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Neuronal Death and Survival under Oxidative Stress in Alzheimer and Parkinson Diseases

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Abstract. Neuronal death is a common feature in neurodegenerative diseases including Alzheimer disease (AD) and Parkinson disease (PD). This occurs over years, not the minutes of classically defined apoptosis, and neurons show both responses of apoptosis and regeneration, evidenced by accumulated oxidative insult and attempts at cell cycle re-entry. There is recent evidence suggesting that several known gene mutations in causing familial AD (amyloid β protein precursor, presenilin-1, or presenilin-2 gene) and familial PD (Parkin, PINK-1, or DJ-1 gene) are associated with increased oxidative stress. Also, several known genetic (e.g. Apolipoprotein Eε4 variant) and environmental (e.g. metals or pesticides exposure) risk factors of sporadic AD and/or PD are associated with increased oxidative stress. In concord, patients at the preclinical stages of AD and PD as well as cellular and animal models of the diseases provide consistent evidence that oxidative insult is a significant early event in the pathological cascade of AD and PD. In contrast to the general aspects of the pathological hallmarks, aggregation of the disease-specific proteins such as amyloid-β, tau, and α-synuclein may act as a compensatory (survival) response against the oxidative insult via the mechanism that the disease-specific structures sequester redox-active metals. Expanding knowledge of the molecular mechanisms of organism longevity indicates that pro-longevity gene products such as forkhead transcription factors and sirtuins are involved in the insulin-like signaling pathway and oxidative stress resistance against aging. An enhancement of the pro-longevity signaling (e.g. caloric restriction) may be a promising approach as anti-oxidative strategy against age-associated neurodegenerative diseases.

Key Words: aging, apoptosis, Alzheimer disease, cell cycle, cell death, neurodegeneration, oxidative stress, Parkinson disease

I. INTRODUCTION

Neuronal death and protein aggregation are common features of Alzheimer disease (AD), Parkinson disease (PD), and other age-associated neurodegenerative disorders. In chronic neurodegenerative disorders, neuronal death occurs over years, not the minutes of classically defined apoptosis and necrosis. Vulnerable neurons show both responses of apoptosis and regeneration, evidenced by accumulated oxidative insult and attempts at cell cycle re-entry. Oxidation of nucleic acids, proteins, and lipids are all seen in post-mortem brains from patients with AD and PD. Some of the oxidatively modified macromolecules are identified also in biological fluids from the patients with AD and PD as well as cellular or animal models of these diseases [1-6]. Indeed, the oxidative modifications are seen at early stages of the diseases and are demonstrated to precede the formation of the pathological hallmark lesions such as senile plaques, neurofibrillary tangles (NFTs) in AD, and Lewy bodies in PD. These structures consist of aggregation of disease-specific proteins such as amyloid-β (Aβ), tau, and α-synuclein, respectively, and have generally been assumed to be responsible for neurodegeneration and subsequent neuronal death. However, in the context of chronic degeneration in AD and PD, accumulation of disease-specific structures may, in fact, be responses to increased oxidative stress to prolong neuronal survival [6,7].

II. NEURONAL DEATH IN AD AND PD

Neurodegenerative disorders are characterized clinically by insidious onset and slowly progressive course. Selective loss of a particular subset of neurons is a common feature of these disorders. In the superior temporal sulcus of AD, loss of 40% of the neuronal population occurs within 10 years [8]. Similarly, in the caudal substantia nigra of PD, loss of 45% of the neuronal population occurs within 10 years [9]. In striking contrast with this chronic process of cell death in neurodegenerative disorders, an apoptotic pathway of physiologically programmed cell death only takes several hours or at most a few days for completion (Table 1). In the development of the lateral motor column of the chick embryo, loss of 40% of the population occurs within 3 days [10]. The fact that only 5-6% of the population in the lateral motor column is undergoing apoptosis at any particular time in this period [10] indicates that apoptotic pathway requires less than 24 hours for completion. Therefore, if we assume that neuronal death actually occurs in the manner of classical apoptosis in chronic diseases like AD and PD, we should encounter only one in several thousands of neurons actively undergoing apoptosis in post-mortem brain samples of these diseases [11]. Indeed, extremely rare apoptotic neuronal death compatible with the chronic progression was demonstrated in the hippocampus in AD. The hippocampal neurons showing condensed, fragmented nucleus and shrunken cytoplasm as well as labeling for activated caspase-3, the effector enzyme of the terminal apoptotic cascade, were observed at a frequency of 1 in 2,600 to 5,650 counted neurons (0.02-0.04%) [12]. On the other hand,

a relatively high percentage of neurons showing activated caspase-3-positivity without morphological features of apoptosis was reported in the parahippocampal gyrus in AD [13] as well as the nigral dopaminergic neurons in PD [14]. Electron microscopic study did not reveal any morphological features of apoptosis such as chromatin condensation in the activated caspase-3-positive neurons, suggesting that the caspase-3 activation in these neurons marks the beginning of the effector phase of apoptosis [14].

Therefore, neurons living in a "sick state" for many years in the chronic neurodegenerative disorders may represent **abortosis** (abortive apoptosis), where apoptotic mechanisms play a role in the process of degeneration while actual completion of apoptosis is absent [15-17]. The term **paraptosis** (next to, or related to apoptosis) [18,19], is also proposed to refer to an alternative non-apoptotic form of cell death in neurodegeneration.

