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Overview ：The Role Of Reactive Oxygen Species In Pathogenesis Of Neurodegenerative Disease

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Abstract: ***Reactive oxygen species (ROS) plays a role in many neurodegenerative diseases. ROS, a family of compounds, not only can damage cellular macromolecules, but also can be a signal of Mitochondrial in many pathway including gene expression, mitosis, auto phage, etc. ROS radicals formed within mitochondria and then participated mitochondrial biogenesis program. Although a high level of oxidative stress is critical damage, ROS also plays an important role in regulation of autophage. ROS mediated autophage is widely involved in the pathogenesis of neurodegenerative diseases including Alzheimer's, Parkinson's, and Huntington's diseases. However, the underlying mechanisms of ROS's role in neurodegenerative remain largely undefined. In this article we briefly discuss the mechanisms of ROS-related autophage in neurodegenerative diseases.***

Keywords: Mitochondria, Oxidative Stress, reactive oxygen species, aging, antioxidants, Alzheimers disease.

I. INTRODUCTION

Reactive oxygen species (ROS) are a group of compounds derived from the incomplete reduction of molecular oxygen. They are highly reactive molecules that consist of a number of diverse chemical species including superoxide anion($O_2^{\cdot-}$), hydroxyl radical (-OH), and hydrogen peroxide (H_2O_2). Primary physiological source of ROS is cellular respiration. During respiration, electrons are passed through four protein complexes (Complex I, II, III, and IV) which reside in the mitochondrial inner membrane. At normal physiological condition, ROS play an important role in cell proliferation; differentiation; apoptosis and some other metabolize activities. However, a small percentage of electrons can escape the electron transport chain prematurely, leading to incomplete reduction of molecular oxygen and formation of the superoxide anion O^{2-} [1]. But excessive ROS can induce the injury to the cell which leads to many diseases. As ROS are generated mainly as by-products of mitochondrial respiration, mitochondria are thought to be the primary target of oxidative damage and play an important role in aging. Especially their potential to cause oxidative deterioration of DNA, protein, and lipid, ROS has been implicated as one of the causative factors of aging [1]. Emerging evidence has linked mitochondrial dysfunction to a variety of age-related diseases, including neurodegenerative diseases and cancer. Details of the precise relationship between ROS-induced damage, mitochondrial dysfunction, and aging remain to be elucidated.

II. MITOCHONDRIA AND ROS PRODUCTION

Although ROS can be generated from different enzymatic reactions such as xanthenes oxidase, monoamine oxidase,

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paroxysmal fatty acyl CoA dehydrogenate, NADPH oxidase, cytochrome P450 dependent enzymes etc. and non-enzymatic reactions e.g. autoxidation of hemoglobin or catecholamine's, mitochondria are the major intracellular source of ROS [2,3]. The evidence that isolated mitochondria can produce ROS came as early as 1966 and following that many studies have verified the mitochondrial production of superoxide radicals and H_2O_2 in isolated preparations and in intact cells [4–6]. The general view is that the thermodynamically favourable leakage of electrons from reduced or partially reduced redox-proteins or other redox molecules of the respiratory chain to molecular oxygen results in the formation of superoxide radicals ($O_2^{\cdot -}$) which undergo dismutation reaction spontaneously or catalyzed by mitochondrial manganese superoxide dismutase (Mn SOD) to produce H_2O_2 which can be decomposed further by transition metals (Fenton's reaction) to give rise to highly reactive hydroxyl radicals [3,7]. The $O_2^{\cdot -}$ radicals can also react with mitochondria derived NO to generate toxic peroxynitrite radicals. The measurement of $O_2^{\cdot -}$ radicals or H_2O_2 in isolated mitochondria or sub mitochondrial particles has been done under different conditions and the results have often been fallaciously extrapolated by others to *in vivo* conditions [3,7]. Superoxide radical generation in isolated mitochondria essentially depends on available local oxygen concentration, the concentrations of reduced redox proteins and the second order rate constants of the reactions between oxygen and the redox proteins [3]. The true quantitative assessment of $O_2^{\cdot -}$ radical production by isolated mitochondria *in vitro*, however, is difficult because of its rapid conversion to H_2O_2 by Mn SOD, but the measurement of H_2O_2 production or rather its release in to medium under similar conditions is probably more accurate. Under *in vivo* conditions a true quantitative estimate of superoxide radical production by mitochondria is virtually impossible because of uncertainties in the measurement of different parameters that affect ROS production. However, mitochondrial transmembrane electrochemical gradient, $NADH/NAD^+$ ratio, QH_2/Q ratio and local concentration of oxygen are important determinants of *in vivo* ROS production in mitochondria [3]. It is also important to realize that steady state level of ROS will depend upon the balance between the rate of ROS production and ROS removal and mitochondria in fact can scavenge H_2O_2 at a significant rate [7]. The elaborate antioxidant defense system present in mitochondria comprising of antioxidant enzymes like Mn SOD, glutathione peroxidase, glutathione reductase, phospholipid hydroperoxide glutathione peroxidase and peroxiredoxins as also non-enzyme molecules like reduced glutathione, thioredoxins etc. can effectively scavenge the generated ROS [3,7,8]. The inter-membrane space of mitochondria also contains copper- and zinc-containing superoxide dismutase (Cu/Zn SOD) which can scavenge superoxide radicals released in to this space.

