monoclonal and polyclonal antibodies, passive immunotherapy) displays anti-A β efficacy, instead induces severe adverse events such as vasogenic edema [330, 331]. Hence, despite that this concept seems pharmacologically available, a lot more work is still needed before its possible clinical usage in the future.

Tau proteins function to stabilize microtubules in neurons and mediate the pathogenesis of AD as central effectors [332]. Its hyper-phosphorylated tangle form is frequently detected throughout AD-affected regions, therefore the pharmaceutical design of anti-Tau strategies mainly concentrate on inhibiting the aberrant phosphorylation and aggregation of tau, such as tau aggregation inhibitors (TRx0237) and tau based immunotherapy (active: AADvac1; passive: RG7345) [333]. Although diverse tau targeted drugs are under investigations, they are lacking phase III data which limits its clinical application at present [334].

As mentioned above, multiple cellular signaling pathways are involved in the development of AD, which eventually converge to the formation of tau tangles and A β plaques [315]. There are three types of drugs that target specific signaling molecules in AD, including phosphodiesterase inhibitors, cyclin-dependent kinase 5 (CDK5) inhibitors and phospholipase A2 (PPA2) inhibitors [315]. First, the working mechanism of phosphodiesterase inhibitors is that they restrict the cellular transduction by down-regulating cAMP, that as a second messenger in neuron, further suppresses the expression of certain genes related to tau aggregation [335]. Second, CDK5 inhibitors aim to reverse the aberrant activation of CDK5 in AD-affected neurons, which could hyper-phosphorylate tau and promote its abnormal aggregation [336]. And finally, PPA2 inhibitors act as clearance enhancer of misfolded tau proteins in neuronal cells, primarily via reducing the excitotoxic impact induced by PPA2 [337]. However, in spite of the benefits these drugs have provided in preclinical and early clinical studies, there is still in scarcity of high-quality clinical trial data to further confirm their efficacy and safety against current regimens.

As we summarized above, cancer-related signaling pathways including FOXO, mTOR, SIRT1, HIF, oxidative stress, inflammation, and metabolism have important roles in regulating aging and AD genesis (Fig. 8). *In vivo* and clinical evidence of these pathways offer a more comprehensive perspective of the functional characteristics of the influence these signaling pathways have on tau-induced tangle aggregation and A β -induce plaques. On basis of our comprehensive review of biological processes and signaling pathways related to AD genesis, both *in vivo* and *in vitro* experiments have revealed the potential role for targeting these pathways for aging-related disorders, especially for AD genesis (Fig. 8).

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References

1. Campisi J. Aging, cellular senescence, and cancer. *Annu Rev Physiol.* 2013; 75:685–705. [PubMed: 23140366]
2. Childs BG, et al. Cellular senescence in aging and age-related disease: from mechanisms to therapy. *Nat Med.* 2015; 21(12):1424–35. [PubMed: 26646499]
3. Ugalde AP, et al. Aging and chronic DNA damage response activate a regulatory pathway involving miR-29 and p53. *EMBO J.* 2011; 30(11):2219–32. [PubMed: 21522133]
4. Cuanalo-Contreras K, Mukherjee A, Soto C. Role of protein misfolding and proteostasis deficiency in protein misfolding diseases and aging. *Int J Cell Biol.* 2013; 2013:638083. [PubMed: 24348562]
5. Soto C. Unfolding the role of protein misfolding in neurodegenerative diseases. *Nat Rev Neurosci.* 2003; 4(1):49–60. [PubMed: 12511861]
6. Hamilton ML, et al. Does oxidative damage to DNA increase with age? *Proc Natl Acad Sci U S A.* 2001; 98(18):10469–74. [PubMed: 11517304]
7. Driver JA. Inverse association between cancer and neurodegenerative disease: review of the epidemiologic and biological evidence. *Biogerontology.* 2014; 15(6):547–57. [PubMed: 25113739]
8. Loeb LA, Loeb KR, Anderson JP. Multiple mutations and cancer. *Proc Natl Acad Sci U S A.* 2003; 100(3):776–81. [PubMed: 12552134]
9. Knudson AG. Two genetic hits (more or less) to cancer. *Nat Rev Cancer.* 2001; 1(2):157–62. [PubMed: 11905807]
10. Bertram L, Tanzi RE. The genetic epidemiology of neurodegenerative disease. *J Clin Invest.* 2005; 115(6):1449–57. [PubMed: 15931380]
11. Dvoretzky PM, et al. Survival time, causes of death, and tumor/treatment-related morbidity in 100 women with ovarian cancer. *Hum Pathol.* 1988; 19(11):1273–9. [PubMed: 3181948]
12. Seeley WW, et al. Neurodegenerative diseases target large-scale human brain networks. *Neuron.* 2009; 62(1):42–52. [PubMed: 19376066]
13. Selkoe DJ. Alzheimer's disease: genes, proteins, and therapy. *Physiol Rev.* 2001; 81(2):741–66. [PubMed: 11274343]
14. Corbett A, Smith J, Ballard C. New and emerging treatments for Alzheimer's disease. *Expert Rev Neurother.* 2012; 12(5):535–43. [PubMed: 22550982]
15. Alzheimer's A. 2009 Alzheimer's disease facts and figures. *Alzheimers Dement.* 2009; 5(3):234–70. [PubMed: 19426951]
16. Zhu X, et al. Alzheimer disease, the two-hit hypothesis: an update. *Biochim Biophys Acta.* 2007; 1772(4):494–502. [PubMed: 17142016]
17. Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. *Science.* 2002; 297(5580):353–6. [PubMed: 12130773]
18. Alonso AC, Grundke-Iqbal I, Iqbal K. Alzheimer's disease hyperphosphorylated tau sequesters normal tau into tangles of filaments and disassembles microtubules. *Nat Med.* 1996; 2(7):783–7. [PubMed: 8673924]
19. Armstrong RA. The molecular biology of senile plaques and neurofibrillary tangles in Alzheimer's disease. *Folia Neuropathol.* 2009; 47(4):289–99. [PubMed: 20054780]
20. Serrano-Pozo A, et al. Neuropathological alterations in Alzheimer disease. *Cold Spring Harb Perspect Med.* 2011; 1(1):a006189. [PubMed: 22229116]
21. Albert M, et al. Use of brief cognitive tests to identify individuals in the community with clinically diagnosed Alzheimer's disease. *Int J Neurosci.* 1991; 57(3–4):167–78. [PubMed: 1938160]
22. Khachaturian ZS. Diagnosis of Alzheimer's disease. *Arch Neurol.* 1985; 42(11):1097–105. [PubMed: 2864910]
23. Rosen C, et al. Fluid biomarkers in Alzheimer's disease - current concepts. *Mol Neurodegener.* 2013; 8:20. [PubMed: 23800368]
24. Ruan Q, et al. Potential fluid biomarkers for pathological brain changes in Alzheimer's disease: Implication for the screening of cognitive frailty. *Mol Med Rep.* 2016; 14(4):3184–98. [PubMed: 27511317]

25. Scheuner D, et al. Secreted amyloid beta-protein similar to that in the senile plaques of Alzheimer's disease is increased in vivo by the presenilin 1 and 2 and APP mutations linked to familial Alzheimer's disease. *Nat Med.* 1996; 2(8):864–70. [PubMed: 8705854]
26. Esquerda-Canals G, et al. Mouse Models of Alzheimer's Disease. *J Alzheimers Dis.* 2017; 57(4): 1171–1183. [PubMed: 28304309]
27. Saunders AM, et al. Association of apolipoprotein E allele epsilon 4 with late-onset familial and sporadic Alzheimer's disease. *Neurology.* 1993; 43(8):1467–72. [PubMed: 8350998]
28. Licastro F, et al. Increased plasma levels of interleukin-1, interleukin-6 and alpha-1-antichymotrypsin in patients with Alzheimer's disease: peripheral inflammation or signals from the brain? *J Neuroimmunol.* 2000; 103(1):97–102. [PubMed: 10674995]
29. Mapstone M, et al. Plasma phospholipids identify antecedent memory impairment in older adults. *Nat Med.* 2014; 20(4):415–8. [PubMed: 24608097]
30. Hall AM, Roberson ED. Mouse models of Alzheimer's disease. *Brain Res Bull.* 2012; 88(1):3–12. [PubMed: 22142973]
31. Sharpless NE, Depinho RA. The mighty mouse: genetically engineered mouse models in cancer drug development. *Nat Rev Drug Discov.* 2006; 5(9):741–54. [PubMed: 16915232]
32. Games D, et al. Mice as models: transgenic approaches and Alzheimer's disease. *J Alzheimers Dis.* 2006; 9(3 Suppl):133–49. [PubMed: 16914852]
33. Citron M, et al. Mutant presenilins of Alzheimer's disease increase production of 42-residue amyloid beta-protein in both transfected cells and transgenic mice. *Nat Med.* 1997; 3(1):67–72. [PubMed: 8986743]
34. Holcomb L, et al. Accelerated Alzheimer-type phenotype in transgenic mice carrying both mutant amyloid precursor protein and presenilin 1 transgenes. *Nat Med.* 1998; 4(1):97–100. [PubMed: 9427614]
35. De Strooper B, Iwatsubo T, Wolfe MS. Presenilins and gamma-secretase: structure, function, and role in Alzheimer Disease. *Cold Spring Harb Perspect Med.* 2012; 2(1):a006304. [PubMed: 22315713]
36. Gotz J, et al. Somatodendritic localization and hyperphosphorylation of tau protein in transgenic mice expressing the longest human brain tau isoform. *EMBO J.* 1995; 14(7):1304–13. [PubMed: 7729409]
37. Lewis J, et al. Neurofibrillary tangles, amyotrophy and progressive motor disturbance in mice expressing mutant (P301L) tau protein. *Nat Genet.* 2000; 25(4):402–5. [PubMed: 10932182]
38. Gotz J, et al. Formation of neurofibrillary tangles in P301L tau transgenic mice induced by Aβeta 42 fibrils. *Science.* 2001; 293(5534):1491–5. [PubMed: 11520988]
39. Yoshiyama Y, et al. Synapse loss and microglial activation precede tangles in a P301S tauopathy mouse model. *Neuron.* 2007; 53(3):337–51. [PubMed: 17270732]
40. Oddo S, et al. Triple-transgenic model of Alzheimer's disease with plaques and tangles: intracellular Aβeta and synaptic dysfunction. *Neuron.* 2003; 39(3):409–21. [PubMed: 12895417]
41. Holtzman DM, et al. Apolipoprotein E isoform-dependent amyloid deposition and neuritic degeneration in a mouse model of Alzheimer's disease. *Proc Natl Acad Sci U S A.* 2000; 97(6): 2892–7. [PubMed: 10694577]
42. Bales KR, et al. Apolipoprotein E is essential for amyloid deposition in the APP(V717F) transgenic mouse model of Alzheimer's disease. *Proc Natl Acad Sci U S A.* 1999; 96(26):15233–8. [PubMed: 10611368]
43. Pastorino L, et al. The prolyl isomerase Pin1 regulates amyloid precursor protein processing and amyloid-beta production. *Nature.* 2006; 440(7083):528–34. [PubMed: 16554819]
44. Kerr JS, et al. Mitophagy and Alzheimer's Disease: Cellular and Molecular Mechanisms. *Trends Neurosci.* 2017; 40(3):151–166. [PubMed: 28190529]
45. Menzies FM, et al. Autophagy and Neurodegeneration: Pathogenic Mechanisms and Therapeutic Opportunities. *Neuron.* 2017; 93(5):1015–1034. [PubMed: 28279350]
46. Cheng J, et al. Autophagy regulates MAVS signaling activation in a phosphorylation-dependent manner in microglia. *Cell Death Differ.* 2017; 24(2):276–287. [PubMed: 28141795]