III. ROLE OF OXIDATIVE STRESS AND CELL CYCLE RE-ENTRY IN THE PATHOLOGICAL CASCADE OF AD AND PD

III.1 Association of Oxidative Stress with Aging, the Major Risk Factor for AD and PD

(a) Brain aging and oxidative stress

AD and PD are the two most common neurodegenerative disorders [20], and advanced age is the major risk factor for AD and PD [21,22]. Especially, prevalence of AD increases exponentially throughout aging, with about half of the population afflicted by the age of 95 [21]. As in other organ systems, cells in the brain encounter a cumulative burden of

oxidative and metabolic stress that may be a universal feature of the aging process as well as a major causal factor of senescence. Each of the macromolecules including nucleic acids, proteins, and lipids, is oxidatively modified during aging. Indeed, the brain is especially vulnerable to free radical damage because of its high oxygen consumption rate (accounting for 20-25% of the total body oxygen consumption, but for less than 2% of the total body weight), high content of easily peroxidizable unsaturated fatty acids, and relative paucity of antioxidant enzymes compared with other organs (e.g., the content of catalase in brain is only 10-20% of liver and heart) [23-25]. Therefore, detailed understanding of the underlying mechanisms between oxidative stress and organism aging, that is rapidly expanding today, may provide a significant insight into the pathogenesis of age-associated neurodegenerative diseases such as AD and PD.

(b) Life-span extending/shortening gene mutations and oxidative stress

The free radical theory of aging, a half-century-old hypothesis [26], has been supported by numerous cell culture, invertebrate, and mammalian models [27]. Recent studies have identified that several mutations affect longevity and the same mutations delay age-related diseases, which suggests that the molecular analysis of the pathways may lead to a mechanistic understanding of the association between aging and the disease susceptibility [28,29]. Evidence that toxicity of reactive oxygen species (ROS) is a limiting factor for life-span was directly demonstrated by showing life-span extension in transgenic fruit fly *Drosophila* by simultaneous overexpression of Cu/Zn-superoxide dismutase (SOD) and

catalase or by overexpression of Cu/Zn-SOD in motor neurons [30,31]. The importance of mitochondrial ROS in longevity has been supported by the observed alterations in life-span and ROS production/detoxification in nematode *C. elegans* mutants, i.e., the *mev-1* mutant, the *clk-1* mutant, and the *isp-1* mutant as well as in the $p66^{shc}$ mutant mice [32-36] (Table 2).

Several mutations that extend life-span perturb endocrine signaling pathways. The best understood of those signaling pathways is the insulin/insulin-like growth factor-1 (IGF-1) pathway, which is evolutionarily conserved in diverse species and influences life-span in worms, flies, and mammals (Table 2). Life-span extending/shortening gene alterations in the insulin/IGF-1 pathway (*daf-2*, *age-1* and *daf-16* in *C. elegans*, *InR* and *chico* in *Drosophila*, and *Ir* in mouse) are associated with an increase/decrease in resistance to oxidative stress [37-44] (Table 2). Mutational inactivation of the insulin/IGF-1 pathway extends life-span by blocking phosphorylation of the FOXO family of forkhead transcription factor and rendering it constitutively transcriptionally active [28,29,45,46]. Indeed, genes that promote DNA-damage repair (GADD45a) and oxidative protection (Mn-SOD and catalase) are up-regulated and genes promoting cell cycle progression (cyclin D) are down-regulated by activation of the *daf-16* forkhead transcription factor [47]. There is some evidence that $p66^{shc}$ may regulate activity of mammalian forkhead ortholog FOXO3a (also known as FKHRL1) and this is in turn may lead to an increase in Mn-SOD and catalase [48,49].

Of particular interest, insulin/IGF-1 signaling in neurons alone, but not muscle or intestinal signalling, is sufficient to specify *C. elegans* life-span, which points to the nervous system as a central regulator of organism longevity [50]. A direct evidence showing the relationship between pro-longevity signaling and neuroprotective adaptation is that long-lived insulin/IGF-1 mutants are resistant to neurodegeneraton in a model of Huntington disease [51]. However, it has been shown that IGF-1 is a potent neurotrophic polypeptide and declining levels of serum IGF-1 levels contribute to age-associated brain impairments and brain Aβ pathology of AD [52,53]. If IGF-1 has a positive influence on neuronal survival, a paradox has become apparent when a reduction or defect in IGF-1 signaling is shown to be beneficial to life-span extension, which may represent a discrepancy between brain aging and organism aging [54]. The paradoxical effects of IGF-1 signaling on brain function and organism longevity may be explained by a possible trade-off between growth/energy production and somatic maintenance [55].

(c) Caloric restriction and oxidative stress

Environmental manipulation, such as caloric restriction (CR), can also influence the rate of aging and extend life-span. For many decades, CR was the only regimen known to promote longevity in mammals. Indeed, CR is also associated with an enhanced resistance to oxidative stress in various species [56-58]. Additionally, animals subjected to CR appear to be less susceptible to a wide range of diseases, including diabetes, cancer, and vascular ischemia [59,60] as well as neurodegeneration in models of AD [61-64] and PD [65,66].

More recently, it has been demonstrated that signaling from central neurons mediates CR-induced longevity in *C. elegans* [67].

Life-span extension under CR and CR mimetics, such as resveratrol, requires the nicotinamide adenine dinucleotide (NAD) dependent deacetylase Sir2 (mammalian ortholog SIRT1) [68,69]. Resveratrol-induced Sir2/SIRT1 is found to be neuroprotective in nematode and mouse models of Huntington disease [70], in a slice culture model of PD [71], in cell-based models of AD and amyotrophic lateral sclerosis [72] and in a mouse model of AD [72]. SIRT1 appears to control the cellular response to stress by regulating the FOXO family of forkhead transcription factors that function as sensors of the insulin/IGF-1 pathway and the induction of SIRT1 by CR is attenuated by insulin/IGF-1 signaling [69,73]. Specifically, SIRT1 and FOXO3a form a complex in cells in response to oxidative stress and SIRT1 has a dual effect on FOXO3a function; SIRT1 increases FOXO3a's ability to induce cell arrest and resistance to oxidative stress but inhibits FOXO3a's ability to induce cell death [73]. Of note, other deacetylation targets of SIRT1 such as p53 and NF-κB might also play an important role in the cellular stress response [71].

In summary, recently expanding insights into the molecular mechanisms of organism longevity may open an avenue to an establishment of therapeutic strategy for age-associated neurodegenerative diseases. Pro-longevity gene products such as forkhead transcription factors and sirtuins are involved in the insulin-like signaling pathway and oxidative stress resistance against aging. An approach that enhances the pro-longevity

signaling, such as CR or CR mimetics, may be promising for the prevention and treatment in age-associated neurodegenerative diseases.