The formation of superoxide radicals in respiratory chain of mitochondria has been the subject of intense research and complex I of inner membrane is considered to be an important source, but other respiratory complexes such as complex III and complex IV along with enzymes like aconitase, α-ketoglutarate dehydrogenase, pyruvate dehydrogenase complex, glycerol-3-phosphate dehydrogenase, dihydroorotate dehydrogenase etc. also contribute to the process [3,7].

ROS mediated damage is too well-known and given the fact that mitochondria form the major source of intracellular ROS, it is expected that a simple cause and effect relationship would explain mitochondrial functional alterations during ROS overload under pathological conditions. The scenario, however, is much more complex, because of the involvement of ROS in different cell signalling pathways. Redox signalling leading to altered expressions of genes has caused a paradigm shift in our understanding of the role of ROS in cell physiology and pathophysiology and this aspect needs to be emphasized while analysing the effects of oxidative stress on mitochondrial functions [9]. Oxidative stress is generally considered as a somewhat uncontrolled process mediated by reactive free radicals including ROS attacking indiscriminately various biomolecules and damaging cellular organelles, but some of the members of ROS and RNS (reactive nitrogen species) may also, under basal conditions or during a low level of oxidative stress, perform as signalling molecules to induce expression of genes coding for antioxidant enzymes and proteins, phase II detoxification enzymes, amino-acid transporters and stress-response proteins [9,10]. These genes generally contain ARE (antioxidant responsive element) sequences in the promoter regions and are activated by several redox-sensitive transcription factors like AP 1 (activator protein 1), Nrf 1, Nrf 2 etc. [9–11]. These transcription factors remain in an inactive form in cytosol usually in combination with inhibitory proteins such as Nrf 2 remaining inactive in association with KEAP 1 (Kelch-like ECH-associating protein 1) which also promotes the degradation of Nrf 2 via ubiquitin-proteasome system [9–11]. Mitochondrial or extramitochondrial ROS, lipid oxidation products, electrophilic molecules or redox-state of the cell may lead to the dissociation of the transcription factor from the clutches of the inhibitory protein and translocation to the nucleus followed by the enhanced expressions of ARE (antioxidant response element) dependent genes [9–12]. For example, the oxidation of several critical cysteine residues in KEAP 1 by oxidants causes release of Nrf 2 from KEAP 1 and the former translocates and binds to ARE containing DNA sequences for which another specific cysteine (cys 506) residue of Nrf 2 in reduced form is needed [13]. It is plausible that the redox state of the cell may lead to oxidation of cys 506 with consequent diminished binding of Nrf 2 to DNA and down regulation of the genes [9,13]. The important proteins coded by ROS responsive genes include catalase, superoxide dismutase (SOD), glutathione peroxidase, glutathione reductase, glutathione-S-transferase, heme oxygenase, γ-glutamyl cysteinyl synthetase, thioredoxin etc., but it is not clear whether such redox-dependent gene expression occurs for mitochondrial proteins in general during oxidative stress [9,10,13]. Scattered reports have, however, indicated that oxidative stress can lead to elevated levels of mitochondrial transcription factors or other proteins of oxidative-phosphorylation machinery [14,15]. Further, mitochondrial biogenesis, which requires expression changes in many nuclear and mitochondrial genes, is modulated by ROS as discussed above, but it is still not established whether ROS signalling mediated by AP 1, Nrf 1, Nrf 2 etc. are also involved in the biogenesis process.

