Review Article

Oxidative Stress in Alzheimer's and Parkinson's Diseases: Insights from the Yeast *Saccharomyces cerevisiae*

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Alzheimer's (AD) and Parkinson's (PD) diseases are the two most common causes of dementia in aged population. Both are protein-misfolding diseases characterized by the presence of protein deposits in the brain. Despite growing evidence suggesting that oxidative stress is critical to neuronal death, its precise role in disease etiology and progression has not yet been fully understood. Budding yeast *Saccharomyces cerevisiae* shares conserved biological processes with all eukaryotic cells, including neurons. This fact together with the possibility of simple and quick genetic manipulation highlights this organism as a valuable tool to unravel complex and fundamental mechanisms underlying neurodegeneration. In this paper, we summarize the latest knowledge on the role of oxidative stress in neurodegenerative disorders, with emphasis on AD and PD. Additionally, we provide an overview of the work undertaken to study AD and PD in yeast, focusing the use of this model to understand the effect of oxidative stress in both diseases.

1. Introduction

Misfolded proteins are typically insoluble and tend to form long linear or fibrillar aggregates known as amyloid deposits. Amyloid-like protein fibrils are a well-known pathological hallmark of age-related neurodegenerative diseases, including Alzheimer's disease (AD) and Parkinson's disease (PD). Alzheimer's and Parkinson's diseases are the most common forms of dementia, currently affecting 30 and 4 million people worldwide, respectively. In AD, the beta-amyloid (Aβ) peptide accumulates mainly extracellularly, whereas in PD, the α-Synuclein (α-Syn) protein accumulates, within neurons, inside the Lewy bodies (LB) and Lewy neurites (LN). Although there is a plethora of factors interfering in those pathological depositions, it is clear that oxidative stress may play a crucial role in neuronal death in neurodegenerative disorders [1–3].

Reactive oxygen species (ROS) are chemically reactive molecules containing oxygen and are produced in all aerobic cells. Oxidative stress occurs when the generation of ROS in a system exceeds that system's ability to neutralize and to eliminate them. All organisms have developed adaptive responses to oxidative stress that involve defensive enzyme and molecular chaperones—the expression of both being orchestrated by stress-responsive transcription factors—as well as antioxidant molecules [4]. Excessive production of ROS, and the consequent disruption of cellular redox balance, drives the oxidation of biological macromolecules, such as DNA, proteins, carbohydrates, and lipids, potentially leading to failure of biological functions [4].

Many ROS possess unpaired electrons and are therefore free radicals. The generation of free radicals is closely linked with the involvement of trace metals, particularly copper and irons [5, 6]. To cope with this potential hazard, the concentration of cytosolic free metals is accurately controlled through regulation of their uptake, storage, and mobilization, in order to maintain redox-active metals in normal physiological limits [7, 8]. Inside cells, "free pools" of copper and iron are avoided through their effective sequester by metal-binding proteins [5, 9]. The chelatable redox-active

iron constitutes the so-called labile iron pool (LIP), which serves as a transient source of iron [5, 9, 10]. Nevertheless, whenever cells are subjected to stress conditions, an excess of superoxide anion radical acts as an oxidant of Fe-S clusters of several enzymes, releasing "free iron." The released iron can in turn participate in Fenton type reactions, producing the highly reactive hydroxyl radical [11].

During the oxidative burst triggered during inflammatory processes, cells of the immune system produce both superoxide anion and nitric oxide (NO) free radicals. Nitric oxide is produced by the NO synthase family of enzymes. NO may directly react with its biological targets, as it is known to regulate the catalytic activity of various enzymes primarily by interacting with Fe-S clusters, oxidized copper centres, heme, and tyrosyl radicals [12]. NO also reacts with superoxide ion (O_2^-) or oxygen to form the nitrogen radical peroxynitrite ($ONOO^-$). Reactive nitrogen species (RNS) are highly reactive towards biological macromolecules and are thought to be responsible for NO-mediated cell death.