III.2 Association of Oxidative Stress with Disease-Causing Genetic Mutations in AD and PD

Not only advanced age but also genetic mutations causing AD and PD are associated with oxidative stress. Recently, an increasing number of *in vitro* and *in vivo* studies have suggested that oxidative stress has an involvement in autosomal dominant familial AD with mutations in amyloid β protein precursor (AβPP), presenilin-1 (PS-1), or presenilin-2 (PS-2) gene. Indeed, increased oxidative stress, elevated vulnerability to oxidative stress-induced cell death and/or reduced antioxidant defences have been demonstrated in: (i) cell lines expressing mutant human AβPP and/or PS-1, or PS-2 [74-78]; (ii) transgenic mice expressing mutant human AβPP and/or PS-1 as well as knock-in mice expressing mutant human PS-1 [79-88]; (iii) fibroblasts and lymphoblasts from familial AD patients with AβPP or PS-1 gene mutations [89]; and (iv) cerebral cortex of autopsied brain samples from patients with AβPP or PS-1 gene mutations [90,91].

Recent studies suggests that several genes linked to autosomal recessive familial PD, i.e., Parkin, PTEN induced putative kinase 1 (PINK-1), and DJ-1 normally have a neuroprotective role against oxidative stress and mutations in these genes impair the anti-oxidative ability. This aspect is supported by studies on (i) cell lines expressing mutant human Parkin [92-94], PINK-1 [95], or DJ-1 [96-99]; (ii) *Drosophila* model with PINK-1

or DJ-1 knock down/knock out and insertion of the human mutant [100-103]; and (iii) DJ-1 deficient mice [104].

III.3 Association of Oxidative Stress with Risk Factors for AD and PD

The possession of one or both apolipoprotein Eε4 (APOEε4) alleles, the major genetic risk factor for early- to late-onset sporadic and familial AD is associated with oxidative stress. *In vitro*, apoE shows allele specific antioxidant activity, with apoE2 the most effective and apoE4 being the least effective [105]. *In vivo*, APOE knockout male mice with human APOEε4 alleles have shown an increased level of oxidized lipid in the brains compared to APOE knockout male mice with human APOEε3 alleles [106]. Indeed, oxidative damage in an APOE genotype-dependent manner has been demonstrated in autopsied brain samples of AD patients [107-109].

Medical risk factors for AD include traumatic brain injury, cerebral infarcts, diabetes mellitus, hypertension, hypercholesterolemia, and hyperhomocysteinemia [110-114]. Environmental and lifestyle-related risk factors for AD include aluminum exposure, high calorie/fat intake and overweight, lack of exercise, and lack of intellectual activities [115-120]. Traumatic brain injury, exposure to metals (aluminum, copper, iron, lead, manganese, mercury, and their combination), exposure to pesticides and herbicides, and high calorie intake are associated with an increased risk of PD [121-123]. Indeed, all these risk factors are associated with an increase in oxidative stress [24,124-130]. With this notion, it is not surprising that agents or nutrients inhibiting free radical formation reduce the incidence of

AD and PD. Indeed, not only agents or nutrients such as vitamins B_6, C, and E, β-carotene, flavonoids and folate, but also estrogen, nonsteroidal anti-inflammatory drugs, statins, n-3 polyunsaturated fatty acids, and wine have been proven to have an antioxidant activity [131-135] and to reduce the incidence of AD [136-145]. Vitamins B_6 and E, nonsteroidal anti-inflammatory drugs, and unsaturated fatty acids may also be associated with a reduced risk of PD [146-151]. Furthermore, not only CR but also exercise and intellectual activity prove to promote neuronal survival through enhancement of endogenous anti-oxidative defence, including increased production of Cu/Zn-SOD, Mn-SOD, glutathione peroxidase, and catalase, and decreased oxidative stress in experimental animals [24,152].

Known genetic mutations and risk factors for AD and PD that cause or promote oxidative damage as well as agents, nutrients, and behavior that prevent or attenuate oxidative damage are summarized in Fig. 1. This evidence strongly suggests that oxidative stress is universally involved in the pathogenesis of AD and PD, especially upstream of the pathological cascade. Of particular interest, several agents and nutrients such as vitamin E, nonsteroidal anti-inflammatory drugs, the metal chelator clioquinol, melatonin, n-3 polyunsaturated fatty acids (docosahexaenoic acid), the curry spice curcumin, and the red wine Cabernet Sauvignon are capable to reduce the levels of Aβ and/or Aβ deposition in brains of transgenic animal models of AD [151-162]. Also, behavioural and environmental interventions such as CR, high activity under environmental enrichment, and voluntary exercise show the same effect on the Aβ pathology in brains of the AD model as the above substances [61-63,163,164].

III.4 Involvement of Oxidative Stress at an Early Stage of Neurodegeneration in AD and PD

An early involvement of oxidative stress in the pathogenesis of AD is demonstrated more directly by recent studies on cell culture models and transgenic animal models, as well as biological fluid and post-mortem brain samples from patients with AD at various stages of progression, young patients with Down syndrome, and subjects with mild cognitive impairment (MCI). We selected an *in situ* approach to identify markers of nucleic acid oxidation and protein oxidation in post-mortem brain samples [165-167]. Surprisingly, the oxidative damage not only is more prominent in AD cases with lesser amounts of Aβ deposition or shorter disease duration [166] but also oxidative damage precedes Aβ deposition in a series of Down syndrome brains, a model of AD neuropathology with known predictable chronology [167]. Our observation corresponds with the results of increased nucleic acid oxidation in cerebrospinal fluid from AD cases, in which the shorter the disease duration, the greater the oxidative damage [168]. Moreover, individuals with MCI who, at least in part, represent the prodromal stage of AD show significantly increased levels of nucleic acid oxidation, protein oxidation, and lipid peroxidation in post-mortem brain samples [169-174] and in peripheral samples [175,176] as well as decreased levels of plasma antioxidants [177,178].