47. Kim J, et al. AMPK and mTOR regulate autophagy through direct phosphorylation of Ulk1. *Nat Cell Biol.* 2011; 13(2):132–41. [PubMed: 21258367]
48. Plaza-Zabala A, Sierra-Torre V, Sierra A. Autophagy and Microglia: Novel Partners in Neurodegeneration and Aging. *Int J Mol Sci.* 2017; 18(3)
49. Coly PM, et al. The Autophagy Machinery: A New Player in Chemotactic Cell Migration. *Front Neurosci.* 2017; 11:78. [PubMed: 28261054]
50. Tanida I, Ueno T, Kominami E. LC3 and Autophagy. *Methods Mol Biol.* 2008; 445:77–88. [PubMed: 18425443]
51. Mathew R, Karantza-Wadsworth V, White E. Role of autophagy in cancer. *Nat Rev Cancer.* 2007; 7(12):961–7. [PubMed: 17972889]
52. Li Q, Liu Y, Sun M. Autophagy and Alzheimer's Disease. *Cell Mol Neurobiol.* 2017; 37(3):377–388. [PubMed: 27260250]
53. Zare-Shahabadi A, et al. Autophagy in Alzheimer's disease. *Rev Neurosci.* 2015; 26(4):385–95. [PubMed: 25870960]
54. Tian Y, et al. A small-molecule enhancer of autophagy decreases levels of Abeta and APP-CTF via Atg5-dependent autophagy pathway. *FASEB J.* 2011; 25(6):1934–42. [PubMed: 21368103]
55. Vingtdoux V, et al. Novel synthetic small-molecule activators of AMPK as enhancers of autophagy and amyloid-beta peptide degradation. *FASEB J.* 2011; 25(1):219–31. [PubMed: 20852062]
56. Mizushima N. A(beta) generation in autophagic vacuoles. *J Cell Biol.* 2005; 171(1):15–7. [PubMed: 16216920]
57. Yu WH, et al. Autophagic vacuoles are enriched in amyloid precursor protein-secretase activities: implications for beta-amyloid peptide over-production and localization in Alzheimer's disease. *Int J Biochem Cell Biol.* 2004; 36(12):2531–40. [PubMed: 15325590]
58. Yang DS, et al. Neuronal apoptosis and autophagy cross talk in aging PS/APP mice, a model of Alzheimer's disease. *Am J Pathol.* 2008; 173(3):665–81. [PubMed: 18688038]
59. Boland B, et al. Autophagy induction and autophagosome clearance in neurons: relationship to autophagic pathology in Alzheimer's disease. *J Neurosci.* 2008; 28(27):6926–37. [PubMed: 18596167]
60. Xu W, Tan L, Yu JT. The Role of PICALM in Alzheimer's Disease. *Mol Neurobiol.* 2015; 52(1):399–413. [PubMed: 25186232]
61. Moreau K, et al. PICALM modulates autophagy activity and tau accumulation. *Nat Commun.* 2014; 5:4998. [PubMed: 25241929]
62. Pickford F, et al. The autophagy-related protein beclin 1 shows reduced expression in early Alzheimer disease and regulates amyloid beta accumulation in mice. *J Clin Invest.* 2008; 118(6):2190–9. [PubMed: 18497889]
63. Kaestner KH, Knochel W, Martinez DE. Unified nomenclature for the winged helix/forkhead transcription factors. *Genes Dev.* 2000; 14(2):142–6. [PubMed: 10702024]
64. Paik JH, et al. FoxOs are lineage-restricted redundant tumor suppressors and regulate endothelial cell homeostasis. *Cell.* 2007; 128(2):309–23. [PubMed: 17254969]
65. Coomans de Brachene A, Demoulin JB. FOXO transcription factors in cancer development and therapy. *Cell Mol Life Sci.* 2016; 73(6):1159–72. [PubMed: 26686861]
66. Hu MC, et al. IkappaB kinase promotes tumorigenesis through inhibition of forkhead FOXO3a. *Cell.* 2004; 117(2):225–37. [PubMed: 15084260]
67. Arden KC. FoxO: linking new signaling pathways. *Mol Cell.* 2004; 14(4):416–8. [PubMed: 15149589]
68. van der Heide LP, Smidt MP. Regulation of FoxO activity by CBP/p300-mediated acetylation. *Trends Biochem Sci.* 2005; 30(2):81–6. [PubMed: 15691653]
69. Motta MC, et al. Mammalian SIRT1 represses forkhead transcription factors. *Cell.* 2004; 116(4):551–63. [PubMed: 14980222]
70. Zheng X, et al. Prolyl hydroxylation by EglN2 destabilizes FOXO3a by blocking its interaction with the USP9x deubiquitinase. *Genes Dev.* 2014; 28(13):1429–44. [PubMed: 24990963]
71. Huang H, et al. Skp2 inhibits FOXO1 in tumor suppression through ubiquitin-mediated degradation. *Proc Natl Acad Sci U S A.* 2005; 102(5):1649–54. [PubMed: 15668399]

72. Yamagata K, et al. Arginine methylation of FOXO transcription factors inhibits their phosphorylation by Akt. *Mol Cell*. 2008; 32(2):221–31. [PubMed: 18951090]
73. Lee SS, et al. DAF-16 target genes that control *C. elegans* life-span and metabolism. *Science*. 2003; 300(5619):644–7. [PubMed: 12690206]
74. Finch CE, Tanzi RE. Genetics of aging. *Science*. 1997; 278(5337):407–11. [PubMed: 9334291]
75. Salih DA, Brunet A. FoxO transcription factors in the maintenance of cellular homeostasis during aging. *Curr Opin Cell Biol*. 2008; 20(2):126–36. [PubMed: 18394876]
76. Xu P, et al. JNK regulates FoxO-dependent autophagy in neurons. *Genes Dev*. 2011; 25(4):310–22. [PubMed: 21325132]
77. Eijkelenboom A, Burgering BM. FOXOs: signalling integrators for homeostasis maintenance. *Nat Rev Mol Cell Biol*. 2013; 14(2):83–97. [PubMed: 23325358]
78. Mei Y, et al. FOXO3a-dependent regulation of Pink1 (Park6) mediates survival signaling in response to cytokine deprivation. *Proc Natl Acad Sci U S A*. 2009; 106(13):5153–8. [PubMed: 19276113]
79. Gilley J, Coffey PJ, Ham J. FOXO transcription factors directly activate bim gene expression and promote apoptosis in sympathetic neurons. *J Cell Biol*. 2003; 162(4):613–22. [PubMed: 12913110]
80. Baar MP, et al. Targeted Apoptosis of Senescent Cells Restores Tissue Homeostasis in Response to Chemotoxicity and Aging. *Cell*. 2017; 169(1):132–147 e16. [PubMed: 28340339]
81. Kops GJ, et al. Forkhead transcription factor FOXO3a protects quiescent cells from oxidative stress. *Nature*. 2002; 419(6904):316–21. [PubMed: 12239572]
82. Zhang X, et al. FOXO1 is an essential regulator of pluripotency in human embryonic stem cells. *Nat Cell Biol*. 2011; 13(9):1092–9. [PubMed: 21804543]
83. Saxton RA, Sabatini DM. mTOR Signaling in Growth, Metabolism, and Disease. *Cell*. 2017; 169(2):361–371.
84. Dibble CC, Manning BD. Signal integration by mTORC1 coordinates nutrient input with biosynthetic output. *Nat Cell Biol*. 2013; 15(6):555–64. [PubMed: 23728461]
85. Laplante M, Sabatini DM. mTOR signaling at a glance. *J Cell Sci*. 2009; 122(Pt 20):3589–94. [PubMed: 19812304]
86. Cornu M, Albert V, Hall MN. mTOR in aging, metabolism, and cancer. *Current opinion in genetics & development*. 2013; 23(1):53–62. [PubMed: 23317514]
87. Chong ZZ, Maiese K. Mammalian target of rapamycin signaling in diabetic cardiovascular disease. *Cardiovascular diabetology*. 2012; 11:45. [PubMed: 22545721]
88. Sarkar S, Rubinshtein DC. Small molecule enhancers of autophagy for neurodegenerative diseases. *Molecular bioSystems*. 2008; 4(9):895–901. [PubMed: 18704227]
89. Dennis PB, Fumagalli S, Thomas G. Target of rapamycin (TOR): balancing the opposing forces of protein synthesis and degradation. *Curr Opin Genet Dev*. 1999; 9(1):49–54. [PubMed: 10072357]
90. Vellai T, et al. Genetics: influence of TOR kinase on lifespan in *C. elegans*. *Nature*. 2003; 426(6967):620.
91. Selman C, et al. Ribosomal protein S6 kinase 1 signaling regulates mammalian life span. *Science*. 2009; 326(5949):140–4. [PubMed: 19797661]
92. Powers RW 3rd, et al. Extension of chronological life span in yeast by decreased TOR pathway signaling. *Genes & development*. 2006; 20(2):174–84. [PubMed: 16418483]
93. Robida-Stubbs S, et al. TOR signaling and rapamycin influence longevity by regulating SKN-1/Nrf and DAF-16/FoxO. *Cell metabolism*. 2012; 15(5):713–24. [PubMed: 22560223]
94. Bjedov I, et al. Mechanisms of life span extension by rapamycin in the fruit fly *Drosophila melanogaster*. *Cell metabolism*. 2010; 11(1):35–46. [PubMed: 20074526]
95. Harrison DE, et al. Rapamycin fed late in life extends lifespan in genetically heterogeneous mice. *Nature*. 2009; 460(7253):392–5. [PubMed: 19587680]
96. Miller RA, et al. Rapamycin, but not resveratrol or simvastatin, extends life span of genetically heterogeneous mice. *The journals of gerontology. Series A, Biological sciences and medical sciences*. 2011; 66(2):191–201.

