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Alzheimer's Disease: Molecular Hallmarks and Yeast Models

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Abstract

Alzheimer's disease is a multifaceted, incurable neurologic disorder characterized by cognitive decline and degeneration of brain neurons. The main factors implicated in Alzheimer's disease including accumulation of misfolded and aggregated proteins (hyperphosphorylated microtubule associated protein referred to as tau and amyloid Aβ), oxidative damage, inflammation, mitochondrial impairments and chronic energy imbalance, chronic endoplasmic reticulum stress, autophagy dysfunction, the abnormality and dysfunction of the mitochondrion-associated endoplasmic reticulum membrane serving as bridges between endoplasmic reticulum and mitochondria and regulating multiple functions such as Ca^{2+} transfer, energy exchange, lipid synthesis and transports and protein folding, genetic variation in lysosomal genes, metabolomic changes are shortly considered. A special emphasis was placed on mitochondrial fission (fragmentation) is a prominent early event preceding Alzheimer's disease pathology in transgenic Aβ-animal models, as well as on marked decrease in extracellular amyloid deposition, prevention of the cognitive deficit development and improvement of synaptic parameters after inhibiting abnormalities in mitochondrial dynamics. The important role of the well-characterized *Saccharomyces cerevisiae* yeast as a valuable eukaryotic model organism in unraveling complex fundamental intracellular mechanisms underlying Alzheimer's disease is highlighted. The benefits of applying a new model organism the yeast *Yarrowia lipolytica*, an obligate aerobe with the respiratory metabolism closely resembling that of mammalian cells, amenable to both classical and molecular genetic techniques, having a long history of use as a producer of heterological proteins, possessing an ability to change its morphology (from yeast-like to true mycelium) in response to environmental conditions as an useful alternative in deciphering a role of mitochondrial dynamics and distribution in an yeast model of Alzheimer's disease are suggested.

Keywords: Alzheimer's disease; Amyloid-β peptide; Tau protein; Mitochondrial dysfunction; Oxidative stress; Yeast

Abbreviations: Aβ: Amyloid-β Peptide; AD: Alzheimer's Disease; APP: Amyloid Precursor Protein; ATG: Autophagy-related Protein; Drp1p: Dynamin-Related Protein 1; ER: Endoplasmic Reticulum; ERK: Extracellular signal–Regulated Kinase; HIF: Hypoxia-Inducible Factor; MAM: Mitochondrion-Associated Endoplasmic Reticulum Membrane; MAP: Microtubule Associated Protein; MAPK: Mitogen-Activated Protein Kinase; Mdivi-1: 3-(2,4-Dichloro-5-methoxyphenyl)-2,3-dihydro-2-thioxo-4(1H)-quinazolinone; mtDNA: Mitochondrial DNA; NF-κB: Nuclear Factor Kappa B; PSEN1: Presenilin 1; PSEN2: Presenilin 2; ROS: Reactive Oxygen Species; STAT3: Signal Transducer and Activator of Transcription 3; TNFα: Tumor Necrosis Factor α

Introduction

Alzheimer's disease (AD) is a multifaceted, incurable neurologic disorder characterized by cognitive decline and degeneration of brain neurons. AD is the most common form of dementia and one of the most important causes of morbidity and mortality among the aging population presently affecting more than 45 million worldwide [1,2] and its prevalence is increasing with the demographic trend of increasing elderly populations in industrialized countries [3,4].

Since AD was first described in 1907 [5], many attempts have been made to reveal its main cause. Nowadays, two forms of the disease are known, and while the very rare hereditary early-onset form of AD is clearly caused by mutations encoding amyloid precursor protein (APP) and presenilin 1 and 2 (PSEN1, PSEN2) [6], fundamental pathogenic mechanisms as well as most hereditary contributions to the predominant age-related sporadic form of AD remain largely unknown.