These data, obtained from human subjects, clearly indicate an early involvement of oxidative stress in AD pathogenesis, which is supported by the experimental studies using

cell culture models and transgenic animal models of AD. Increased lipid peroxidation or protein oxidation precedes Aβ plaque deposition or Aβ fibril formation in transgenic mouse or *C.elegans* model of AD amyloidosis [179,180]. Furthermore, increased nitration of Mn-SOD and decreased Mn-SOD activity occur prior to Aβ plaque formation in AβPP/PS-1 double kock-in mouse model of AD [181]. Indeed, oxidative stress induces intracellular Aβ accumulation and tau phosphorylation in cell cultures [182-184], and vitamin E reduces Aβ and tau lesions in transgenic animals [153,185]. Furthermore, dietary copper stabilizes brain copper/zinc superoxide dismutase (SOD) activity and reduces Aβ production in AβPP transgenic mice [186]. Moreover, AβPP mutant mice crossed with Mn-SOD heterozygous knockout mice show increased Aβ plaque deposition in the brain [187].

Several lines of evidence support an early involvement of oxidative stress also in PD. Studies demonstrating oxidative dimmer formation as the critical rate-limiting step for fibrillogenesis of α-synuclein have revealed that overproduction of ROS and/or impairments of cellular anti-oxidative mechanisms are primary events in the initiation and propagation of PD [188]. Experimentally, α-synuclein can be induced by oxidative stress in rat hippocampal astrocytes [189]. In a human study, a reduced level of glutathione is found in brains of patients with incidental Lewy body disease, which is supposed to represent pre-symptomatic PD [190]. In the substantia nigra of patients with PD, there is an increase of 176% in the level of total iron content, with a shift of the Fe(III)/Fe(II)-ratio in favor of Fe(III) [191]. Data from transcranial ultrasound studies imply that iron accumulation

occurs very early in the disease [192]. Of note, an increased level of iron leads to an amplification of ROS via the Fenton reaction. Furthermore, a primary role of mitochondrial dysfunction and oxidative damage in PD is supported by an animal model of PD with chronic infusion of the complex I inhibitor, rotenone. In this model, the infusion of rotenone produces a selective loss of substantia nigra dopaminergic neurons as well as cytoplasmic α-synuclein-immunoreactive inclusions closely resembling Lewy bodies [193]. A subsequent *in vitro* experiment with rotenone clearly indicates that the mechanisms of the neuronal loss and the inclusion formation involve oxidative damage [194]. Indeed, evidence for mitochondrial dysfunction in the substantia nigra of PD patients comes from a decrease in complex I activity and an increase in mitochondrial deletion/rearrangements [195,196]. Therefore, mitochondrial dysfunction and metal dysregulation are key features associated with oxidative insult in PD, that are common to the pathophysiology of AD [197-200].

III.5 Aberrant Cell Cycle Re-entry in AD and PD

The *harlequin* mutant mouse showing progressive degeneration of cerebellar and retinal neurons provided a genetic model of oxidative stress-mediated neurodegeneration with a direct connection between cell cycle re-entry and oxidative stress in the aging central nervous system [201]. In this model, oxidative DNA damage is likely to precede cell cycle re-entry, while the exact mechanism(s) by which oxidative stress induces cell cycle abnormalities in post-mitotic neurons is unknown. Recently, a *Drosophila* model of human

tauopathy shows that oxidative stress acts to enhance tau-induced cell cycle activation and cause subsequent neurodegeneration [202]. On the basis of studies of mitogenic and oxidative stress signaling pathways in AD, it has been suggested that although either oxidative stress or abnormalities in mitotic signalling can independently serve as initiators in the pathological cascade of neurodegeneration, both processes are necessary to propagate the pathogenesis (*the two-hit hypothesis*) [203,204].

In vulnerable neurons in AD, various components of the cell cycle machinery are activated; namely, cyclin-dependent kinases, cyclins, cyclin-dependent kinase inhibitors, and proliferation-associated nuclear proteins [205,206]. Interestingly, some of the cell cycle-related proteins are expressed in 5-10% of neurons in the vulnerable regions not only in patients with AD but also in MCI cases [207]. These findings suggest that cell cycle events are involved at an early stage of neurodegeneration and that cell cycle-induced death should be abortive in the absence of actual completion at least for months, if not years. Remarkably, recent cellular and animal experiments have directly demonstrated that aberrant cell cycle activation in neurons induces AD-type pathological changes. In primary cortical neurons with adenoviral-mediated expression of c-MYC and Ras, cell cycle re-entry in the neurons leads to tau phosphorylation and conformational changes [208]. Furthermore, in transgenic mice with forced cell cycle activation in neurons via expression of the simian virus 40 T antigen, NFT-like tau accumulation and diffuse plaque-like deposits of Aβ are observed in the brain [209]. In transgenic mice expressing non-mutant human tau, the animals exhibit NFT formation and extensive neuronal death, and that the

neurodegeneration is independent of NFT formation but actually involves re-expression of cell cycle regulatory proteins [210].

Compared with AD, there are fewer reports on cell cycle dysregulation in PD. However, there is increasing evidence that vulnerable neurons in PD also activate the molecular cell-cycle program. α-synuclein over-expression in PC12 cells is demonstrated to increase the levels of phosphorylated extracellular signal-regulated kinases, with subsequent enhancement of proliferation rate and enrichment of the cells in the S phase of the cell cycle [211]. In the pos-tmortem substantia nigra of PD patients, cyclin B immunoreactivity is found in Lewy bodies [211], and phosphorylated retinoblastoma protein and E2F transcription factor that trigger cell cycle progression as well as E2F-inducible proliferating cell nuclear antigen are observed in dopaminergic neurons [212,213]. The aberrant expression of E2F is demonstrated also in 1-methyl-4-phenylpyridinium (MPP^+)–treated cultures and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated mice, cellular and animal models of PD [213]. Finally, inhibition of the cell cycle-related kinase cdk2 or deficiency of E2F provides some neuroprotection in the MPTP mouse model of PD [213,214].