97. Anisimov VN, et al. Rapamycin increases lifespan and inhibits spontaneous tumorigenesis in inbred female mice. *Cell cycle*. 2011; 10(24):4230–6. [PubMed: 22107964]
98. Miller RA, et al. Rapamycin, but not resveratrol or simvastatin, extends life span of genetically heterogeneous mice. *J Gerontol A Biol Sci Med Sci*. 2011; 66(2):191–201. [PubMed: 20974732]
99. Drechsel DN, et al. Modulation of the dynamic instability of tubulin assembly by the microtubule-associated protein tau. *Mol Biol Cell*. 1992; 3(10):1141–54. [PubMed: 1421571]
100. Caccamo A, et al. mTOR regulates tau phosphorylation and degradation: implications for Alzheimer's disease and other tauopathies. *Aging Cell*. 2013; 12(3):370–80. [PubMed: 23425014]
101. Sontag JM, Sontag E. Protein phosphatase 2A dysfunction in Alzheimer's disease. *Front Mol Neurosci*. 2014; 7:16. [PubMed: 24653673]
102. Kickstein E, et al. Biguanide metformin acts on tau phosphorylation via mTOR/protein phosphatase 2A (PP2A) signaling. *Proc Natl Acad Sci U S A*. 2010; 107(50):21830–5. [PubMed: 21098287]
103. Pei JJ, et al. P70 S6 kinase mediates tau phosphorylation and synthesis. *FEBS Lett*. 2006; 580(1): 107–14. [PubMed: 16364302]
104. Syntichaki P, Troulinaki K, Tavernarakis N. eIF4E function in somatic cells modulates ageing in *Caenorhabditis elegans*. *Nature*. 2007; 445(7130):922–6. [PubMed: 17277769]
105. Lafay-Chebassier C, et al. mTOR/p70S6k signalling alteration by Aβ exposure as well as in APP-PS1 transgenic models and in patients with Alzheimer's disease. *J Neurochem*. 2005; 94(1): 215–25. [PubMed: 15953364]
106. Majumder S, et al. Inducing autophagy by rapamycin before, but not after, the formation of plaques and tangles ameliorates cognitive deficits. *PLoS One*. 2011; 6(9):e25416. [PubMed: 21980451]
107. Caccamo A, et al. Molecular interplay between mammalian target of rapamycin (mTOR), amyloid-beta, and Tau: effects on cognitive impairments. *J Biol Chem*. 2010; 285(17):13107–20. [PubMed: 20178983]
108. Spilman P, et al. Inhibition of mTOR by rapamycin abolishes cognitive deficits and reduces amyloid-beta levels in a mouse model of Alzheimer's disease. *PLoS One*. 2010; 5(4):e9979. [PubMed: 20376313]
109. Amaral T, et al. MAPK pathway in melanoma part II-secondary and adaptive resistance mechanisms to BRAF inhibition. *Eur J Cancer*. 2017; 73:93–101. [PubMed: 28162869]
110. Atay O, Skotheim JM. Spatial and temporal signal processing and decision making by MAPK pathways. *J Cell Biol*. 2017; 216(2):317–330. [PubMed: 28043970]
111. Kim EK, Choi EJ. Compromised MAPK signaling in human diseases: an update. *Arch Toxicol*. 2015; 89(6):867–82. [PubMed: 25690731]
112. Soares-Silva M, et al. The Mitogen-Activated Protein Kinase (MAPK) Pathway: Role in Immune Evasion by Trypanosomatids. *Front Microbiol*. 2016; 7:183. [PubMed: 26941717]
113. Dhillon AS, et al. MAP kinase signalling pathways in cancer. *Oncogene*. 2007; 26(22):3279–90. [PubMed: 17496922]
114. Prior IA, Lewis PD, Mattos C. A comprehensive survey of Ras mutations in cancer. *Cancer Res*. 2012; 72(10):2457–67. [PubMed: 22589270]
115. Zakowski MF, et al. EGFR mutations in small-cell lung cancers in patients who have never smoked. *N Engl J Med*. 2006; 355(2):213–5. [PubMed: 16837691]
116. Heimberger AB, et al. The natural history of EGFR and EGFRvIII in glioblastoma patients. *J Transl Med*. 2005; 3:38. [PubMed: 16236164]
117. Davies H, et al. Mutations of the BRAF gene in human cancer. *Nature*. 2002; 417(6892):949–54. [PubMed: 12068308]
118. Pratico D. Oxidative stress hypothesis in Alzheimer's disease: a reappraisal. *Trends Pharmacol Sci*. 2008; 29(12):609–15. [PubMed: 18838179]
119. Giraldo E, et al. Aβ and tau toxicities in Alzheimer's are linked via oxidative stress-induced p38 activation: protective role of vitamin E. *Redox Biol*. 2014; 2:873–7. [PubMed: 25061569]

120. Bach JP, et al. The role of CNI-1493 in the function of primary microglia with respect to amyloid-beta. *J Alzheimers Dis.* 2011; 26(1):69–80. [PubMed: 21593565]
121. Kitazawa M, et al. Blocking IL-1 signaling rescues cognition, attenuates tau pathology, and restores neuronal beta-catenin pathway function in an Alzheimer's disease model. *J Immunol.* 2011; 187(12):6539–49. [PubMed: 22095718]
122. Gan X, et al. Inhibition of ERK-DLP1 signaling and mitochondrial division alleviates mitochondrial dysfunction in Alzheimer's disease cybrid cell. *Biochim Biophys Acta.* 2014; 1842(2):220–31. [PubMed: 24252614]
123. Scip A, et al. c-Jun N-terminal kinase has a key role in Alzheimer disease synaptic dysfunction in vivo. *Cell Death Dis.* 2014; 5:e1019. [PubMed: 24457963]
124. Chong YH, et al. Effects of the beta-amyloid and carboxyl-terminal fragment of Alzheimer's amyloid precursor protein on the production of the tumor necrosis factor-alpha and matrix metalloproteinase-9 by human monocytic THP-1. *J Biol Chem.* 2001; 276(26):23511–7. [PubMed: 11306564]
125. Kim C, et al. Amyloid precursor protein processing is separately regulated by protein kinase C and tyrosine kinase in human astrocytes. *Neurosci Lett.* 2002; 324(3):185–8. [PubMed: 12009519]
126. Frasca G, et al. Beta-amyloid-activated cell cycle in SH-SY5Y neuroblastoma cells: correlation with the MAP kinase pathway. *J Mol Neurosci.* 2004; 22(3):231–6. [PubMed: 14997017]
127. Koistinaho M, et al. Beta-amyloid precursor protein transgenic mice that harbor diffuse A beta deposits but do not form plaques show increased ischemic vulnerability: role of inflammation. *Proc Natl Acad Sci U S A.* 2002; 99(3):1610–5. [PubMed: 11818564]
128. Paris D, et al. Pro-inflammatory effect of freshly solubilized beta-amyloid peptides in the brain. *Prostaglandins Other Lipid Mediat.* 2002; 70(1–2):1–12. [PubMed: 12428674]
129. Veeranna, et al. Calpain mediates calcium-induced activation of the erk1,2 MAPK pathway and cytoskeletal phosphorylation in neurons: relevance to Alzheimer's disease. *Am J Pathol.* 2004; 165(3):795–805. [PubMed: 15331404]
130. Sanchez A, et al. p38 MAPK: a mediator of hypoxia-induced cerebrovascular inflammation. *J Alzheimers Dis.* 2012; 32(3):587–97. [PubMed: 22886009]
131. Munoz L, et al. A novel p38 alpha MAPK inhibitor suppresses brain proinflammatory cytokine up-regulation and attenuates synaptic dysfunction and behavioral deficits in an Alzheimer's disease mouse model. *J Neuroinflammation.* 2007; 4:21. [PubMed: 17784957]
132. Zou L, et al. Inhibiting p38 mitogen-activated protein kinase attenuates cerebral ischemic injury in Swedish mutant amyloid precursor protein transgenic mice. *Neural Regen Res.* 2012; 7(14):1088–94. [PubMed: 25722699]
133. Stanley M, Macauley SL, Holtzman DM. Changes in insulin and insulin signaling in Alzheimer's disease: cause or consequence? *J Exp Med.* 2016; 213(8):1375–85. [PubMed: 27432942]
134. Peng Y, et al. Mitochondrial dysfunction precedes depression of AMPK/AKT signaling in insulin resistance induced by high glucose in primary cortical neurons. *J Neurochem.* 2016; 137(5):701–13. [PubMed: 26926143]
135. Diehl T, Mullins R, Kapogiannis D. Insulin resistance in Alzheimer's disease. *Transl Res.* 2017; 183:26–40. [PubMed: 28034760]
136. Asghar A, Sheikh N. Role of immune cells in obesity induced low grade inflammation and insulin resistance. *Cell Immunol.* 2017
137. Di Meo S, Iossa S, Venditti P. Skeletal muscle insulin resistance: role of mitochondria and other ROS sources. *J Endocrinol.* 2017; 233(1):R15–R42. [PubMed: 28232636]
138. Azziz R, et al. Polycystic ovary syndrome. *Nat Rev Dis Primers.* 2016; 2:16057. [PubMed: 27510637]
139. Artunc F, et al. The impact of insulin resistance on the kidney and vasculature. *Nat Rev Nephrol.* 2016; 12(12):721–737. [PubMed: 27748389]
140. Tawo R, et al. The Ubiquitin Ligase CHIP Integrates Proteostasis and Aging by Regulation of Insulin Receptor Turnover. *Cell.* 2017; 169(3):470–482 e13. [PubMed: 28431247]
141. de la Monte SM. Insulin Resistance and Neurodegeneration: Progress Towards the Development of New Therapeutics for Alzheimer's Disease. *Drugs.* 2017; 77(1):47–65. [PubMed: 27988872]