The aim of this paper is to provide an overview on the role of oxidative stress in neurodegenerative disorders, with emphasis on AD and PD. Despite the absence of a nervous system in yeast, several studies have shown that this eukaryotic unicellular organism is a suitable model system to understand the molecular mechanisms underlying neurodegenerative diseases. The knowledge from those studies is summarized herein. Finally, we discuss how yeast models have been or may be used to extend our understanding on the role of oxidative stress in AD and PD.

2. Oxidative Stress and Neurodegenerative Diseases

The human brain is responsible for approximately 20% of our body oxygen consumption and thus subjected to a high metabolically derived level of ROS [13, 14]. An increasing body of evidence suggests that oxidative stress is involved in the etiology and pathogenesis of neurological disorders. The lipid bilayer of the brain is rich in polyunsaturated fatty acids and oxygen and is therefore highly susceptible to lipid peroxidation, a complex process involving the interaction of polyunsaturated fatty acids with free radicals that results in production of reactive electrophilic aldehydes. Lipid peroxidation occurs in several neurodegenerative diseases [15]. Evidence of oxidative stress in these diseases is further supported by increased DNA (and often RNA) base oxidation products and oxidative protein damages in specific regions of the brain [4]. The destruction of cellular components can induce a diversity of cellular responses through generation of secondary reactive species and ultimately lead to cell death via apoptosis and necrosis [16–18]. Mitochondrion is the center of ROS production. About 90% of mammalian oxygen consumption is mitochondrial, making mitochondria particularly important in neurons due to their high demands for energy. This fact, together with the observation that mitochondrial perturbation occurs in multiple neurodegenerative disorders [19], suggests that neurodegenerative diseases are mitochondrial diseases.

3. Alzheimer's Disease and Oxidative Stress

Alzheimer's disease (AD) is an age-related progressive neurodegenerative disease caused by severe neurodegeneration in the hippocampus and neocortical regions of the brain of affected individuals [20].

AD pathological hallmarks include extracellular amyloid plaques and intracellular aggregates (neurofibrillary tangles). The major component of the amyloid plaques is the amyloid peptide Aβ, which results from the proteolysis of the amyloid precursor protein (APP). APP is a ubiquitously expressed transmembrane protein exerting a critical role in neuron growth and survival [21, 22]. APP proteolysis to form the Aβ peptide involves the sequential action of aspartic protease BACE1 (β-secretase) and of γ-secretase, a multiprotein complex [23]. The length of Aβ peptide may range from 39 to 43 aminoacid residues, due to different γ-secretase cleavage sites. Aβ appears to be unfolded, under physiological conditions [24]. In amyloid plaques, the most frequent species are Aβ40 and Aβ42, the latter being the most prone to aggregation [23]. Neurofibrillary tangles are composed of hyperphosphorylated tau protein, a microtubule-binding protein thought to be involved in microtubules stabilization and in regulation of axonal transport in the brain [25].

The causes of Alzheimer's disease are not well understood, except for a small percentage of cases that are linked to familial genetic mutations [26]. Several hypotheses have been put forward with the aim to explain the cause of the sporadic form of the disease. One widely discussed of those hypotheses assumes that amyloid deposits of Aβ peptides are the causative agents of AD [27]. The "amyloid" theory is further supported by the link between mutations in the APP gene and some inherited forms of the disease [26].

Aβ toxicity is dependent on Aβ's conformational state, peptide length, and concentration [28, 29]. Moreover, it has been described that Aβ toxicity is also related to Aβ's ability to form hydrogen peroxide and free radicals [30, 31]. These findings are supported by the significant lipid peroxidation, protein oxidation, and DNA oxidation observed in AD brains [29, 32, 33]. In addition, two factors reinforce the role of oxidative stress in AD pathogenesis: pro-oxidants increase Aβ production, whereas several antioxidants, namely vitamin E, melatonin, and several free radical scavengers, can protect neurons from Aβ-induced toxicity [34].