Of note, genetic factors of AD and PD are likely to be associated with cell cycle events. AβPP, PS-1, and PS-2 have important roles in cell cycle control and the disruption caused by familial AD mutations may impair the cell-cycle control [204]. Cyclin E is a substrate of the parkin ubiquitin ligase complex and parkin deficiency potentiates the accumulation of cyclin E [215].

VI. PATHOLOGICAL HALLMARKS AND NEURONAL SURVIVAL RESPONSE

VI.1 Pathological Hallmarks: Pathogenic, Incidental, or a Beneficial Coping Response?

AD is defined pathologically by extraneuronal deposition of Aβ senile plaques and cytoplasmic inclusion of NFTs composed of tau. PD is defined pathologically by cytoplasmic inclusion of Lewy bodies composed of α-synuclein. From the time of their original description, a major focus has been to understand the role that these lesions play in the pathogenesis of AD and PD. However, it is still questionable whether senile plaques and/or NFTs in AD or Lewy bodies in PD cause associated neurodegeneration or neurological, behavioral and cognitive deficits that accompany the disease.

(a) Huntingtin inclusion bodies

There is recent evidence that the inclusions found in the affected brain may, in fact, be protective. In a cellular model of Huntington's disease, a neurodegenerative disorder caused by an abnormal polyglutamine expansion, the formation of neuronal inclusion bodies has been demonstrated to be associated with improved neuronal survival and decreased levels of mutant huntingtin throughout the neuron. Inclusion bodies may sequester the diffuse form of mutant huntingtin. Indeed, many neurons die without forming an inclusion body. Thus, the formation of neuronal inclusion bodies can function as a coping response to toxic mutant huntingtin [216]. Similarly, the notion that inclusion

protects cells from deleterious effects of misfolded proteins is supported in a cellular model of spinobulbar muscular atrophy, a neurodegenerative disease caused by an expanded polyglutamine tract [217]. These interesting findings encourage us to reconsider roles of intraneuronal and even extraneuronal aggregates of specific protein in neurodegenerative disorders.

(b) Senile plaques and NFTs

Senile plaques and NFTs are present in a considerable percentage of brains of cognitively normal elderly subjects. Surprisingly, a study investigating autopsied subjects aged between 69 and 100 who were cognitively normal revealed that 49% of those normal subjects met the Khachaturian criteria for AD based on senile plaque density, 25% met the CERAD criteria based on senile plaque density, and 24% were in stages IV-VI of the Braak and Braak staging of AD based on NFT density [218]. Furthermore, it is well known that there is no correlation, or at best a poor correlation between neuronal loss and senile plaque density as well as between disease severity and senile plaque density in AD [219]. Accordingly, AβPP transgenic mice showing massive deposition of Aβ plaques in brains lack consistent widespread neuronal loss [220]. By contrast, neuronal loss and clinical severity correlate with NFT density. However, the amount of neuronal loss largely exceeds the amount of NFTs [8]. In a tau transgenic mouse in which the overexpression of mutant human tau can be regulated by tetracycline, turning off tau expression halts neuronal loss and reverses memory defects. But surprisingly, in this model, NFTs continue to accumulate,

suggesting that NFTs are not responsible for neurodegeneration [221]. This result is consistent with reports on transgenic mice expressing nonmutant human tau as well as transgenic *Drosophila* expressing wild-type or mutant form of human tau, in which neurodegeneration or neuronal death occurs independently of NFT formation [210,222]. In a human study, an ultrastructural analysis demonstrated that a reduction in number and total length of microtubules seen in pyramidal neurons in AD was unrelated to the presence of NFTs [223]. Indeed, neurons with NFTs are estimated to be able to survive for decades [224], which suggests that NFTs themselves are not obligatory for neuronal death in AD.

(c) Lewy bodies

The aspect of the inclusions in the brain of neurodegenerative diseases that protect cells from deleterious effects of misfolded proteins is suggested not only by cellular models of polyglutamine diseases [216,217,225] but also by a cellular model of PD [225]. In the cellular model of PD, a compound that promotes α-synuclein inclusion formation prevents α-synuclein-mediated toxicity [225]. In fact, the appearance of Lewy bodies is not uncommon in brains of the normal elderly, which is not necessarily linked with neuronal loss [226]. Incidental Lewy bodies in brains from individuals without clinical PD show age specific prevalence rising from 3.8 to 12.8% between the sixth and ninth decade [227]. Because the prevalence of PD has been estimated at 0.6% for individuals between the ages of 65 and 69 years and 2.6% for those between 85 and 89 years [228], the prevalence of incidental Lewy bodies in the population is much higher than that of PD. In an

investigation of the prevalence of Lewy body pathology in a community-based population, 15.1% of non-demented and non-PD subjects show Lewy body formation in the cortical and subcortical regions. Surprisingly, there is no significant difference in Lewy body density scored by the consensus guideline between these subjects with incidental Lewy bodies and patients with Lewy body dementia [229]. Indeed, analysis of surviving nigral neurons that lack or contain Lewy bodies show no quantifiable difference in viability estimated by cell size, nucleolar size, and messenger RNA level of the low molecular weight neurofilament subunit [230,231]. Furthermore, mutations in the parkin gene cause juvenile PD exhibiting nigral degeneration largely in the absence of Lewy bodies [232]. In α-synuclein transgenic animals, over-expression of α-synuclein causes the formation of inclusions but does not always cause neuronal loss [233,234].

Therefore, senile plaques and NFTs in AD and Lewy bodies in PD may not be indispensable for death of vulnerable neurons. Interestingly, recent findings in a cellular system are consistent with a toxic oligomer hypothesis or toxic protofibril hypothesis, which provides ideas that oligomer or protofibril of specific proteins such as Aβ or α-synuclein may be responsible for cell death and that the fibrillar form being typically observed at autopsy may actually be neuroprotective [235,236]. Giving our consideration to the chronological primacy of oxidative stress in the pathological cascade, we cannot exclude the possibility that the processes of the pathology formation are involved in compensatory changes against oxidative insult of AD and PD.