142. Chen Y, et al. Targeting Insulin Signaling for the Treatment of Alzheimer's Disease. *Curr Top Med Chem*. 2016; 16(5):485–92. [PubMed: 26268336]
143. Diehl T, Mullins R, Kapogiannis D. Insulin resistance in Alzheimer's disease. *Transl Res*. 2016
144. Qiu WQ, et al. Insulin-degrading enzyme regulates extracellular levels of amyloid beta-protein by degradation. *J Biol Chem*. 1998; 273(49):32730–8. [PubMed: 9830016]
145. Bedse G, et al. Aberrant insulin signaling in Alzheimer's disease: current knowledge. *Front Neurosci*. 2015; 9:204. [PubMed: 26136647]
146. Ma R, et al. Erythropoietin protects PC12 cells from beta-amyloid(25–35)-induced apoptosis via PI3K/Akt signaling pathway. *Neuropharmacology*. 2009; 56(6–7):1027–34. [PubMed: 19268480]
147. Cross DA, et al. Inhibition of glycogen synthase kinase-3 by insulin mediated by protein kinase B. *Nature*. 1995; 378(6559):785–9. [PubMed: 8524413]
148. Ishiguro K, et al. Glycogen synthase kinase 3 beta is identical to tau protein kinase I generating several epitopes of paired helical filaments. *FEBS Lett*. 1993; 325(3):167–72. [PubMed: 7686508]
149. Herskovits AZ, Guarente L. SIRT1 in neurodevelopment and brain senescence. *Neuron*. 2014; 81(3):471–83. [PubMed: 24507186]
150. Donmez G, Outeiro TF. SIRT1 and SIRT2: emerging targets in neurodegeneration. *EMBO Mol Med*. 2013; 5(3):344–52. [PubMed: 23417962]
151. Igarashi M, Guarente L. mTORC1 and SIRT1 Cooperate to Foster Expansion of Gut Adult Stem Cells during Calorie Restriction. *Cell*. 2016; 166(2):436–50. [PubMed: 27345368]
152. Kauppinen A, et al. Antagonistic crosstalk between NF-kappaB and SIRT1 in the regulation of inflammation and metabolic disorders. *Cell Signal*. 2013; 25(10):1939–48. [PubMed: 23770291]
153. Rodgers JT, et al. Metabolic adaptations through the PGC-1 alpha and SIRT1 pathways. *FEBS Lett*. 2008; 582(1):46–53. [PubMed: 18036349]
154. Godoy JA, et al. Role of Sirt1 during the ageing process: relevance to protection of synapses in the brain. *Mol Neurobiol*. 2014; 50(3):744–56. [PubMed: 24496572]
155. Coppari R. Metabolic actions of hypothalamic SIRT1. *Trends Endocrinol Metab*. 2012; 23(4): 179–85. [PubMed: 22382036]
156. Bonda DJ, et al. The sirtuin pathway in ageing and Alzheimer disease: mechanistic and therapeutic considerations. *Lancet Neurol*. 2011; 10(3):275–9. [PubMed: 21349442]
157. Pasinetti GM, et al. Roles of resveratrol and other grape-derived polyphenols in Alzheimer's disease prevention and treatment. *Biochim Biophys Acta*. 2015; 1852(6):1202–8. [PubMed: 25315300]
158. Cao L, et al. SIRT1 negatively regulates amyloid-beta-induced inflammation via the NF-kappaB pathway. *Braz J Med Biol Res*. 2013; 46(8):659–69. [PubMed: 24036938]
159. Feng X, et al. Resveratrol inhibits beta-amyloid-induced neuronal apoptosis through regulation of SIRT1-ROCK1 signaling pathway. *PLoS One*. 2013; 8(3):e59888. [PubMed: 23555824]
160. Han MK, et al. SIRT1 regulates apoptosis and Nanog expression in mouse embryonic stem cells by controlling p53 subcellular localization. *Cell Stem Cell*. 2008; 2(3):241–51. [PubMed: 18371449]
161. Brunet A, et al. Stress-dependent regulation of FOXO transcription factors by the SIRT1 deacetylase. *Science*. 2004; 303(5666):2011–5. [PubMed: 14976264]
162. Min SW, et al. Acetylation of tau inhibits its degradation and contributes to tauopathy. *Neuron*. 2010; 67(6):953–66. [PubMed: 20869593]
163. Chen J, et al. SIRT1 protects against microglia-dependent amyloid-beta toxicity through inhibiting NF-kappaB signaling. *J Biol Chem*. 2005; 280(48):40364–74. [PubMed: 16183991]
164. Harris AL. Hypoxia--a key regulatory factor in tumour growth. *Nat Rev Cancer*. 2002; 2(1):38–47. [PubMed: 11902584]
165. Guo J, et al. pVHL suppresses kinase activity of Akt in a proline-hydroxylation-dependent manner. *Science*. 2016; 353(6302):929–32. [PubMed: 27563096]
166. Safran M, Kaelin WG Jr. HIF hydroxylation and the mammalian oxygen-sensing pathway. *J Clin Invest*. 2003; 111(6):779–83. [PubMed: 12639980]

167. Ivan M, et al. HIF α targeted for VHL-mediated destruction by proline hydroxylation: implications for O₂ sensing. *Science*. 2001; 292(5516):464–8. [PubMed: 11292862]
168. Epstein AC, et al. C. elegans EGL-9 and mammalian homologs define a family of dioxygenases that regulate HIF by prolyl hydroxylation. *Cell*. 2001; 107(1):43–54. [PubMed: 11595184]
169. Pugh CW, Ratcliffe PJ. Regulation of angiogenesis by hypoxia: role of the HIF system. *Nat Med*. 2003; 9(6):677–84. [PubMed: 12778166]
170. Carmeliet P, et al. Role of HIF-1 α in hypoxia-mediated apoptosis, cell proliferation and tumour angiogenesis. *Nature*. 1998; 394(6692):485–90. [PubMed: 9697772]
171. Cho H, et al. On-target efficacy of a HIF-2 α antagonist in preclinical kidney cancer models. *Nature*. 2016; 539(7627):107–111. [PubMed: 27595393]
172. Shen C, et al. Genetic and functional studies implicate HIF1 α as a 14q kidney cancer suppressor gene. *Cancer Discov*. 2011; 1(3):222–35. [PubMed: 22037472]
173. Koivunen P, et al. Transformation by the (R)-enantiomer of 2-hydroxyglutarate linked to EGLN activation. *Nature*. 2012; 483(7390):484–8. [PubMed: 22343896]
174. Peers C, et al. Hypoxia and neurodegeneration. *Ann N Y Acad Sci*. 2009; 1177:169–77. [PubMed: 19845619]
175. Zhang CE, et al. Hypoxia-induced tau phosphorylation and memory deficit in rats. *Neurodegener Dis*. 2014; 14(3):107–16. [PubMed: 24993525]
176. Bazan NG, Palacios-Pelaez R, Lukiw WJ. Hypoxia signaling to genes: significance in Alzheimer's disease. *Mol Neurobiol*. 2002; 26(2–3):283–98. [PubMed: 12428761]
177. Green KN, Boyle JP, Peers C. Hypoxia potentiates exocytosis and Ca²⁺ channels in PC12 cells via increased amyloid beta peptide formation and reactive oxygen species generation. *J Physiol*. 2002; 541(Pt 3):1013–23. [PubMed: 12068059]
178. Grammas P, et al. Brain microvasculature and hypoxia-related proteins in Alzheimer's disease. *Int J Clin Exp Pathol*. 2011; 4(6):616–27. [PubMed: 21904637]
179. Wouters BG, Koritzinsky M. Hypoxia signalling through mTOR and the unfolded protein response in cancer. *Nat Rev Cancer*. 2008; 8(11):851–64. [PubMed: 18846101]
180. Guglielmotto M, Tamagno E, Danni O. Oxidative stress and hypoxia contribute to Alzheimer's disease pathogenesis: two sides of the same coin. *ScientificWorldJournal*. 2009; 9:781–91. [PubMed: 19705038]
181. Masson N, Ratcliffe PJ. Hypoxia signaling pathways in cancer metabolism: the importance of co-selecting interconnected physiological pathways. *Cancer Metab*. 2014; 2(1):3. [PubMed: 24491179]
182. Chong ZZ, Li F, Maiese K. Erythropoietin requires NF- κ B and its nuclear translocation to prevent early and late apoptotic neuronal injury during beta-amyloid toxicity. *Curr Neurovasc Res*. 2005; 2(5):387–99. [PubMed: 16375720]
183. Wang Y, et al. Vascular endothelial growth factor overexpression delays neurodegeneration and prolongs survival in amyotrophic lateral sclerosis mice. *J Neurosci*. 2007; 27(2):304–7. [PubMed: 17215390]
184. Sun X, et al. Hypoxia facilitates Alzheimer's disease pathogenesis by up-regulating BACE1 gene expression. *Proc Natl Acad Sci U S A*. 2006; 103(49):18727–32. [PubMed: 17121991]
185. Mobasheri A, et al. Hypoxia inducible factor-1 and facilitative glucose transporters GLUT1 and GLUT3: putative molecular components of the oxygen and glucose sensing apparatus in articular chondrocytes. *Histol Histopathol*. 2005; 20(4):1327–38. [PubMed: 16136514]
186. Liu Y, et al. Decreased glucose transporters correlate to abnormal hyperphosphorylation of tau in Alzheimer disease. *FEBS Lett*. 2008; 582(2):359–64. [PubMed: 18174027]
187. Fang H, et al. Acute hypoxia promote the phosphorylation of tau via ERK pathway. *Neurosci Lett*. 2010; 474(3):173–7. [PubMed: 20304032]
188. Zhang S, et al. Evidence of oxidative stress-induced BNIP3 expression in amyloid beta neurotoxicity. *Brain Res*. 2007; 1138:221–30. [PubMed: 17274962]
189. Mittler R. Oxidative stress, antioxidants and stress tolerance. *Trends Plant Sci*. 2002; 7(9):405–10. [PubMed: 12234732]