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III. ROS AND AUTOPHAGE

ROS Induces ATG4 Inactivation In response to starvation, oxidative stress is activated and induces the formation of ROS, especially H_2O_2, which serve as signaling molecules in the induction of autophagosomes by regulating the activity of ATG4. H_2O_2 could bind to the cysteine site of ATG4, forming reversible sulfuric acid or disulfide bonds that shield cysteine that can directly activate ATG4, and drive lipidation of LC3 (a mammalian ATG8 homolog), priming it for subsequent conjugation with phosphatidylethanolamine . This process is essential for autophagosome formation. After autophagosomes mature and fuse with lysosomes, the local environment changes to H_2O_2− deficiency, where ATG4 turns to an active state, and thus LC3 is delipidated and recycles once again[16].

ATG4 exists in the CNS, and so oxidative stress may influence the activity of ATG4 and induce autophagy. Atg4b/ATG4B has been cloned as a mammalian homolog of yeast ATG4 in humans and mice. Yoshimura et al found that mRNA levels of Atg4B are high in brain tissues, especially in the olfactory bulb, cerebellum,and retina[17]. Rodriguez-Muela et al. found that retinas from atg4b−/− mice show a clear reduction in LC3 lipidation and an increase in the expression of SQSTM1 (sequestosome 1) levels[18]. Compared with the control group, the number of living RGCs in atg4b−/− mice is also lower after axotomy, suggesting that ATG4 exerts a crucial function in the autophagy of retinas and RGCs.(as shown in fig.1)

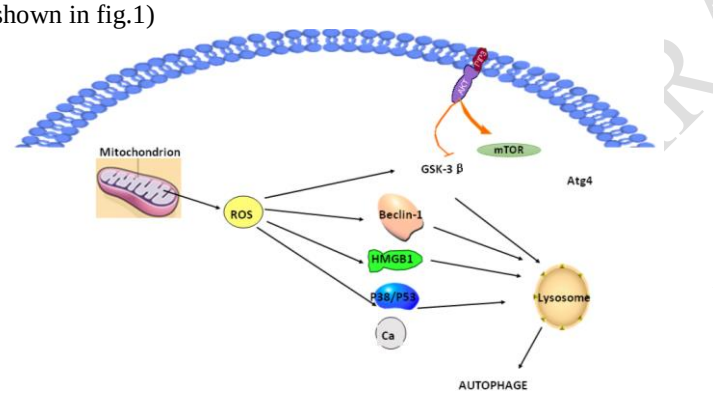

Figure 1: autophage signal pathway

IV. ROS-RELATIVE AUTO PHAGE IN NEURODEGENERATIVE DISEASES

ROS MEDIATED AUTO PHAGE IN AD

A heterogeneous class of disorders with a broad spectrum of complex clinical phenotypes has been linked to mitochondrial defect and oxidative stress [19, 20]. Particularly, mitochondria are thought to play an important role in the pathogenesis of age-associated neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, and Huntington's disease. This is not surprising as neurons are especially sensitive and vulnerable to any abnormality in mitochondrial function because of their high energy demand.