Interestingly, the Aβ peptide is not toxic in the absence of redox metal ions, and many recent studies implicate biometals in the development or progression of Alzheimer's disease [6, 35–37]. Accordingly, sophisticated techniques have shown an overaccumulation of copper, iron, and zinc within the amyloid plaques compared with the surrounding tissues [38]. Aβ has high affinity for redox-active metals being able to reduce them and consequently lead to the formation of hydrogen peroxide and oxidized amyloid [6]. Butterfield and Bush proposed that a single methionine residue (Met35) of Aβ42 is critical for the oxidative and

neurotoxic properties of this peptide [39, 40]. Substitution of Met35 renders the Aβ peptide nonoxidative and nonneurotoxic [40]. The sulphur atom of Met35 is highly susceptible to oxidation, forming the sulfide radical MetS$^{\bullet+}$ and reducing copper(II) to its high-active low-valency form [5, 40]. The MetS$^{\bullet+}$ radical is able to undergo very fast reactions with superoxide ion, leading to the formation of methionine sulfoxide (MetO). In AD senile plaques, a significant fraction of Aβ has Met35 in the form of MetO [41].

Another well-studied source of oxidative stress in AD is mitochondria damage and its consequent functional abnormality that favors the production of ROS. Indeed, it was shown that neurons in AD exhibit a significantly higher percentage of damaged mitochondria compared to an aged-matched group [42]. Furthermore, mitochondrial dysfunction has been widely implicated in the etiology of AD, since early impairments of mitochondrial function and oxidative stress may precede Aβ overproduction and deposition [43]. Also inflammation can induce oxidative damage in AD, especially via microglia, leading to increased ROS and RNS formation and the resulting damage to lipid, proteins, and nucleic acids [44–46].

4. Parkinson's Disease and Oxidative Stress

Parkinson's disease is an age-related neurodegenerative disorder affecting the central nervous system. It is characterized by the progressive degeneration of nigrostriatal dopaminergic neurons within the *substantia nigra pars compacta*, which is the pathological process responsible for the motor symptoms attributed to PD [47]. The pathological hallmark of the disease is the presence of proteinaceous cytoplasmic inclusions designated as Lewy bodies and Lewy neurites. These are predominantly composed of the presynaptic protein α-Synuclein (α-Syn) [48] together with proteasomal and lysosomal subunits as well as molecular chaperones [49].

The ubiquitous α-Syn brain protein is implicated in both hereditary and sporadic PD. Its encoding gene, *SNCA,* was the first genetic determinant associated with the disease and, for this reason, much of the work on PD converges on α-Syn [50]. α-Syn was shown to interact with lipids and membranes, accelerating amyloid fibril formation [51], and it has been proposed to regulate the dynamics of synaptic vesicles at the synapse [52]. Indeed, α-Syn exhibits a remarkable conformational plasticity being its structure largely dependent on the surrounding environment. The monomeric α-Syn is a typical natively unfolded protein under physiological conditions [53, 54]. However, under specific conditions, such as the increase of its intracellular levels, α-Syn can adopt different conformations, including several α-helical and β-sheet species folded to different degrees in both monomeric and oligomeric states [55].

Although PD is a recognized multifactorial disease, a large body of evidence has implicated oxidative stress in the pathogenesis of PD. The conclusive connection between PD and oxidative stress is supported by the increased oxidative damage of sugars, lipids, nucleic acids, and proteins observed in *postmortem* dopaminergic neurons within the *substantia nigra pars compacta* of PD brains [6, 56, 57].

Auluck et al. proposed that the impairment of α-Syn function leads to its local accumulation, favoring the formation of toxic oligomeric species that interfere with ER-to-Golgi trafficking, mitochondria turnover—through the abrogation of mitophagy—and generate oxidative stress. Moreover, the abnormal interaction of α-Syn with membranes has been implicated in the cytoplasmic retention of catecholaminergic neurotransmitters yielding cytotoxicity through the generation of dopamine adducts and ROS [52]. This effect is potentiated in the presence of iron-rich environments, as it is the case of Lewis bodies in the neurons decorating the *substantia nigra* of PD patients [58–61]. Indeed, it is known that dopamine is able to coordinate iron and regenerate Fe^{2+}, possibly providing an equally important source of hydroxyl radical production [62].