190. Cooke MS, et al. Oxidative DNA damage: mechanisms, mutation, and disease. *FASEB J.* 2003; 17(10):1195–214. [PubMed: 12832285]
191. Hancock JT, Desikan R, Neill SJ. Role of reactive oxygen species in cell signalling pathways. *Biochem Soc Trans.* 2001; 29(Pt 2):345–50. [PubMed: 11356180]
192. Morgan MJ, Liu ZG. Crosstalk of reactive oxygen species and NF-kappaB signaling. *Cell Res.* 2011; 21(1):103–15. [PubMed: 21187859]
193. Qutub AA, Popel AS. Reactive oxygen species regulate hypoxia-inducible factor 1alpha differentially in cancer and ischemia. *Mol Cell Biol.* 2008; 28(16):5106–19. [PubMed: 18559422]
194. Birben E, et al. Oxidative stress and antioxidant defense. *World Allergy Organ J.* 2012; 5(1):9–19. [PubMed: 23268465]
195. Kohchi C, et al. ROS and innate immunity. *Anticancer Res.* 2009; 29(3):817–21. [PubMed: 19414314]
196. Yan LJ. Positive oxidative stress in aging and aging-related disease tolerance. *Redox Biol.* 2014; 2:165–9. [PubMed: 25460727]
197. Circu ML, Aw TY. Reactive oxygen species, cellular redox systems, and apoptosis. *Free Radic Biol Med.* 2010; 48(6):749–62. [PubMed: 20045723]
198. Son Y, et al. Mitogen-Activated Protein Kinases and Reactive Oxygen Species: How Can ROS Activate MAPK Pathways? *J Signal Transduct.* 2011; 2011:792639. [PubMed: 21637379]
199. Leslie NR, et al. Redox regulation of PI 3-kinase signalling via inactivation of PTEN. *EMBO J.* 2003; 22(20):5501–10. [PubMed: 14532122]
200. Ahn J, et al. Reactive oxygen species-mediated activation of the Akt/ASK1/p38 signaling cascade and p21(Cip1) downregulation are required for shikonin-induced apoptosis. *Apoptosis.* 2013; 18(7):870–81. [PubMed: 23546866]
201. Smoot DT, et al. Influence of *Helicobacter pylori* on reactive oxygen-induced gastric epithelial cell injury. *Carcinogenesis.* 2000; 21(11):2091–5. [PubMed: 11062173]
202. Finkel T, Holbrook NJ. Oxidants, oxidative stress and the biology of ageing. *Nature.* 2000; 408(6809):239–47. [PubMed: 11089981]
203. Van Raamsdonk JM, Hekimi S. Deletion of the mitochondrial superoxide dismutase sod-2 extends lifespan in *Caenorhabditis elegans*. *PLoS Genet.* 2009; 5(2):e1000361. [PubMed: 19197346]
204. Melov S, et al. Lifespan extension and rescue of spongiform encephalopathy in superoxide dismutase 2 nullizygous mice treated with superoxide dismutase-catalase mimetics. *J Neurosci.* 2001; 21(21):8348–53. [PubMed: 11606622]
205. Nunomura A, et al. Oxidative damage is the earliest event in Alzheimer disease. *J Neuropathol Exp Neurol.* 2001; 60(8):759–67. [PubMed: 11487050]
206. Manczak M, et al. Mitochondria are a direct site of A beta accumulation in Alzheimer's disease neurons: implications for free radical generation and oxidative damage in disease progression. *Hum Mol Genet.* 2006; 15(9):1437–49. [PubMed: 16551656]
207. Lin MT, Beal MF. Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases. *Nature.* 2006; 443(7113):787–95. [PubMed: 17051205]
208. Bondy SC, Guo-Ross SX, Truong AT. Promotion of transition metal-induced reactive oxygen species formation by beta-amyloid. *Brain Res.* 1998; 799(1):91–6. [PubMed: 9666089]
209. Rodrigo-Moreno A, Poschenrieder C, Shabala S. Transition metals: a double edge sword in ROS generation and signaling. *Plant Signal Behav.* 2013; 8(3):e23425. [PubMed: 23333964]
210. Muller M, Cheung KH, Foscett JK. Enhanced ROS generation mediated by Alzheimer's disease presenilin regulation of InsP3R Ca²⁺ signaling. *Antioxid Redox Signal.* 2011; 14(7):1225–35. [PubMed: 20701429]
211. Lovell MA, Markesbery WR. Ratio of 8-hydroxyguanine in intact DNA to free 8-hydroxyguanine is increased in Alzheimer disease ventricular cerebrospinal fluid. *Arch Neurol.* 2001; 58(3):392–6. [PubMed: 11255442]
212. Huang X, et al. The A beta peptide of Alzheimer's disease directly produces hydrogen peroxide through metal ion reduction. *Biochemistry.* 1999; 38(24):7609–16. [PubMed: 10386999]

213. Yatin SM, Varadarajan S, Butterfield DA. Vitamin E Prevents Alzheimer's Amyloid beta-Peptide (1–42)-Induced Neuronal Protein Oxidation and Reactive Oxygen Species Production. *J Alzheimers Dis.* 2000; 2(2):123–131. [PubMed: 12214102]
214. Barnes DE, Yaffe K. Vitamin E and donepezil for the treatment of mild cognitive impairment. *N Engl J Med.* 2005; 353(9):951–2. author reply 951–2. [PubMed: 16135844]
215. Haynes CM, Titus EA, Cooper AA. Degradation of misfolded proteins prevents ER-derived oxidative stress and cell death. *Mol Cell.* 2004; 15(5):767–76. [PubMed: 15350220]
216. Huang X, et al. Redox-active metals, oxidative stress, and Alzheimer's disease pathology. *Ann N Y Acad Sci.* 2004; 1012:153–63. [PubMed: 15105262]
217. Smith MA, et al. Increased iron and free radical generation in preclinical Alzheimer disease and mild cognitive impairment. *J Alzheimers Dis.* 2010; 19(1):363–72. [PubMed: 20061651]
218. House E, et al. Aluminium, iron, zinc and copper influence the in vitro formation of amyloid fibrils of Aβ42 in a manner which may have consequences for metal chelation therapy in Alzheimer's disease. *J Alzheimers Dis.* 2004; 6(3):291–301. [PubMed: 15201484]
219. Cherny RA, et al. Treatment with a copper-zinc chelator markedly and rapidly inhibits beta-amyloid accumulation in Alzheimer's disease transgenic mice. *Neuron.* 2001; 30(3):665–76. [PubMed: 11430801]
220. Guo C, et al. Intranasal deferoxamine reverses iron-induced memory deficits and inhibits amyloidogenic APP processing in a transgenic mouse model of Alzheimer's disease. *Neurobiol Aging.* 2013; 34(2):562–75. [PubMed: 22717236]
221. Montine TJ, et al. Lipid peroxidation in aging brain and Alzheimer's disease. *Free Radic Biol Med.* 2002; 33(5):620–6. [PubMed: 12208348]
222. Cairns RA, Harris IS, Mak TW. Regulation of cancer cell metabolism. *Nat Rev Cancer.* 2011; 11(2):85–95. [PubMed: 21258394]
223. Shimobayashi M, Hall MN. Making new contacts: the mTOR network in metabolism and signalling crosstalk. *Nat Rev Mol Cell Biol.* 2014; 15(3):155–62. [PubMed: 24556838]
224. Canto C, et al. AMPK regulates energy expenditure by modulating NAD⁺ metabolism and SIRT1 activity. *Nature.* 2009; 458(7241):1056–60. [PubMed: 19262508]
225. Alberti KG, et al. The metabolic syndrome--a new worldwide definition. *Lancet.* 2005; 366(9491):1059–62. [PubMed: 16182882]
226. Kinnaird A, et al. Metabolic control of epigenetics in cancer. *Nat Rev Cancer.* 2016; 16(11):694–707. [PubMed: 27634449]
227. Vander Heiden MG, Cantley LC, Thompson CB. Understanding the Warburg effect: the metabolic requirements of cell proliferation. *Science.* 2009; 324(5930):1029–33. [PubMed: 19460998]
228. Choi ES, et al. Total lesion glycolysis by 18F-FDG PET/CT is a reliable predictor of prognosis in soft-tissue sarcoma. *Eur J Nucl Med Mol Imaging.* 2013; 40(12):1836–42. [PubMed: 23880967]
229. Brown GK, et al. Pyruvate dehydrogenase deficiency. *J Med Genet.* 1994; 31(11):875–9. [PubMed: 7853374]
230. Lei KJ, et al. Mutations in the glucose-6-phosphatase gene that cause glycogen storage disease type 1a. *Science.* 1993; 262(5133):580–3. [PubMed: 8211187]
231. Cani PD, et al. Changes in gut microbiota control metabolic endotoxemia-induced inflammation in high-fat diet-induced obesity and diabetes in mice. *Diabetes.* 2008; 57(6):1470–81. [PubMed: 18305141]
232. Zhu X, et al. Mitochondrial abnormalities and oxidative imbalance in Alzheimer disease. *J Alzheimers Dis.* 2006; 9(2):147–53. [PubMed: 16873962]
233. Hoglinger GU, et al. The mitochondrial complex I inhibitor rotenone triggers a cerebral tauopathy. *J Neurochem.* 2005; 95(4):930–9. [PubMed: 16219024]
234. Crouch PJ, et al. Copper-dependent inhibition of human cytochrome c oxidase by a dimeric conformer of amyloid-beta1–42. *J Neurosci.* 2005; 25(3):672–9. [PubMed: 15659604]
235. Hirai K, et al. Mitochondrial abnormalities in Alzheimer's disease. *J Neurosci.* 2001; 21(9):3017–23. [PubMed: 11312286]
236. Parker WD Jr, Filley CM, Parks JK. Cytochrome oxidase deficiency in Alzheimer's disease. *Neurology.* 1990; 40(8):1302–3. [PubMed: 2166249]