VI.2 Possible Protective Function of Aβ against Oxidative Stress

Although high concentrations of Aβ, in a micromolar range, can lead to oxidative stress in various biological systems [237], it is apparent from cell [182], animal [153,179-181,186,187] and human [167] studies that oxidative stress chronologically precedes Aβ deposition. Moreover, increases in density of Aβ plaque deposition are associated with decreased levels of nucleic acid oxidation in neurons in post-mortem brains from patients with sporadic and familial AD and Down syndrome [91,166,167]. These findings indicate that the process of Aβ plaque formation is a neuronal protective response against oxidative stress.

Recently, *in vitro* and *in vivo* studies have demonstrated an antioxidant activity of Aβ. Monomeric $A\beta_{1-40}$ and $A\beta_{1-42}$ have been shown to protect cultured neurons from iron and copper induced toxicity [238]. Remarkably, co-injection of iron and $A\beta_{1-42}$ into rat cerebral cortex is significantly less toxic than injection of iron alone [239]. Furthermore, addition of physiological concentrations (in a low nanomolar range) of $A\beta_{1-40}$ and $A\beta_{1-42}$ has been shown to protect lipoproteins from oxidation in cerebrospinal fluid and plasma [240]. These Aβ peptides fail to prevent metal-independent oxidation and $A\beta_{25-35}$ lacking metal binding site located N-terminal part (histidine at positions 6, 13, and 14, and tyrosine at position 10) is less effective at inhibiting oxidation. Therefore, it is likely that the mechanism by which Aβ inhibits oxidation is via chelating metal ions [240]. In concord, we have recently demonstrated that *in vitro* Aβ shows a potent inhibitory activity in Cu(II)-

mediated generation of hydroxyl radical and 4-hydroxynonenal [241,242]. Indeed, copper, iron, and zinc are elevated in the rims and cores of Aβ plaques in post-mortem brains of AD [243,244]. We suppose that chelation of redox-active copper and iron is a most important mechanism of the protective function of Aβ, and that an elevation of zinc, a redox-inert antioxidant, may be a homeostatic response to oxidative stress, which subsequently accelerates the formation of Aβ plaques [245]. Zinc binding has been shown to cause conformational changes in the Aβ peptide towards a more structured state. Zinc binding-induced Aβ aggregation might also result from the formation of intermolecular (histidine-zinc-histidine) bridges [246]. The high affinity of Aβ for copper and zinc, its strong redox potential and recruitment of O_2 are features that resemble the electrochemistry of a genuine antioxidant, Cu/Zn-SOD [247].

By this logic, therefore, AD kindreds with AβPP mutations lose effective antioxidant capacity (as a result of mutation-driven protein dysfunction), whereas the extensive Aβ deposits themselves are signatures not of neurotoxicity *per se* but of oxidative imbalance and an oxidative stress response. This idea is consistent with the findings that (i) the prevalence of biochemically detectable Aβ and immunocytochemically detectable Aβ deposits in cognitively normal aging individuals starts to increase around the age of forty and fifty, respectively [248,249], and (ii) a large percentage of cognitively normal elderly contain Aβ loads equivalent to those of patients with AD [218]. Conversely, Aβ is not always present in the brains of cognitively normal elderly. Whether this observation

indicates that some individuals have efficient endogenous antioxidant defence systems and thus age more effectively, or whether such individuals may have supplemented their diets with antioxidants throughout their life-span, compensating for age-related declines in antioxidant defences, remains to be elucidated [250,251]. If the process of Aβ deposition is closely associated with antioxidant function, this process will be recruited during times when oxidative stress is high and the endogenous antioxidant-defences are compromised. On the other hand, if this system is efficient and/or is supported by exogenous antioxidant supplementation, the antioxidant effects of Aβ may not be necessary.

VI.3 Possible Protective Function of Tau against Oxidative Stress

The aspect of Aβ that actually plays an important role in antioxidant defences may be able to apply equally to tau. Cellular [183], animal [185], and human [167] studies suggest that oxidative stress chronologically precedes NFTs formation. Oxidative stress activates several kinases including glycogen synthase kinase-3 and mitogen-activated protein kinases, which are activated in AD and are capable of phosphorylating tau. Once phosphorylated, tau becomes particularly vulnerable to oxidative modification and consequently aggregates into fibrils [252]. Therefore, NFT formation is likely to be a result of neuronal oxidation. Furthermore, in neurons of post-mortem AD brains, a decrease in oxidative damage in nucleic acids (mainly cytoplasmic RNAs) is associated with the presence of NFTs, as determined by a comparison of neurons with and without NFTs, an observation that is particularly striking in light of the abundance of RNA on NFTs [166]. One possible

mechanism as to how NFT formation opposes oxidative stress may be associated with metal-binding capability of tau, in common with the capability of Aβ. Redox-active iron accumulation is strikingly associated with NFTs [252] and tau is found capable of binding to iron and copper and thereby possibly exerts antioxidant activities [254].

Additionally, tau and neurofilament proteins that are modified by lipid peroxidation products and carbonyls [255-258] may work as a physiological "buffer" against toxic intermediates derived from oxidative reactions and thereby enhance neuronal survival. Although tau and neurofilaments are cytoskeletal proteins with long half lives, the extent of carbonyl modification is comparable in young and aged mice. as well as along the length of the axon [259]. A logical explanation for this finding is that the oxidative modification of cytoskeletal proteins is under tight regulation. A high content of lysine-serine-proline (KSP) domains on both tau and neurofilament protein suggests that they are uniquely adapted to undergoing oxidative attack. Exposure of these domains on the protein surface is effected by extensive phosphorylation of the serine residues, resulting in an oxidative "sponge" of surface-accessible lysine residues, which are specifically modified by products of lipid peroxidation [259]. Because phosphorylation plays this pivotal role in redox balance, it is not surprising that oxidative stress leads to phosphorylation through activation of MAP kinase pathways [203,260,261] nor that conditions associated with chronic oxidant stress, such as AD, are associated with extensive phosphorylation of cytoskeletal elements. Indeed, other neurological conditions in which phosphorylated tau and neurofilament protein accumulations occur (such as progressive supranuclear palsy,

corticobasal degeneration, and frontotemporal dementia) also show evidence of oxidative adducts on these proteins [262,263]. This protective role of tau phosphorylation explains the finding that embryonic neurons that survive after treatment with oxidants have more phospho-tau immunoreactivity relative to neurons under degeneration [264]. Further, the induction of heme oxygenase, an antioxidant enzyme (which cleaves the oxidant heme) reduces tau expression and phosphorylation, indicating a crucial role for tau in redox homeostasis [258,265]. Supporting this notion, there is reduced oxidative damage in neurons with tau accumulation that we suspect is due to the antioxidant function of phosphorylated tau.