Mitochondria have been claimed as dominant sites for oxidative stress-driven initiation and propagation in PD. The direct implication of this organelle in PD was first suggested by the use of the mitochondrial complex I (CI) inhibitor MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) [63, 64]. This chemical mimics human PD in animal models and is associated with development of Parkinsonism in humans subjected to accidental exposure [65]. Further corroborating the relevance of mitochondria in PD, it was shown that the well-known CI inhibitor rotenone induces death of dopaminergic cells [66–69]. In addition, depletion of the antioxidant peptide glutathione (GSH) in PD cells, which may be caused by a decrease in its synthesis and recycling [70], has been associated with a decrease of mitochondrial CI activity, resulting in mitochondrial dysfunction [71, 72]. Moreover, defective mitochondrial CI function is observed in the *substantia nigra* of PD brains [73, 74]. Recent studies have also demonstrated that α-Syn monomers and oligomers associate with the inner mitochondrial membrane where they can physically associate with CI, thereby interfering with the mitochondrial function and increasing free radicals production [72, 75]. Further highlighting the relevance of mitochondrial dysfunction and oxidative stress in the pathological process of the disease, several genes associated with familial cases of PD were shown to encode either mitochondrial proteins or mitochondria-associated proteins [6, 76]. Among the latter is DJ-1, a protein that shares structural homology with the *Escherichia coli* chaperone Hsp31 and is thought to have a protective role against oxidative stress [77]. Under conditions of oxidative stress, DJ-1 is relocated to the mitochondria, affecting the sensitivity of specific neuron populations to compounds targeting mitochondrial CI, namely, rotenone, paraquat, and MPTP [6, 78–80].

Several evidences support as well an unbalanced generation of RNS as a feature of PD pathology. First, nitrated α-Syn accumulates in LB of PD cells. Secondly, the treatment of GSH-depleted dopaminergic cells with RNS inhibitors prevents mitochondrial CI inhibition [6], indicating that RNS itself has a role in mitochondrial dysfunction and ROS generation in PD. Lastly, glial cells within the *substantia nigra* exhibit increased NO levels [81], possibly due to the accumulation of interferon-γ (IFN-γ) [82], a cytokine which was shown to promote induction of RNS in brain.

5. *S. cerevisiae* as Model Organism to Study Neurodegenerative Diseases

Budding yeast *Saccharomyces cerevisiae* has been introduced as an experimental organism in the midthirties of the 20 century. Since then, its potential as a model organism has been exploited in many areas of biology [83]. Despite lacking the physiological complexity of the mammalian nervous system, yeast was recently used in the study of neurodegenerative disorders, such as Alzheimer's and Parkinson's Diseases. This became possible due to the development of powerful yeast genetic tools as well as the high conservation of fundamental biological processes and pathways associated with neurodegeneration including protein folding, cellular trafficking, and secretion [84]. It is noteworthy that about one-fifth of yeast genes are members of orthologous gene families associated with human diseases [85]. This is an important aspect to consider when studying human diseases in yeast. If a homologue of the gene implicated in the disease is present in yeast genome, a unique opportunity to directly study its function is offered, either through its deletion or overexpression. Otherwise, if the disease-associated gene does not have a yeast counterpart, functional analysis can still be performed via heterologous expression [86, 87]. Equally important "humanized" yeasts are being used as platforms for high-throughput screenings of compounds with therapeutic potential.

6. Yeast as a Model for Studying Alzheimer's Disease

Yeast models have been extensively used to study several molecular aspects of AD, even though yeast lacks for some AD-associated genes. Studies in yeast have been mainly focused on the *in vivo* APP processing, Aβ oligomerization, and toxicity.

The usage of heterologous expression of human secretases in yeast has greatly contributed to the understanding of human APP processing. It has allowed the discovery of BACE1 inhibitors and prompted the study of the individual function of each component of the γ-secretase complex [88].

Growing evidence suggests that the oligomeric forms of the Aβ peptide, rather than amyloid fibrils, are the most toxic forms [89–92]. These findings have shifted the focus of investigation towards the earliest stages of Aβ oligomerization. As a result, the following described yeast systems were developed and are now useful tools not only in the study of Aβ-oligomerization, but also in the understanding of the molecular events triggered by aggregation as well as in the screening of potential therapeutic compounds that affect the aggregation process.