237. Dumont M, Beal MF. Neuroprotective strategies involving ROS in Alzheimer disease. *Free Radic Biol Med.* 2011; 51(5):1014–26. [PubMed: 21130159]
238. Wood JG, et al. Sirtuin activators mimic caloric restriction and delay ageing in metazoans. *Nature.* 2004; 430(7000):686–9. [PubMed: 15254550]
239. Colman RJ, et al. Caloric restriction reduces age-related and all-cause mortality in rhesus monkeys. *Nat Commun.* 2014; 5:3557. [PubMed: 24691430]
240. Colman RJ, et al. Caloric restriction delays disease onset and mortality in rhesus monkeys. *Science.* 2009; 325(5937):201–4. [PubMed: 19590001]
241. Mattison JA, et al. Impact of caloric restriction on health and survival in rhesus monkeys from the NIA study. *Nature.* 2012; 489(7415):318–21. [PubMed: 22932268]
242. Halagappa VK, et al. Intermittent fasting and caloric restriction ameliorate age-related behavioral deficits in the triple-transgenic mouse model of Alzheimer's disease. *Neurobiol Dis.* 2007; 26(1): 212–20. [PubMed: 17306982]
243. Hardie DG, Ross FA, Hawley SA. AMPK: a nutrient and energy sensor that maintains energy homeostasis. *Nat Rev Mol Cell Biol.* 2012; 13(4):251–62. [PubMed: 22436748]
244. Cheng J, et al. Functional characterization of AMP-activated protein kinase signaling in tumorigenesis. *Biochim Biophys Acta.* 2016; 1866(2):232–251. [PubMed: 27681874]
245. Thornton C, et al. AMP-activated protein kinase (AMPK) is a tau kinase, activated in response to amyloid beta-peptide exposure. *Biochem J.* 2011; 434(3):503–12. [PubMed: 21204788]
246. Vingtdoux V, et al. AMPK is abnormally activated in tangle- and pre-tangle-bearing neurons in Alzheimer's disease and other tauopathies. *Acta Neuropathol.* 2011; 121(3):337–49. [PubMed: 20957377]
247. Chen Y, et al. Antidiabetic drug metformin (GlucophageR) increases biogenesis of Alzheimer's amyloid peptides via up-regulating BACE1 transcription. *Proc Natl Acad Sci U S A.* 2009; 106(10):3907–12. [PubMed: 19237574]
248. Salminen A, et al. AMP-activated protein kinase: a potential player in Alzheimer's disease. *J Neurochem.* 2011; 118(4):460–74. [PubMed: 21623793]
249. Cho MH, et al. Autophagy in microglia degrades extracellular beta-amyloid fibrils and regulates the NLRP3 inflammasome. *Autophagy.* 2014; 10(10):1761–75. [PubMed: 25126727]
250. Chaplin DD. Overview of the immune response. *J Allergy Clin Immunol.* 2010; 125(2 Suppl 2):S3–23. [PubMed: 20176265]
251. Hotamisligil GS. Inflammation and metabolic disorders. *Nature.* 2006; 444(7121):860–7. [PubMed: 17167474]
252. Coussens LM, Werb Z. Inflammation and cancer. *Nature.* 2002; 420(6917):860–7. [PubMed: 12490959]
253. Ostrand-Rosenberg S, Sinha P. Myeloid-derived suppressor cells: linking inflammation and cancer. *J Immunol.* 2009; 182(8):4499–506. [PubMed: 19342621]
254. Wang CY, Mayo MW, Baldwin AS Jr. TNF- and cancer therapy-induced apoptosis: potentiation by inhibition of NF-kappaB. *Science.* 1996; 274(5288):784–7. [PubMed: 8864119]
255. Darnell JE Jr, Kerr IM, Stark GR. Jak-STAT pathways and transcriptional activation in response to IFNs and other extracellular signaling proteins. *Science.* 1994; 264(5164):1415–21. [PubMed: 8197455]
256. Tamura T, et al. The IRF family transcription factors in immunity and oncogenesis. *Annu Rev Immunol.* 2008; 26:535–84. [PubMed: 18303999]
257. Miyamoto K, et al. Foxo3a is essential for maintenance of the hematopoietic stem cell pool. *Cell Stem Cell.* 2007; 1(1):101–12. [PubMed: 18371339]
258. van Grevenynghe J, et al. Loss of memory B cells during chronic HIV infection is driven by Foxo3a- and TRAIL-mediated apoptosis. *J Clin Invest.* 2011; 121(10):3877–88. [PubMed: 21926463]
259. Luke JJ, Ott PA. Kinase inhibitors and immune check-point blockade for the treatment of metastatic melanoma and advanced cancer: synergistic or antagonistic? *Expert Opin Pharmacother.* 2013; 14(18):2457–62. [PubMed: 24138302]

260. Heneka MT, et al. Neuroinflammation in Alzheimer's disease. *Lancet Neurol.* 2015; 14(4):388–405. [PubMed: 25792098]
261. Twine NA, et al. Whole transcriptome sequencing reveals gene expression and splicing differences in brain regions affected by Alzheimer's disease. *PLoS One.* 2011; 6(1):e16266. [PubMed: 21283692]
262. McGeer PL, McGeer EG. The amyloid cascade-inflammatory hypothesis of Alzheimer disease: implications for therapy. *Acta Neuropathol.* 2013; 126(4):479–97. [PubMed: 24052108]
263. Meraz-Rios MA, et al. Inflammatory process in Alzheimer's Disease. *Front Integr Neurosci.* 2013; 7:59. [PubMed: 23964211]
264. Cramer PE, et al. ApoE-directed therapeutics rapidly clear beta-amyloid and reverse deficits in AD mouse models. *Science.* 2012; 335(6075):1503–6. [PubMed: 22323736]
265. Matsuoka Y, et al. Inflammatory responses to amyloidosis in a transgenic mouse model of Alzheimer's disease. *Am J Pathol.* 2001; 158(4):1345–54. [PubMed: 11290552]
266. Jantzen PT, et al. Microglial activation and beta -amyloid deposit reduction caused by a nitric oxide-releasing nonsteroidal anti-inflammatory drug in amyloid precursor protein plus presenilin-1 transgenic mice. *J Neurosci.* 2002; 22(6):2246–54. [PubMed: 11896164]
267. Reed-Geaghan EG, et al. CD14 and toll-like receptors 2 and 4 are required for fibrillar A β -stimulated microglial activation. *J Neurosci.* 2009; 29(38):11982–92. [PubMed: 19776284]
268. Valerio A, et al. NF-kappaB pathway: a target for preventing beta-amyloid (A β)-induced neuronal damage and A β 42 production. *Eur J Neurosci.* 2006; 23(7):1711–20. [PubMed: 16623827]
269. Akama KT, et al. Amyloid beta-peptide stimulates nitric oxide production in astrocytes through an NFkappaB-dependent mechanism. *Proc Natl Acad Sci U S A.* 1998; 95(10):5795–800. [PubMed: 9576964]
270. Bell KA, et al. MAPK recruitment by beta-amyloid in organotypic hippocampal slice cultures depends on physical state and exposure time. *J Neurochem.* 2004; 91(2):349–61. [PubMed: 15447668]
271. Limatola C, Ransohoff RM. Modulating neurotoxicity through CX3CL1/CX3CR1 signaling. *Front Cell Neurosci.* 2014; 8:229. [PubMed: 25152714]
272. Bhaskar K, et al. Regulation of tau pathology by the microglial fractalkine receptor. *Neuron.* 2010; 68(1):19–31. [PubMed: 20920788]
273. Rubio-Perez JM, Morillas-Ruiz JM. A review: inflammatory process in Alzheimer's disease, role of cytokines. *ScientificWorldJournal.* 2012; 2012:756357. [PubMed: 22566778]
274. Wang WY, et al. Role of pro-inflammatory cytokines released from microglia in Alzheimer's disease. *Ann Transl Med.* 2015; 3(10):136. [PubMed: 26207229]
275. Hartlage-Rubsamen M, et al. Astrocytic expression of the Alzheimer's disease beta-secretase (BACE1) is stimulus-dependent. *Glia.* 2003; 41(2):169–79. [PubMed: 12509807]
276. Gasparini L, Ongini E, Wenk G. Non-steroidal anti-inflammatory drugs (NSAIDs) in Alzheimer's disease: old and new mechanisms of action. *J Neurochem.* 2004; 91(3):521–36. [PubMed: 15485484]
277. Stewart WF, et al. Risk of Alzheimer's disease and duration of NSAID use. *Neurology.* 1997; 48(3):626–32. [PubMed: 9065537]
278. Lemere CA, et al. Nasal vaccination with beta-amyloid peptide for the treatment of Alzheimer's disease. *DNA Cell Biol.* 2001; 20(11):705–11. [PubMed: 11788048]
279. Morgan D, et al. A beta peptide vaccination prevents memory loss in an animal model of Alzheimer's disease. *Nature.* 2000; 408(6815):982–5. [PubMed: 11140686]
280. Dodart JC, et al. Immunization reverses memory deficits without reducing brain A β burden in Alzheimer's disease model. *Nat Neurosci.* 2002; 5(5):452–7. [PubMed: 11941374]
281. Zheng Y, Wang Z, Zhou Z. miRNAs: novel regulators of autoimmunity-mediated pancreatic beta-cell destruction in type 1 diabetes. *Cell Mol Immunol.* 2017
282. Basavaraju M, de Lencastre A. Alzheimer's disease: presence and role of microRNAs. *Biomol Concepts.* 2016; 7(4):241–52. [PubMed: 27505094]