Alzheimer's disease (AD) is the most common form of dementia and often diagnosed in people over 65 years of age. AD is characterized by severe neurodegenerative changes, such as cerebral atrophy, loss of neurons and synapses, and selective depletion of neurotransmitter systems in cerebral cortex and certain subcortical region [21]. Mitochondria are significantly reduced in various types of cells obtained from patients with AD [22–24]. Dysfunction of mitochondrial electron transport chain has also been associated with the pathophysiology of AD [25]. The most consistent defect in mitochondrial electron transport enzymes in AD is a deficiency in cytochrome *c* oxidase [26, 27], which leads to an increase in ROS production, a reduction in energy stores, and disturbance in energy metabolism [28].

ROS MEDIATED AUTO PHAGE IN PD

Parkinson's disease (PD) is the second most common progressive disorder of the central nervous system, which is characterized prominently by loss of dopaminergic neurons in the substantia nigra and formation of intraneuronal protein aggregates [29]. The finding that exposure to environmental toxins, which inhibit mitochondrial respiration and increase production of ROS, causes loss of dopaminergic neurons in human and animal models leads to a hypothesis that oxidative stress and mitochondrial dysfunction are involved in PD pathogenesis [30]. Consistent with this notion, a significant decrease in the activity of complex I of the electron transport chain is observed in the substantia nigra from PD patients [31]. Furthermore, neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, which acts as an inhibitor of complex I, can induce parkinsonism in human, monkey, and rodent [32,33]. Genetic studies of *PINK1* and *PARKIN* further support the role of mitochondrial dysfunction in pathogenesis of PD [34,35]. Autosomal recessive mutations in *PINK1* and *PARKIN* are associated with juvenile Parkinsonism [36,37]. Studies in *Drosophila* have provided strong evidence that *PINK1* and *PARKIN* act in the same genetic pathway to control mitochondrial morphology in tissues with high energy demand and requirement of proper mitochondrial function, such as indirect flight muscle and dopaminergic neurons [38,39]. Consistent with the finding in *Drosophila*, primary fibroblasts derived from patients with *PINK1* mutations show similar abnormalities in mitochondrial morphology [40]. The morphologic changes of mitochondria can be rescued by expression of wild-type *PARKIN* but not pathogenic *PARKIN* mutants [41], suggesting that mitochondrial dynamics plays an important role in PD pathogenesis.

ROS MEDIATED AUTO PHAGE IN HD

Huntington's disease (HD) is another hereditary neurodegenerative disorder that affects muscle coordination and leads to cognitive decline and dementia. HD is caused by an autosomal dominant mutation in the Huntingtin (HTT) gene [42]. Morphologic defects of mitochondria, such as reduced mitochondrial movement and alterations in mitochondrial ultrastructures, have been observed in patients with HD or transgenic HD mouse models [43,44]. In addition, expression of mutant HTT leads to impaired energy metabolism, abnormal Ca^{2+} signaling and mitochondrial

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membrane potential, and drastic changes in mitochondrial ultrastructures [45,46]. Although the underlying molecular mechanism remains to be determined, it is recently proposed that mutant HTT conveys its neurotoxicity by evoking defects in mitochondrial dynamics, mitochondrial fission and fusion, and organelle trafficking, which in turn result in bioenergetic failure and HD-associated neuronal dysfunction [47].

Mitochondrial dysfunction and increased oxidative damage are often associated with AD, PD, and HD, suggesting that oxidative stress may play an important role in the pathophysiology of these diseases [48]. Increased production of cellular ROS and oxidative stress have been reported to induce autophagy, a homeostatic process that enables cells to degrade cytoplasmic proteins and organelles [49-51]. The observation of increased autophagy in the brains of patients with AD, PD, and HD suggests that autophagy contributes to the pathogenesis of these neurodegenerative diseases, possibly by causing cell death [52-56]. Consistently, oxidative stress-induced autophagy of accumulated amyloid β-protein in AD causes permeabilization of lysosomal membrane and leads to neuronal cell death [57]. Mitochondria damaged by significantly increased oxidative stress in pyramidal neurons of AD are subjected to autophagic degradation, ultimately leading to neurodegeneration [58]. Furthermore, overexpression of wild-type PINK1 increases mitochondrial interconnectivity and suppresses toxin-induced autophagy, whereas knockdown of PINK1 expression potentiates mitochondrial fragmentation and induces autophagy [51], suggesting that induced autophagy as a consequence of loss of function of *PINK1* may contribute to the pathogenesis of PD.