The first yeast study on Aβ oligomerization used a two-hybrid approach to analyze Aβ dimerization. Protein-protein interactions were measured by fusing the Aβ peptide to a LexA DNA-binding domain and also to a B42 transactivation domain, and then monitoring the expression of a *lacZ* reporter driven by a LexA-dependent promoter [93]. The authors showed that Aβ peptide was able to form dimers, *in vivo*, in the yeast cell nucleus.

Bagriantsev and Liebman and von der Haar et al. implemented a different yeast model system that may constitute a valuable tool to seek for agents that interfere with the initial steps of Aβ42 oligomerization [94, 95]. In this study, the ability of Aβ42 peptide to aggregate was monitored by fusing it to the middle and C-terminal domain of Sup35. The Sup35 yeast translational termination factor can undergo spontaneous conversion into a prion state, losing its function [96]. Sup35 loses the ability to aggregate when its prion-forming (N-terminal) domain is deleted. However, the insertion of Aβ peptide sequences in place of the original prion domain of Sup35 protein restores its ability to aggregate [94, 95]. Using this reporter system, it was possible to confirm *in vivo* the impact of point mutations, previously shown to inhibit Aβ42 aggregation *in vitro* [94, 97]. Furthermore, it was shown that the Hsp104 yeast chaperone, a chaperone known to rescue proteins from the aggregated state in other yeast models of neurodegenerative diseases [98, 99], appears to have a contrary function in AD, protecting Aβ-fusion protein from disaggregation and degradation [94, 95].

Oligomerization of Aβ was also the subject of a third yeast study, by the use of a reporter consisting of Aβ fragment fused to GFP [100]. The assay was based on the premise that aggregates of the fusion protein suppressed green fluorescence. The Aβ-GFP fusion was shown to cause slight but significant yeast growth reduction and to induce a heat shock response (HSR), as indicated by the cotransformation of yeast with Aβ-GFP and HSE2 element fused to a downstream *lacZ* gene. The authors put forward the hypothesis that HSR could arise from Aβ inducing ROS and/or the presence of misfolded proteins and suggested that HSR might be a target for further studies seeking for inhibitors of Aβ effects [100].

Recently, Treusch et al. engineered a yeast model for studying Aβ toxicity [101]. The overexpression of a construct harboring the Aβ42 fragment fused at the N-terminus to an endoplasmatic reticulum targeting sequence was driven by a galactose-inducible promoter. Aβ oligomers localized to secretory compartments and, like in neurons, contributed to toxicity in yeast. A screen for genetic modifiers allowed the identification of 40 genes that were able to modulate Aβ toxicity. Among those, 12 had homologues in humans, 3 being related to clathrin-mediated endocytosis, and 7 functionally associated with the cytoskeleton. Interestingly, all the former genes behaved as Aβ toxicity suppressors and had been previously shown to be or interact with validated risk factors for AD. The authors further showed that Aβ affects clathrin-mediated endocytosis and proposed that Aβ oligomers may interact with transmembranar receptors and prevent their correct destination [101].

7. Yeast as a Model for Studying Parkinson's Disease

As a common feature of sporadic and familial cases of PD, the understanding of the pathological processes associated with α-Syn has attracted special attention. In order to gain insight into α-Syn pathobiology, Outeiro and Lindquist

exploited a myriad of advantages of using *S. cerevisiae* as a model organism, by developing a powerful "humanized" yeast system. As a means to study the α-Syn dynamics *in vivo*, the authors overexpressed in yeast cells a construct harboring the wild type or the mutant versions of human *SNCA* gene fused to GFP [102]. This pioneering system faithfully reproduces several features of PD in yeast, allowing to thoroughly investigate the pathological processes involved in the disease. Three strains, designated as NonTox, InTox, and HiTox, were created to express α-Syn at different levels [52]. As it happens in complex eukaryotic models, the appearance of cytoplasmic foci, cytotoxicity, and α-Syn-decorated vesicle accumulation was shown to be dose dependent [102, 103]. Moreover, high doses of α-Syn lead to increased toxicity, accumulation of cytoplasmic lipid droplets, vesicle trafficking defects, ER stress, activation of the heat-shock response, impairment of the ubiquitin-proteasome pathway, and mitochondrial dysfunction in the HiTox strain, therefore recapitulating the pathological features displayed by PD patients whose genome encodes duplications or triplications of *SNCA* locus [52].