Hallmarks of AD

Accumulation of misfolded and aggregated proteins in AD, loss of synapses, neuronal death

Both hereditary and sporadic forms of AD forms share similar sets of neuropathological manifestations, including accumulation of misfolded and aggregated proteins, the extracellular deposition of senile plaques, followed by the intracellular neurofibrillary tangles, consisting mainly of aggregates of hyperphosphorylated microtubule associated protein (MAP) referred to as tau [7,8]. MAP tau is a key protein in stabilizing the microtubule architecture that regulates neuron morphology and synaptic strength. In the course of AD hyperphosphorylated tau gets truncated by proteolytic cleavage, being a subject to O-glycosylation, sumoylation, ubiquitinylation, acetylation and some other modifications [3,4]. When MAP tau is degraded in tauopathic disorders, neuron dysfunction results [9]. Senile plaques are deposits of the amyloid-β peptide (Aβ) produced by the sequential cleavage of β- and γ-secretase at the C terminus of APP. This peptide has an extraordinary ability to undergo conformational changes and is highly amyloidogenic. More than 20 mutations in APP have been linked to familial AD that have altered APP processing with respect to enhanced Aβ generation or aggregation. It is now generally accepted that a progressive accumulation of Aβ aggregates eventually triggers a cascade of cellular changes, including mitochondrial oxidative damage, the hyperphosporylation of tau, synaptic failure and inflammation [10]. This is associated with the loss of synapses and then neuronal death, initially in focal areas including the entorhinal cortex and hippocampus,

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and ultimately more broadly in the cortex [11]. The loss of synapses in the affected brain regions correlates best with cognitive impairment in AD patients and has been considered as the early mechanism that precedes neuronal loss.

However, the amyloid cascade hypothesis, postulating the key role of Aβ in AD development does not fully explain all of the molecular abnormalities in AD [12]. Evidence is presented suggesting amyloid oligomers as necessary but insufficient causes of the dementia and that, for dementia to develop, additional cofactors are required [13]. Those cofactors include several subcellular processes including oxidative damage [10,14-23], recruitment of peripheral immune cells and excessive production of pro-inflammatory mediators [10,24-29], mitochondrial impairments and chronic energy imbalance [12,20,30-47], chronic endoplasmic reticulum (ER) stress [48] and autophagy dysfunction [22,49-54], the abnormality and dysfunction of MAM (the mitochondrion-associated endoplasmic reticulum membrane serving as bridges between ER and mitochondria and regulating multiple functions such as Ca^{2+} transfer, energy exchange, lipid synthesis and transports and protein folding [55-57], genetic variation in lysosomal genes [58].

Mitochondrial dysfunction in AD

Recently, multiple lines of evidence have stated major roles for the accumulation of mitochondrial dysfunctions, coupled with increased reactive oxygen species (ROS) generation, defects in mitochondrial biogenesis and transport/distribution, aberrant cell cycle re-entry in neurons and mitophagy in sporadic AD etiopathogenesis (so called mitochondrial cascade hypothesis) [12].

Neurons, post-mitotic and excitable cells have high energy requirements to maintain the resting potential through ion pumps, releasing neurotransmitters during synaptic transmissions to communicate with other neurons, and transporting organelles by consuming ATP [30,42]. They rely almost exclusively on the mitochondrial oxidative phosphorylation system to fulfill their energy needs. In addition, neurons are exceedingly compartmentalized, comprising structures like: cell body, axon, dendrites and even more specific compartments that are the synapses, which makes a proper mitochondrial distribution pivotal to sustaining the energy requirement at specific locations within the different neuronal compartments [31,35,36]. The crucial role of mitochondria in supporting synaptic function and the concomitant occurrence of impaired mitochondrial energy production, deregulated mitochondrial calcium handling, excess of mitochondrial ROS generation and release with mediating synaptic transmission deregulation in AD seem to lend the credibility to the hypothesis that mitochondrial defects underlie synaptic failure in AD [32-34,37,41,43,47].

A number of reports suggest the involvement of mitochondrial alterations through intracellular accumulation of oligomeric Aβ. One of the possible mediators for Aβ-impaired mitochondrial function is thought to be the nuclear factor kappa B (NF-κB) signaling pathway, playing important roles in brain inflammation and antioxidant defense, as well as in the regulation of mitochondrial function; studies have confirmed altered NF-κB signaling in AD brain [51]. The mitochondrial alterations include increased ROS production, mitochondrial DNA (mtDNA) depletion, decreased oxidative phosphorylation and ATP production, membrane depolarization, reduced number of mitochondria etc. All these defects cumulatively caused neural toxicity and alterations in cellular energy homeostasis, a significant reduction in neuronal viability [44,45].