VI.4 Possible Protective Function of α-synuclein against Oxidative Stress

α-synuclein also may play a protective role against oxidative stress. There are *in vitro* [188,194] and *in vivo* models [193] suggesting a primary role of oxidative stress in α-synuclein aggregation. The herbicide paraquat causes oxidative stress and α-synuclein aggregation as well as nigral neurodegeneration in mouse brains, and surprisingly, mice overexpressing α-synuclein display α-synuclein aggregation but are completely protected against neurodegeneration [266]. Similarly, in an α-synuclein-transfected neuronal cell line under oxidative stress conditions, increased α-synuclein expression protects cells from oxidative stress via inactivation of c-Jun N-terminal kinase, a member of the mitogen-activated protein kinase family [267]. More specifically, it is proposed that α-synuclein can limit oxidative damage to cells involving its methionines (at positions 1, 5, 116, and 127)

serving as a natural scavenger of ROS [268]. Furthermore, Lewy bodies can sequester redox-active iron [269], being similar to senile plaques and NFTs. Like Aβ, at nanomolar concentrations but not at the micromolar scale, α-synuclein protects neurons against oxidative stress in cellular models where an activation of PI3/Akt signalling pathway or an induction of heat shock protein 70 is involved [270,271]. The protection mechanism requires the presence of the C-terminal domain of α-synuclein [271].

VI.5 Oligomeric Aβ, Tau and α-synuclein, and Their Proteotoxicity

As we have reviewed here, every disease-specific protein potentially plays a protective role against oxidative stress. However, the efficiency of the protective function may be dependent on the concentrations or the aggregation state of the protein [238,240,270,271]. Recently, an increasing body of evidence has been collected to support the hypothesis that oligomers, not monomers or fibrils, represent the toxic form of Aβ, tau, and α-synuclein [235,236,272-276]. Interestingly, the aggregation-mediated toxicities of Aβ and α-synuclein are likely modified by insulin/IGF-1 signaling or sirtuins, which suggests a link between neurodegeneration and stress responses in aging organism including antioxidant defence [277,278]. *In vitro*, an oxidative stress metabolite 4-hydroxynonenal can promote formation of Aβ protofibrils and oligomeric α-synuclein [279,280]. On the contrary, Aβ oligomers can induce neuronal oxidative stress in a cell culture experiment [281]. More detective work is required before this small intermediate fraction (oligomers) can be convicted as the real culprit. However, if only the oligomeric fraction is detrimental and

monomeric peptides *per se* as well as mature fibrils are protective, therapeutic approaches targeting the protein should be highly specific for the oligomeric aggregation state. Therefore, further study is required to adequately assess the relationship between oxidative stress and oligomer formation, which may provide an important clue to early therapeutic intervention in neurodegenerative disorders.

V. CONCLUSIONS

Most of the known genetic, medical, environmental, and lifestyle-related factors of AD and PD are associated with increased oxidative stress. Moreover, patients at the preclinical stages of AD and PD as well as cellular and animal models of the diseases provide consistent evidence that oxidative insult is a significant early event in the pathological cascade of AD and PD. In contrast to the general aspects of the pathological hallmarks, aggregation of the disease-specific protein may be involved in a compensatory response against the oxidative insult. Although a common underlying mechanism for the protective response is presently obscure, sequestration of redox-active metals by the disease-specific structures may be associated with the neuronal survival response against oxidative insult.

Despite the abundant evidence for an involvement of oxidative insults as an early-stage of the neurodegenerative process, interventions such as the administration of one or a few antioxidants have been, at best, modestly successful in clinical trials. The complexity of the metabolism of ROS suggests that such interventions may be too simplistic and requires more integrated approaches not only to enrich the exogenous antioxidants but also to up-

regulate the multilayered endogenous anti-oxidative defence systems [5,6]. Recently expanding knowledge of the molecular mechanisms of organism longevity indicate that pro-longevity gene products such as forkhead transcription factors and sirtuins are involved in the insulin-like signaling pathway and oxidative stress resistance against aging. An approach that enhances the pro-longevity signaling, which is possibly realized by CR or CR mimetics not only in mammalian models [282,283] but also in humans [284], may be promising as anti-oxidative strategy against age-associated neurodegenerative diseases.

VI. ABBREVIATIONS

Aβ	=	amyloid-β
AβPP	=	amyloid β protein precursor
AD	=	Alzheimer disease
APOE	=	apolipoprotein E
CR	=	caloric restriction
FOXO	=	forkhead transcription factor
IGF-1	=	insulin-like growth factor 1
MCI	=	mild cognitive impairment
MPTP	=	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
NFTs	=	neurofibrillary tangles
PD	=	Parkinson disease
PINK-1	=	PTEN induced putative kinase 1

PS-1	=	presenilin-1
PS-2	=	presenilin-2
ROS	=	reactive oxygen species
SOD	=	superoxide dismutase

VII. REFERENCES

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Figure Legend

Figure 1. Genetic, medical, environmental and lifestyle-related factors for AD and PD: relation to oxidative stress.

Several known genetic mutations linked to familial AD and PD and risk factors for sporadic AD and PD are associated with an increase of oxidative stress. In contrast, several agents and nutrients that are known to reduce the incidence of AD and/or PD have antioxidant property *per se* or help to prevent/reduce free radical generation/propagation. Low calorie diet as well as physical and intellectual activities are suggested to enhance the production of antioxidant enzymes in the brain. See the text for details.