The α-Syn yeast model developed by Outeiro and Lindquist has been the basis of several genome wide and high-throughput analyses aimed at unveiling the intricacies of PD. The systematic screening of a galactose-inducible overexpression library in the InTox strain revealed the Rab GTPase Ypt1 (Rab1) as suppressor of α-Syn toxicity [104], reinforcing the role of α-Syn in vesicle formation and delivery. In addition, an unbiased genome-wide screen for modifiers of α-Syn toxicity was performed in the InTox strain, allowing the identification of the polyamine transporter Tpo4 [105] and highlighting the significance of polyamine pathway in PD pathogenesis. Using the ResponseNet algorithm to integrate α-Syn mRNA profiling and genome-wide genetic data, it was found that trehalose might be involved in the protection pathway against α-Syn toxicity possibly promoting misfolded protein clearance. In addition, mitochondrial dysfunction and oxidative/nitrosative stress also appeared as consequences of α-Syn overexpression in yeast [106]. Comparison of the transcriptome of HiTox and NonTox strains provides further evidence supporting the assumption that mitochondrial dysfunction and oxidative stress are associated to conditions in which α-Syn is expressed at high levels. It has also been verified that mitochondria morphology is affected and ROS is accumulated in the HiTox strain further suggesting that high levels of α-Syn elicit global mitochondrial dysfunction [107]. This may suggest that α-Syn accumulation is the origin of oxidative damage of specific neuronal cells in PD.

More recently, overexpression of α-Syn in yeast revealed that the knockout of genes encoding lipid elongases, namely, *ELO1*, *ELO2*, and *ELO3*, impairs cell growth, dramatically decreases the survival of aged cells, and leads also to ROS accumulation and aberrant protein trafficking [108]. A similar strategy, using a different plasmid to drive galactose-inducible α-Syn expression in distinct *S. cerevisiae* backgrounds, disclosed the significance of fatty acid synthase activity and intracellular redox status in the mechanisms of α-Syn toxicity [109].

α-Syn-humanized yeasts have also been exploited to search for compounds with therapeutic potential. In this context, the HiTox strain was used in a high-throughput chemical screen to identify agents capable of rescuing the robust toxicity of this strain. A class of small molecules of 1,2,3,4-tetrahydroquinolinones were identified and shown to revert the formation of α-Syn foci, to reestablish ER-to-Golgi trafficking, to ameliorate mitochondria damage, to limit ROS production, and consequently to reduce α-Syn toxicity not only in yeast but also in other more complex PD models [107].

8. Concluding Remarks

Although AD and PD have been extensively studied, the exact mechanism of disease progression or pathogenesis remains largely unknown. As outlined in this paper, several *in vivo* and *in vitro* studies point towards a role of oxidative stress in AD and PD pathogenesis. Nevertheless, whether it is a primary cause or simply a consequence of the neurodegenerative process is still an unanswered question. In addition, specifically concerning AD, there are quite a few contradictory reports regarding the role of oxidative stress in the disease. Indeed, it has been described that oxidative stress may as well lead to an increase in Aβ [14, 110], and *in vivo* studies showed a negative correlation between oxidative stress and Aβ, indicating an antioxidant role for Aβ [111].

Yeast can be a powerful tool as a means to clarify several of these issues. Within this context, yeast models of AD may in the future be used to monitor Aβ oligomerization and toxicity under an oxidative environment or in the absence of ROS (hypoxia). Interestingly, a yeast model consisting of Aβ peptide fused to GFP has been successfully used to test whether folate, an antioxidant, was able to prevent Aβ aggregation [112]. To better understand the relationship between oxidative stress and α-Syn aggregation, in the pathological processes triggering PD, it would be interesting to assess both the behavior of α-Syn in the "humanized" NonTox strain under oxidative environments and in the InTox and HiTox strains under hypoxia conditions.

Future studies combining yeast and animal models of AD and PD will certainly provide valuable insights into the role of oxidative stress in these neurodegenerative diseases.

Acknowledgments

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