However, dysfunctional mitochondria located in synapses can trigger synaptotoxicity through multifaceted mechanisms and that it is not the susceptibility of mitochondria to Aβ [59]. Complementary, in some cases beneficial effects of some agents on survival and cognitive performance were independent of Aβ levels and amyloid plaque deposition, but were associated with improved brain mitochondrial respiration, a reversal of mitochondrial complex I dysfunction, restored ATP production and reduced ROS levels [38].

Many investigators have suggested that epigenetic changes in the copy numbers of mtDNA and mtDNA mutations might be involved in AD pathogenesis [60-65]. However, the analysis of the literature reveals the existence of inconsistent findings and methodological shortcomings affecting a large proportion of mtDNA association studies on AD [66-69].

Unlike static organelles, mitochondria in various eukaryotes change size and shape by undergoing fission and fusion, processes that are orchestrated by the cellular machinery comprised of dynamin-related proteins [70]. It is argued that this kind of organellar dynamics has the power to restore the function of impaired organelles by content mixing with intact organelles.

Excessive mitochondrial fission (fragmentation) is a prominent early event, contributing to mitochondrial dysfunction, synaptic failure, and neuronal cell death in the progression of AD [40,71,72]. Moreover, mitochondria fragmentation, like a mitochondrial bioenergetic deficit, is an early feature preceding AD pathology in APP transgenic animal models [40] and mouse model CRND8 [73].

Treatment by mdivi-1, a mitochondrial fission inhibitor, rescued the mitochondrial fragmentation and distribution deficits and improve mitochondrial function in the Aβ-treated [72] and CRND8 [73] neurons both *in vitro* and *in vivo*. Importantly, mdivi-1 treatment markedly decreased extracellular amyloid deposition, prevented the development of cognitive deficits in Y-maze test and improved synaptic parameters, supporting the notion that abnormal mitochondrial dynamics plays an early and causal role in mitochondrial dysfunction and AD-related pathological and cognitive impairments *in vivo* [72,73]. These results suggest that neuropathology and combined cognitive decline can be attributed to hyperactivation of Drp1p (responsible for mitochondrial fragmentation) in the pathogenesis of AD and that inhibiting excessive Drp1p-mediated mitochondrial fission may be a new efficient therapeutic strategy for AD. However, according to other data [46], mdivi-1 works better in prevention than treatment in AD neurons.

Mitochondria in neurons challenged with extracellular Aβ and neurons expressing APP show decreased motility and density in axons. Similarly, tau, especially hyperphosphorylated tau, disrupts mitochondrial transport in neuronal cells. An Aβ- or APP- induced mitochondrial trafficking deficit could be alleviated by inhibiting mitochondrial fragmentation, indicating the impairment of mitochondrial movement possibly downstream of mitochondrial fragmentation [40].

Oxidative stress in AD

Oxidative stress reflects an imbalance between the generation and clearance of ROS [14]. ROS is formed as a natural by-product of metabolism and has important roles in cell signaling and homeostasis. However, excessive production of ROS, largely derived from mitochondrial dysfunction [16], can induce significant damage to cell components, including DNA, proteins and lipids [15] and disturb

multiple cellular signaling, including NF-κB, HIF and STAT3 pathways, leading to expression of proteins that control inflammation, cellular transformation, survival and metastasis [74-76]. Oxidative stress has been shown to increase with age in the brain, where oxidative damage is a major contributor to functional decline [10]. Moreover, oxidative stress is also the major cause of glial inflammation and apoptosis. All these findings suggest a critical role for oxidative stress in promoting AD and highlight the for antioxidants as potential drugs for combating AD [17-23].