283. Wen MM. Getting miRNA Therapeutics into the Target Cells for Neurodegenerative Diseases: A Mini-Review. *Front Mol Neurosci*. 2016; 9:129. [PubMed: 27920668]
284. Dickson JR, et al. Alternative polyadenylation and miR-34 family members regulate tau expression. *J Neurochem*. 2013; 127(6):739–49. [PubMed: 24032460]
285. Hernandez-Rapp J, Rainone S, Hebert SS. MicroRNAs underlying memory deficits in neurodegenerative disorders. *Prog Neuropsychopharmacol Biol Psychiatry*. 2017; 73:79–86. [PubMed: 27117821]
286. Hebert SS, et al. Loss of microRNA cluster miR-29a/b-1 in sporadic Alzheimer's disease correlates with increased BACE1/beta-secretase expression. *Proc Natl Acad Sci U S A*. 2008; 105(17):6415–20. [PubMed: 18434550]
287. Muller M, et al. MicroRNA-29a Is a Candidate Biomarker for Alzheimer's Disease in Cell-Free Cerebrospinal Fluid. *Mol Neurobiol*. 2016; 53(5):2894–9. [PubMed: 25895659]
288. Kung JT, Colognori D, Lee JT. Long noncoding RNAs: past, present, and future. *Genetics*. 2013; 193(3):651–69. [PubMed: 23463798]
289. Adams BD, et al. Targeting noncoding RNAs in disease. *J Clin Invest*. 2017; 127(3):761–771. [PubMed: 28248199]
290. Wan P, Su W, Zhuo Y. The Role of Long Noncoding RNAs in Neurodegenerative Diseases. *Mol Neurobiol*. 2017; 54(3):2012–2021. [PubMed: 26910817]
291. Chen Y, Zhou J. LncRNAs: macromolecules with big roles in neurobiology and neurological diseases. *Metab Brain Dis*. 2017; 32(2):281–291. [PubMed: 28161776]
292. Quinn JJ, Chang HY. Unique features of long non-coding RNA biogenesis and function. *Nat Rev Genet*. 2016; 17(1):47–62. [PubMed: 26666209]
293. Modarresi F, et al. Knockdown of BACE1-AS Nonprotein-Coding Transcript Modulates Beta-Amyloid-Related Hippocampal Neurogenesis. *Int J Alzheimers Dis*. 2011; 2011:929042. [PubMed: 21785702]
294. Faghihi MA, et al. Expression of a noncoding RNA is elevated in Alzheimer's disease and drives rapid feed-forward regulation of beta-secretase. *Nat Med*. 2008; 14(7):723–30. [PubMed: 18587408]
295. Mus E, Hof PR, Tiedge H. Dendritic BC200 RNA in aging and in Alzheimer's disease. *Proc Natl Acad Sci U S A*. 2007; 104(25):10679–84. [PubMed: 17553964]
296. Wu P, et al. Roles of long noncoding RNAs in brain development, functional diversification and neurodegenerative diseases. *Brain Res Bull*. 2013; 97:69–80. [PubMed: 23756188]
297. Dupont C, Armant DR, Brenner CA. Epigenetics: definition, mechanisms and clinical perspective. *Semin Reprod Med*. 2009; 27(5):351–7. [PubMed: 19711245]
298. Qazi TJ, et al. Epigenetics in Alzheimer's Disease: Perspective of DNA Methylation. *Mol Neurobiol*. 2017
299. Klein HU, Bennett DA, De Jager PL. The epigenome in Alzheimer's disease: current state and approaches for a new path to gene discovery and understanding disease mechanism. *Acta Neuropathol*. 2016; 132(4):503–14. [PubMed: 27573688]
300. Sanchez-Mut JV, Graff J. Epigenetic Alterations in Alzheimer's Disease. *Front Behav Neurosci*. 2015; 9:347. [PubMed: 26734709]
301. Lardenoije R, et al. The epigenetics of aging and neurodegeneration. *Prog Neurobiol*. 2015; 131:21–64. [PubMed: 26072273]
302. Hodgson N, et al. Soluble oligomers of amyloid-beta cause changes in redox state, DNA methylation, and gene transcription by inhibiting EAAT3 mediated cysteine uptake. *J Alzheimers Dis*. 2013; 36(1):197–209. [PubMed: 23579332]
303. Sung HY, et al. Amyloid protein-mediated differential DNA methylation status regulates gene expression in Alzheimer's disease model cell line. *Biochem Biophys Res Commun*. 2011; 414(4):700–5. [PubMed: 22001921]
304. Lunnon K, et al. Methylomic profiling implicates cortical deregulation of ANK1 in Alzheimer's disease. *Nat Neurosci*. 2014; 17(9):1164–70. [PubMed: 25129077]
305. De Jager PL, et al. Alzheimer's disease: early alterations in brain DNA methylation at ANK1, BIN1, RHBDF2 and other loci. *Nat Neurosci*. 2014; 17(9):1156–63. [PubMed: 25129075]

306. Rumbaugh G, et al. Pharmacological Selectivity Within Class I Histone Deacetylases Predicts Effects on Synaptic Function and Memory Rescue. *Neuropsychopharmacology*. 2015; 40(10): 2307–16. [PubMed: 25837283]
307. Graff J, et al. An epigenetic blockade of cognitive functions in the neurodegenerating brain. *Nature*. 2012; 483(7388):222–6. [PubMed: 22388814]
308. Zhou XZ, Lu KP. The isomerase PIN1 controls numerous cancer-driving pathways and is a unique drug target. *Nat Rev Cancer*. 2016; 16(7):463–78. [PubMed: 27256007]
309. Rustighi A, et al. PIN1 in breast development and cancer: a clinical perspective. *Cell Death Differ*. 2017; 24(2):200–211. [PubMed: 27834957]
310. Lu Z, Hunter T. Prolyl isomerase Pin1 in cancer. *Cell Res*. 2014; 24(9):1033–49. [PubMed: 25124924]
311. Lin CH, et al. Landscape of Pin1 in the cell cycle. *Exp Biol Med (Maywood)*. 2015; 240(3):403–8. [PubMed: 25662955]
312. Blair LJ, et al. The emerging role of peptidyl-prolyl isomerase chaperones in tau oligomerization, amyloid processing, and Alzheimer's disease. *J Neurochem*. 2015; 133(1):1–13. [PubMed: 25628064]
313. Lu PJ, et al. The prolyl isomerase Pin1 restores the function of Alzheimer-associated phosphorylated tau protein. *Nature*. 1999; 399(6738):784–8. [PubMed: 10391244]
314. Ma SL, et al. Prolyl isomerase Pin1 promotes amyloid precursor protein (APP) turnover by inhibiting glycogen synthase kinase-3beta (GSK3beta) activity: novel mechanism for Pin1 to protect against Alzheimer disease. *J Biol Chem*. 2012; 287(10):6969–73. [PubMed: 22184106]
315. Cazarim de MS, et al. Perspectives for treating Alzheimer's disease: a review on promising pharmacological substances. *Sao Paulo Med J*. 2016; 134(4):342–54. [PubMed: 27557144]
316. Grimm A, Eckert A. Brain aging and neurodegeneration: from a mitochondrial point of view. *J Neurochem*. 2017
317. Blagosklonny MV. Validation of anti-aging drugs by treating age-related diseases. *Aging (Albany NY)*. 2009; 1(3):281–8. [PubMed: 20157517]
318. Lamming DW, et al. Rapalogs and mTOR inhibitors as anti-aging therapeutics. *J Clin Invest*. 2013; 123(3):980–9. [PubMed: 23454761]
319. Richardson A, et al. How longevity research can lead to therapies for Alzheimer's disease: The rapamycin story. *Exp Gerontol*. 2015; 68:51–8. [PubMed: 25481271]
320. Awasthi M, et al. Alzheimer's disease: An overview of amyloid beta dependent pathogenesis and its therapeutic implications along with in silico approaches emphasizing the role of natural products. *J Neurol Sci*. 2016; 361:256–71. [PubMed: 26810552]
321. Braidy N, et al. Sirtuins in cognitive ageing and Alzheimer's disease. *Curr Opin Psychiatry*. 2012; 25(3):226–30. [PubMed: 22327552]
322. Albani D, et al. Neuroprotective properties of resveratrol in different neurodegenerative disorders. *Biofactors*. 2010; 36(5):370–6. [PubMed: 20848560]
323. Bachurin SO, Bovina EV, Ustyugov AA. Drugs in Clinical Trials for Alzheimer's Disease: The Major Trends. *Med Res Rev*. 2017
324. Kennedy ME, et al. The BACE1 inhibitor verubecestat (MK-8931) reduces CNS beta-amyloid in animal models and in Alzheimer's disease patients. *Sci Transl Med*. 2016; 8(363):363ra150.
325. Hawkes N. Merck ends trial of potential Alzheimer's drug verubecestat. *BMJ*. 2017; 356:j845. [PubMed: 28202490]
326. Cebers G, et al. AZD3293: Pharmacokinetic and Pharmacodynamic Effects in Healthy Subjects and Patients with Alzheimer's Disease. *J Alzheimers Dis*. 2017; 55(3):1039–1053. [PubMed: 27767991]
327. Kummar S, et al. Clinical Activity of the gamma-Secretase Inhibitor PF-03084014 in Adults With Desmoid Tumors (Aggressive Fibromatosis). *J Clin Oncol*. 2017; JCO2016711994.
328. Papayannidis C, et al. A Phase I study of the novel gamma-secretase inhibitor PF-03084014 in patients with T-cell acute lymphoblastic leukemia and T-cell lymphoblastic lymphoma. *Blood Cancer J*. 2015; 5:e350. [PubMed: 26407235]