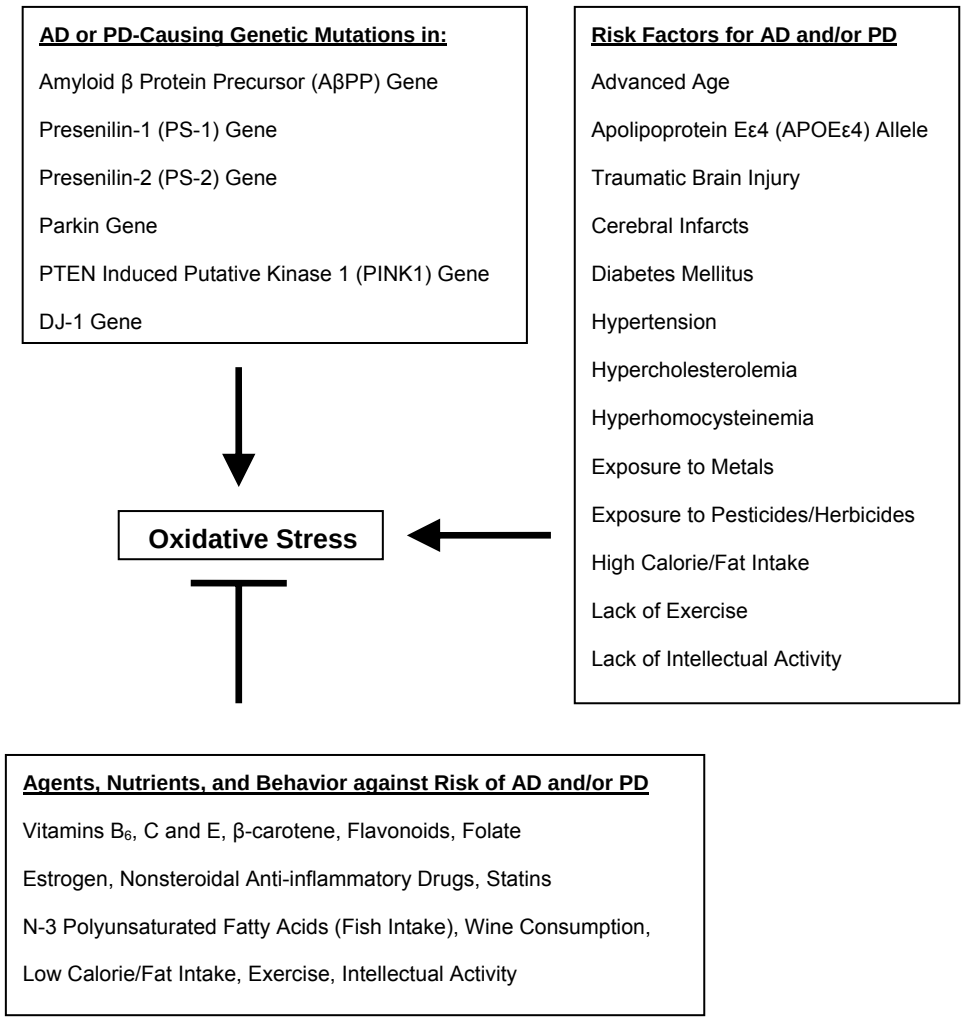

Fig. 1 Nunomura et al.

Table 1. Cell death in development (apoptosis) and in chronic neurodegeneration

	Apoptosis[a)]	Neuronal death in AD and PD[b)]
Time for 40% cell loss	3 days	ca. 10 years
% neuronal population undergoing apoptosis or degeneration	5-6 %[c)]	Unknown

[a)] in the lateral motor column of the chick embryo [10]; [b)] in the superior temporal sulcus of AD [8] and the pars compacta of the caudal substantia nigra of PD [9]; [c)] by counting pyknotic cells

Table 2. Gene Mutations that Alter Life-span in Diverse Organisms and Their Relevance to Oxidative Stress Resistance

gene	gene product	*life-span*	changes in oxidative stress resistance	ref.
nematodes (Caenorhabditis elegans)				
daf-2	insulin/IGF-1-receptor	***extension***	enhanced resistance (paraquat, UV, heat); increase in mRNA levels of Mn-SOD	37
age-1	phosphatidylinositol-3 kinase	***extension***	enhanced resistance (H_2O_2, paraquat, UV, heat); increase in Cu/Zn-SOD and catalase activities	38, 39
daf-16	forkhead transcription factor	***suppression of longevity and resistance conferred by mutations in daf-2 or age-1***		40
mev-1	a subunit of succinate dehydrogenase cytochrome b of mitochondrial complex II	***shortening***	increased rate of mitochondrial ROS production; hypersensitive to high O_2 concentration and paraquat	32
clk-1	an enzyme involved in ubiquinone (coenzyme Q) biosynthesis	***extension***	decreased ROS due to an accumulation of demethoxyubiquinone, a strong ROS scavenger; enhanced resistance (UVC)	33
isp-1	iron sulfur protein of mitochondrial complex III	***extension***	decreased rate of mitochondrial ROS production; enhanced resistance (paraquat); increase in mRNA levels of Mn-SOD	34
fruit flies (Drosophila melanogaster)				
InR	insulin/IGF-1-receptor	***extension***	increase in Cu/Zn-SOD activity	41
chico	insulin receptor substrate	***extension***	increase in overall SOD activity	42
mth	G-protein-coupled receptor (?)	***extension***	enhanced resistance (paraquat, UV, heat)	43
mouse (Mus musculus)				
Ir	insulin receptor	***extension***	enhanced resistance (high O_2 concentration, paraquat); increase in Mn-SOD activity	44
p66^{shc}	cytoplasmic signal transduction adaptor protein	***extension***	decreased rate of mitochondrial ROS production; enhanced resistance (H_2O_2, paraquat, UV)	35, 36

IGF-1, insulin-like growth factor 1; **ROS**, reactive oxygen species; **SOD**, superoxide dismutase; **UV**, ultraviolet light