Inflammation in AD

Inflammation is a complex and dynamic process, and during the course of AD, it probably has protective and deleterious effects in different phases [29]. The initial accumulation of Aβ triggers glial cells, such as microglia and astrocytes, the resident immune cells of the central nervous system, which subsequently activates immune reactions. Microglia can identify and bind to Aβ oligomers and fibrils through receptors present on the cell surface; microglia activation reduces Aβ deposits by increasing its phagocytosis. Aβ, in turn, is able to activate the NF-κB pathway, which is a central signaling pathway for cytokine production [24]. When astrocytes are stimulated by pro-inflammatory cytokines such as IL-1 and IL-6, they become activated (reactive astrocytes) and promote inflammation through the secretion of cytokines such as tumor necrosis factor α (TNF-α) and IL-6. In addition to having a direct cytotoxic effect on the adjacent neurons, these cytokines result in a decrease in scavenger receptors and Aβ-degrading enzymes in the microglia, canceling their neuroprotective role as the disease progresses. The ongoing production and release of pro-inflammatory cytokines (such as TNFα, interleukin-1, interleukin-12, and interleukin-23), prostaglandin E2, NO, ROS, and matrix metalloproteinases leads to a chronic inflammatory state and microglial dysfunction that hinders Aβ clearance [27]. Chemokines such as TNFα may enhance APP and Aβ peptide production [26]. Additionally, Aβ may directly bind to the surface of microglial cells for the activation of MAPK/ERK pathway and induce pro-inflammatory genes including cytokines and chemokines [25], thus leading to a downward spiral of chronic inflammation and causing direct neuronal cell damage and furthering the pathogenesis of AD.

ER stress in AD pathology

Mounting evidence suggests that ER stress is involved in the pathology of AD. The ER is an organelle that functions to facilitate protein folding. However, exposure to stress results in loss of function and causes ER stress. Intriguingly, crosstalk between ER stress and immune function has been suggested [48]. However, the mechanisms linking the progression of AD with ER and immunological stress are still not clear.

Autophagy in AD genesis

Autophagy (from the Greek meaning "selfeating") is a key homeostatic evolutionarily conserved catabolic process involved in the lysosomal degradation of dysfunctional or unnecessary cellular components (e.g., organelles and proteins [77]). Mechanistically, the cellular components (misfolded proteins (aggrephagy), overloaded peroxisomes (pexophagy), pathogenic organisms (xenophagy) and dysfunctional mitochondria (mitophagy)) are engulfed by autophagosomes which then move towards and fuse with lysosomes and are then degraded [53]. A complicated series of signaling cascades and autophagy-related proteins (ATG) contribute to the completion of autophagy [50].

Recent studies have revealed the protective role of autophagy in neurophysiology, particularly, in AD. Autophagy negatively regulates inflammation. Increased activity of the autophagy pathway leads to increased degradation of the tau protein and hence reduced intracellular tau aggregation [49], suggesting that the aberrant accumulation of tau proteins may, at least in part, be due to impaired autophagy inside neurons [54]. Another major protective role of autophagy is the elimination of abnormal mitochondria, a source of oxidative stress. The molecular interaction between autophagy and Aβ remains controversial [52] and more in-depth investigations are still needed to clarify the functional role of autophagy on pathological alteration of AD.

Metabolic changes associated with AD

Metabolomic studies have also shown that a range of fundamental changes occur during AD progression. Mounting evidence suggests a link between diabetes, obesity, non-alcoholic fatty liver disease and the progression of AD [78].

Metabolic changes observed in AD patients and AD models include glucose breakdown and pyruvate oxidation [79], impairment of protein synthesis in early-stage AD [80], increased levels of some amino acids, serotonin, catecholamine and Krebs cycle metabolites [79,81,82], alterations in purine metabolic pathways [79,81], imbalanced cholesterol [83] and sphingolipid [84] homeostasis, large network-wide disruptions in ceramide and phosphoinositide biosynthesis and signaling [85], disruptions in the cellular systems for handling (uptake, intracellular transport, protein loading and storage) transition metals [86,87], dysregulated one-carbon metabolism [88] and some others.

Models for AD

Mouse models for AD

Within the scope of mini-review, we only recall that mouse models, which feature highly genetic kinship with the human genome, have been widely regarded as a suitable tool for AD researches. However, despite many scientific achievements [52], 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 there is a need to generation more robust models closely resembling the human pathophysiology of AD.

Yeast models for AD

On the other hand, the growing need to better understand the molecular basis of AD with its diversity of symptoms and sophisticated cross-talk of cofactors has led to the development of simple eukaryotic models amenable for mechanistic studies. In recent years, the field of neurodegeneration, AD particularly, has derived significant benefit from the use of the simple and well-characterized eukaryote *Saccharomyces cerevisiae* [89]. Yeast cells possess most of the same fundamental cellular machinery as neurons in the brain. Moreover, numerous processes and mechanisms such as cell signaling pathways that regulate metabolism, cell growth and division, organelle function, cellular homeostasis and stress responses were first identified in yeasts and then shown to be conserved in higher eukaryotes. The high degree of conservation between yeast and higher eukaryotes is one of the reasons why yeast cells are so reliable as biological model for age-related diseases [90,91]. Despite nearly a billion years of evolutionary divergence, recent estimates showed that a fifth of yeast genes have human disease orthologs lending support to functional discovery investigations using this model [92]. Moreover, thanks to amenability of *S. cerevisiae* to both classical and advanced molecular genetic techniques, to relatively