329. Carrera I, et al. Validating Immunotherapy in Alzheimer's Disease: The EB101 Vaccine. *Curr Pharm Des.* 2016; 22(7):849–58. [PubMed: 26648469]
330. Barrera-Ocampo A, Lopera F. Amyloid-beta immunotherapy: the hope for Alzheimer disease? *Colomb Med (Cali).* 2016; 47(4):203–212. [PubMed: 28293044]
331. Busche MA, et al. Decreased amyloid-beta and increased neuronal hyperactivity by immunotherapy in Alzheimer's models. *Nat Neurosci.* 2015; 18(12):1725–7. [PubMed: 26551546]
332. Schroeder SK, et al. Tau-Directed Immunotherapy: A Promising Strategy for Treating Alzheimer's Disease and Other Tauopathies. *J Neuroimmune Pharmacol.* 2016; 11(1):9–25. [PubMed: 26538351]
333. Panza F, et al. Tau-Centric Targets and Drugs in Clinical Development for the Treatment of Alzheimer's Disease. *Biomed Res Int.* 2016; 2016:3245935. [PubMed: 27429978]
334. Waite LM. Treatment for Alzheimer's disease: has anything changed? *Aust Prescr.* 2015; 38(2):60–3. [PubMed: 26648618]
335. Heckman PR, Wouters C, Prickaerts J. Phosphodiesterase inhibitors as a target for cognition enhancement in aging and Alzheimer's disease: a translational overview. *Curr Pharm Des.* 2015; 21(3):317–31. [PubMed: 25159073]
336. Liu SL, et al. The Role of Cdk5 in Alzheimer's Disease. *Mol Neurobiol.* 2016; 53(7):4328–42. [PubMed: 26227906]
337. Ong WY, et al. Synthetic and natural inhibitors of phospholipases A2: their importance for understanding and treatment of neurological disorders. *ACS Chem Neurosci.* 2015; 6(6):814–31. [PubMed: 25891385]
338. Games D, et al. Alzheimer-type neuropathology in transgenic mice overexpressing V717F beta-amyloid precursor protein. *Nature.* 1995; 373(6514):523–7. [PubMed: 7845465]
339. Sturchler-Pierrat C, et al. Two amyloid precursor protein transgenic mouse models with Alzheimer disease-like pathology. *Proc Natl Acad Sci U S A.* 1997; 94(24):13287–92. [PubMed: 9371838]
340. Mucke L, et al. High-level neuronal expression of abeta 1–42 in wild-type human amyloid protein precursor transgenic mice: synaptotoxicity without plaque formation. *J Neurosci.* 2000; 20(11):4050–8. [PubMed: 10818140]
341. Janus C, et al. A beta peptide immunization reduces behavioural impairment and plaques in a model of Alzheimer's disease. *Nature.* 2000; 408(6815):979–82. [PubMed: 11140685]
342. Rockenstein E, et al. Early formation of mature amyloid-beta protein deposits in a mutant APP transgenic model depends on levels of Abeta(1–42). *J Neurosci Res.* 2001; 66(4):573–82. [PubMed: 11746377]
343. Duff K, et al. Increased amyloid-beta42(43) in brains of mice expressing mutant presenilin 1. *Nature.* 1996; 383(6602):710–3. [PubMed: 8878479]
344. Andorfer C, et al. Hyperphosphorylation and aggregation of tau in mice expressing normal human tau isoforms. *J Neurochem.* 2003; 86(3):582–90. [PubMed: 12859672]
345. Zhang B, et al. Retarded axonal transport of R406W mutant tau in transgenic mice with a neurodegenerative tauopathy. *J Neurosci.* 2004; 24(19):4657–67. [PubMed: 15140937]
346. Allen B, et al. Abundant tau filaments and nonapoptotic neurodegeneration in transgenic mice expressing human P301S tau protein. *J Neurosci.* 2002; 22(21):9340–51. [PubMed: 12417659]
347. Santacruz K, et al. Tau suppression in a neurodegenerative mouse model improves memory function. *Science.* 2005; 309(5733):476–81. [PubMed: 16020737]
348. Bales KR, et al. Lack of apolipoprotein E dramatically reduces amyloid beta-peptide deposition. *Nat Genet.* 1997; 17(3):263–4. [PubMed: 9354781]
349. Dodart JC, et al. Gene delivery of human apolipoprotein E alters brain Abeta burden in a mouse model of Alzheimer's disease. *Proc Natl Acad Sci U S A.* 2005; 102(4):1211–6. [PubMed: 15657137]
350. Liou YC, et al. Role of the prolyl isomerase Pin1 in protecting against age-dependent neurodegeneration. *Nature.* 2003; 424(6948):556–61. [PubMed: 12891359]

351. Borchelt DR, et al. Accelerated amyloid deposition in the brains of transgenic mice coexpressing mutant presenilin 1 and amyloid precursor proteins. *Neuron*. 1997; 19(4):939–45. [PubMed: 9354339]
352. Lewis J, et al. Enhanced neurofibrillary degeneration in transgenic mice expressing mutant tau and APP. *Science*. 2001; 293(5534):1487–91. [PubMed: 11520987]
353. Graybeal JJ, et al. Human ApoE epsilon4 alters circadian rhythm activity, IL-1beta, and GFAP in CRND8 mice. *J Alzheimers Dis*. 2015; 43(3):823–34. [PubMed: 25159669]

Key issues

Cancer and AD are two of the major diseases associated aging.

Tau-mediated neurofibrillary tangle and A β -mediated senile plaque are the major lesions of AD.

Multiple cell signaling governing tumorigenesis are associated with pathological lesions of AD.

Cancer-related pathways will become promising options for anti-aging and AD treatment.

Figure 1.

The protective role of autophagy pathway in AD pathogenesis. Where indicated, red arrow indicates positive regulation and black line means negative regulation.

Figure 2.

The protective role of the FOXO pathway in aging and AD pathogenesis. Briefly, FOXO could be phosphorylated by distinct kinase(s), acetylated or de-acetylated by SIRT and p300, respectively. Where indicated, red arrow indicates positive regulation and black line implicates negative regulation.

Figure 3.

The role of the IR/Akt/mTOR signaling pathway in promoting aging and AD pathogenesis. Briefly, Akt kinase could phosphorylate or regulate many downstream substrates including GSK3, FOXO, GLUT and mTOR to manipulate metabolic and protein homeostasis as well as autophagy. Where indicated, red arrow indicates positive regulation and black line suggests negative regulation.

Figure 4.

The protective role of the SIRT pathway in aging and AD pathogenesis. Briefly, low energy-induced SIRT could deacetylate various downstream transcriptional factors including PGC1, FOXO, p53 or p65 to govern the biological processes including autophagy and apoptosis. Where indicated, red arrow indicates positive regulation, and black line suggests negative regulation.

Figure 5.

The controversial role of the hypoxia/HIF signaling pathway in aging and AD pathogenesis. Briefly, the HIF transcription factors induce angiogenesis to inhibit the brain injury. At the same time, HIF could promote BACE1 to enhance A β and contribute to AD. Where indicated, red arrow indicates positive regulation and black line suggests negative regulation.

Figure 6.

The role of the ROS pathway in aging and AD pathogenesis. Briefly, different stress-induced ROS, which could subsequently regulate multiple kinases and transcriptional factors to contribute aging and AD pathogenesis. Where indicated, red arrow indicates positive regulation and black line suggests negative regulation.

Figure 7.

The protective role of the AMPK pathway in aging and AD pathogenesis. Where indicated, red arrow indicates positive regulation and black line suggests negative regulation.

Figure 8.

Major cancer-related signaling pathways that confer to aging and AD pathogenesis, and potential inhibitors that could be used for aging/AD intervention. Where indicated, red arrow indicates positive regulation and black line suggests negative regulation.

Table 1

A summary of mouse models for Alzheimer's disease.

Line		Mutation	Genetic pathology	References
APP models	<i>PDAPP</i>	<i>AβPP_{Ind}</i>	Plaque pathology begins 6–9 months without NFT pathology	[25]
	<i>Tg2576</i>	<i>AβPP_{Swe}</i>	Plaque pathology begins 9 months without NFT pathology	[338]
	<i>APP23</i>	<i>AβPP_{Swe}</i>	Plaque pathology begins 6 months with hippocampal neuronal loss without NFT pathology	[339]
	<i>J20</i>	<i>AβPP_{Ind/Swe}</i>	High levels of Aβ ₄₂ and plaque	[340]
	<i>TgCRND8</i>	<i>AβPP_{Ind/Swe}</i>	Plaque pathology begins 3 months	[341]
	<i>TASD-41</i>	<i>AβPP_{Lon/Swe}</i>	Plaque pathology begins 3–4 months with Tau pathology	[342]
PSEN1 models	<i>PSEN1</i>	<i>PSEN1_{M146V}</i>	With elevated Aβ ₄₂ without plaque pathology	[343]
	<i>PSEN1</i>	<i>PSEN1_{M146L}</i>	With elevated Aβ ₄₂ without plaque pathology	[343]
Tau models	<i>Htau</i>	<i>Human tau</i>	High levels of hyperphosphorylated Tau in 6 months, develop NFT in 15 months	[344]
	<i>JNPL3</i>	<i>Tau_{P301L}</i>	Develop tangle pathology and nerve loss	[345]
	<i>TauP301S</i>	<i>Tau_{P301S}</i>	Develop tangle pathology in 5–6 months	[346]
	<i>rTg4510</i>	<i>Tet-on Tau</i>	Develop tangle pathology with cognitive deficits in 2.5 months	[347]
Noncanonical models	<i>APOE</i>	<i>Apoe^{-/-}</i>	Low levels of Aβ ₄₂	[348, 349]
	<i>Pin^{-/-}</i>	<i>Pin^{-/-}</i>	High levels of hyperphosphorylated Tau and Aβ ₄₂	[43, 350]
Combination al models	<i>PSAPP</i>	<i>Tg2576/PSEN1_{M146L}</i>	Plaque pathology begins earlier than <i>Tg2576</i> with high levels of Aβ ₄₂	[34, 351]
	<i>TAPP</i>	<i>Tg2576/Tau_{P301L}</i>	Tau pathology begins earlier than <i>Tau_{P301L}</i> with plaque pathology	[352]
	<i>3xTg-AD</i>	<i>PSEN1_{M146L}/AβPP_{Swe}/Tau_{P301L}</i>	Plaque pathology begins 6 months and Tau pathology begins in 12 months	[40]
	<i>APP/APOE</i>	<i>AβPP_{Swe}/Apoe^{-/-}</i>	High levels of IL1 β and GFAP activity compared to <i>TgCRND8</i>	[353]