Interestingly, autophagy also serves as a protective mechanism in age-related neurodegenerative diseases. Several studies demonstrate that basal level of autophagy clears the deleterious protein aggregates that are associated with AD, PD, and HD [59-61], therefore playing a protective role in the maintenance of neural cells. For instance, autophagy is involved in degradation of HTT aggregates [52]. Administration of rapamycin induces autophagy and enhances the clearance of mutant HTT, improving cell viability and ameliorating HD phenotypes in cell and animal models [62]. Furthermore, PARKIN, whose loss of function mutation causes early onset PD, has been found to promote autophagy of depolarized mitochondria [63], suggesting that a failure to eliminate damaged mitochondria by mutant PARKIN is responsible for the pathogenesis of PD. It is not entirely clear why autophagy can exert protective or deleterious effects on pathogenesis of these neurodegenerative diseases. A better understanding of autophagy, mitochondrial dysfunction, and oxidative stress is necessary in order to dissect the pathogenesis of AD, PD, and HD.

There is growing evidence that oxidative stress is increased in myocardial failure and may contribute to the structural and functional changes that lead to disease progression. What is driving oxidative stress in the failing heart? It appears that many recognized remodeling stimuli such as mechanical strain and tumor necrosis factor-α can increase the formation of ROS in the myocardium. If mitochondria are the principle source of ROS in response to these or other remodeling stimuli, the results of Ide et al suggest that such stimuli may regulate electron transport activity and "oxygen wastage" directly. This thesis would further imply that chronic remodeling stimuli control, in part, the activity of the mitochondrial electron transport system, and according to the work of Ide et al, may thereby alter the level of myocardial oxidative stress. This speculation is supported by the finding that mechanical unloading with a left ventricular assist device in patients with severe heart failure resulted in an increase in mitochondrial complex I activity [64,65].

Xanthine oxidase may be another source of oxidative stress and "oxygen wastage" in the failing heart. In the rapid pacing–induced canine model of heart failure, there is a 4-fold increase in myocardial xanthine oxidase activity that is associated with a decrease in myocardial efficiency. Treatment with the xanthine oxidase inhibitor allopurinol improved mechanical efficiency and increased myocardial contractile function. How these observations relate to the current work by Ide et al remains to be seen, but it is possible that activation of xanthine oxidase in the failing heart is a downstream effect of the increase in mitochondrial ROS [66,67].

V. CONCLUSION

Oxidative stress and mitochondrial dysfunction are two important factors contributing to the aging process. The importance of mitochondrial dynamics in aging is illustrated by its association with a growing number of age-associated pathogenesis. A better understanding of response to oxidative stress and mitochondrial dynamics will lead to new therapeutic approaches for the prevention or amelioration of age-associated degenerative diseases like Alzheimer's disease and Parkinson's disease where ROS and mitochondrial dysfunctions play critical roles.

The direct demonstration of oxidative stress in a model of myocardial failure should help to focus attention on the potential therapeutic value of antioxidants.

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ABBREVIATIONS

Aβ, amyloid-β peptide; APP, amyloid precursor protein; ANT, adenine nucleotide translocase; CoQ10, coenzyme Q; CypD, cyclophilin D; GSH, glutathione; Gpx, GSH peroxidase; KGDHC, α-ketoglutarate dehydrogenase complex; MAO, monoamine oxidase; MPT, mitochondrial permeability transition; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NO, nitric oxide; PGC-1α, PPARgamma coactivator 1; PINK1, PTEN induced putative kinase 1; Prx, peroxiredoxin; PS1, preseniline; ROS, reactive oxygen species; SOD, superoxide dismutase; TCA, tricarboxylic acid; Trx, thioredoxin; TrxR, Trx reductase; UCP, uncoupling protein; VDAC, voltage-dependent anion channel.

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