simple, cheap and quick genetic and environmental manipulations, to the large knowledge base and data collections, high-throughput screening technologies and functional genomics that are not possible in humans [93-95], this organism has become a valuable and prevalent eukaryotic model organism to unravel complex and fundamental intracellular mechanisms underlying neurodegeneration [96-104].

Humanized yeasts are also utilized in high-throughput screening of genes that affect the toxicity of heterologously expressed human proteins, for large-scale chemical screens aiming at the discovery of novel compounds delaying aging or protecting against human age-related diseases.

Several excellent reviews have dealt with specific aspects of AD, including Aβ toxicity, using this model ([3,4,7,102,105,106] and references therein).

Improved yeast models for AD

However, the fermentation-oriented yeast *S. cerevisiae* (selected for thousands of years for its capacity for alcoholic fermentation) with less abundant mitochondria is hardly a bioenergetic equivalent of high-energy demanding neurons relying almost exclusively on mitochondrial oxidative phosphorylation. *S. cerevisiae* is not the best model organism for studying fragmentation of mitochondria, as they contain small-sized, poorly structured mitochondria. In these respects, *Yarrowia lipolytica*, a non-toxic ascomycetous yeast species having a haploid genome and sexual life cycle and amenable to both classical and molecular genetic techniques [107], an obligate aerobe with the respiratory metabolism closely resembling that of mammalian cells [108,109], vigorously growing on a variety of simple, well defined and inexpensive media [110], having a long history of use as a producer of heterological proteins [111], possessing an ability to change its morphology (from yeast-like to true mycelium) in response to environmental conditions [112,113], may be a useful alternative in deciphering a role of mitochondrial dynamics and distribution in an yeast model of AD.

Limitations of yeast models for AD

However, it should be noted that although yeast offers many advantages for mechanistic dissection of neurotoxic disorders and has contributed greatly to the understanding of the molecular underpinnings of human diseases [89,106], there are some natural limitations; unicellular organisms such as yeast fails as a model to study the multicellularity and cell-cell interactions, particularly important in the neuronal cross-talk that is of major importance to neurodegeneration [114]. Yeasts lack neuron-specific morphological structures, such as dendrites, axons and synapses. Consequently, the underlying neuron-specific molecular inventories are missing. Therefore, age-related and disease-associated processes uncovered in yeasts must be carefully extrapolated to human aging and diseases. Ultimately, these findings must be validated in neuronal model systems and more complex eukaryotic models.

Conclusion

AD is a complex, multifaceted neurologic disorder characterized by cognitive decline and degeneration of brain neurons, arising from interplay of many factors including accumulation of misfolded and aggregated proteins, mitochondrial impairments, oxidative damage, inflammation, endoplasmic reticulum stress, autophagy dysfunction, the abnormalities in Ca^{2+} homeostasis, transfer and energy exchange, protein folding, genetic variation in lysosomal genes, metabolic changes and others. Despite tremendous efforts in elucidating the molecular and cellular players involved in AD pathology, to date, there is no treatment that could prevent or cure this disease. Current treatments are only useful in slowing down the progression of AD and helping patients manage some of their behavioral and cognitive symptoms instead of reversing the ultimate consequence [115]. These unsatisfactory effects force people to pay attention on more targeted and etiology-oriented strategies [116]. Due to the notion that age-related oxidative stress has been acknowledged as one of the major risk factors of AD pathogenesis and the early manifestation of AD [18], anti-aging drugs (antioxidants) have become the prevailing therapeutic strategy against AD. In this respect, yeasts, relatively simple unicellular organisms, vigorously growing on simple and inexpensive media may be exceptionally promising models for searching for and treating the newly synthesized effective antioxidants, especially mitochondria-targeted antioxidants [109,117-119]. Further research exploring these data and other finding obtained from analysis of other models will help put together the pieces of the puzzle to create a unifying theory of this highly complex AD process.

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