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Oxidative Stress and Transcriptional Regulation in Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is defined by progressive impairments in memory and cognition and by the presence of extra-cellular neuritic plaques and intracellular neurofibrillary tangles. However, oxidative stress and impaired mitochondrial function always accompany AD. Mitochondria are a major site of production of free radicals [i.e., reactive oxygen species (ROS)] and primary targets of ROS. ROS are cytotoxic, and evidence of ROS-induced damage to cell membranes, proteins and DNA in AD is overwhelming. Nevertheless, therapies based on antioxidants have been disappointing. Thus, alternative strategies are necessary. ROS also act as signaling molecules including for transcription. Thus, chronic exposure to ROS in AD could activate cascades of genes. Although initially protective, prolonged activation may be damaging. Thus, therapeutic approaches based on modulation of these gene cascades may lead to effective therapies. Genes involved in several pathways including antioxidant defense, detoxification, inflammation, etc. are induced in response to oxidative stress and in AD. However, genes that are associated with energy metabolism, which is necessary for normal brain function, are mostly down-regulated. Redox sensitive transcription factors such as activator protein-1 (AP-1), nuclear factor κ B (NF- κ B), specificity protein-1 and hypoxia-inducible factor (HIF) are important in redox-dependent gene regulation. PPAR γ co-activator (PGC-1 α) is a co-activator of several transcription factors and is a potent stimulator of mitochondrial biogenesis and respiration. Down-regulated expression of PGC-1 α has been implicated in Huntington's disease (HD) and in several HD animal models. Its role in regulation of ROS metabolism makes it a potential candidate player between ROS, mitochondria and neurodegenerative diseases. This review summarizes the current progress on how oxidative stress regulates the expression of genes that might contribute to AD pathophysiology and the implications of the transcriptional modifications for AD. Finally, potential therapeutic strategies based on the updated understandings of redox state-dependent gene regulation in AD are proposed to overcome the lack of efficacy of antioxidant therapies.

Keywords

Oxidative stress; transcription factors; Krebs' cycle; redox; metabolism; Alzheimer's disease

Oxidative stress and Alzheimer's disease

AD is defined by progressive impairments in memory and cognition and by the presence of extracellular neuritic plaques and intracellular neurofibrillary tangles. β -amyloid peptide (A β) is the major component of the plaque, while the tangles are composed of hyperphosphorylated tau proteins. Since these three features define AD, any hypothesis

about AD must explain their presence. Nevertheless, formation of plaques and tangles may be end point lesions and an adaptive response rather than deleterious response. Many other changes occur in AD brains including nerve cell death, synaptic loss, proliferation of reactive astrocytes and microglial activation. All of these may reflect some other initiating factor.^{1,2,3,4,5} These same initial events may cause the cascades of gene responses that have been identified in AD. Although the genetic responses may be beneficial in early stages, they may be harmful in the long term (e.g., they can further diminish metabolism). Defining changes that initiate AD and lead to cascades of genetic responses as well as the formation of plaques and tangles would provide attractive therapeutic targets.

Overwhelming evidence suggests that oxidative stress increases with age through variations in ROS generation, ROS elimination or both.⁶ Studies have shown that ROS levels are increased with age in major organs including brain.^{7,8} Mitochondria are the major sites for ROS generation. Mitochondrial DNA (mtDNA) is situated very close to the site of mitochondrial ROS production. Mutations in mtDNA occur with aging especially in postmitotic tissues such as brain and increase to high levels in old people.^{9,10,11} Increased mtDNA mutations have been linked directly to an accelerated rate of aging in mice.¹² These alterations in mtDNA can impair mitochondrial respiration and lead to enhanced ROS generation.¹³ In addition, free radical-scavenging enzymes are also altered with aging. For example, the activity of Cu/Zn superoxide dismutase (Cu/ZnSOD) is decreased in aged rat brains¹⁴ and in brains from AD patients.¹⁵ Thus, the concurrent age-related changes in ROS generation and elimination result in the elevation of oxidative stress in aging tissues. Although overwhelming evidence links increased mtDNA mutations directly with aging, studies on postmortem brain have failed to find consistent mutations in AD mtDNA beyond those associated with aging.¹⁶ A cybrid model of AD has been developed by fusion of the membranes of platelets from AD patients to human neural host cells that are devoid of mitochondrial genes.^{17,18} AD cybrids replicate multiple abnormalities found in AD brain, suggesting that alterations in mtDNA may contribute to pathogenesis and progression of AD.¹⁶ Direct expression of mtDNA mutations that are either linked with or beyond aging in isolated heterogenous AD neurons will provide a definitive test of whether a specific mutation in mtDNA is pathogenic to AD.

Accumulating evidence suggests that oxidative stress is an early event in AD. Oxidative stress occurs when the oxidative balance is disturbed i.e., excessive production of reactive oxygen species (ROS) to cellular antioxidant defenses. The brain is particularly vulnerable to oxidative stress because it is rich in unsaturated fatty acids, it consumes much more oxygen per gm compared to other tissue and it has less antioxidant enzymes than other organs.^{19,20,21} The early involvement of oxidative stress in AD is demonstrated by oxidative modifications of lipids,^{22,23,24} proteins,^{25,26,27} and nuclei acids^{28,29} in brains from AD patients, as well as in cellular and animal models of AD. Oxidative stress-modified molecules are detected not only in extra-cellular plaques, but also within cells. For example, elevated 4-Hydroxynonenal (4-HNE), a marker of lipid peroxidation, is found in amyloid beta peptide (A β) plaques associated with AD.³⁰ 4-hydroxynonenal (HNE)-pyrrole immunoreactivity also occurs in neurons with or without neurofibrillary tangles (NFTs) in brains of AD patients.²⁴ Oxidized RNA nucleoside 8-hydroxyguanosine (8OHG) is significantly increased in neurons from the frontal cortex of familial Alzheimer's disease (FAD) with a mutation in presenilin-1 (PS-1) or amyloid beta protein precursor (A β PP) gene.²⁸ Moreover, the activity of a mitochondrial enzyme α -ketoglutarate dehydrogenase complex (KGDHC) is reduced in brains of AD patients. KGDHC is sensitive to various oxidants whether they are added to cells or generated internally in cells.³¹ Biomolecules modified by oxidative stress exist in neurons with or without NFTs and plaques suggests that oxidative stress precedes the formation of AD pathologies and is a very early contributor to the disease. In mouse models of plaque formation, evidence of oxidative stress

is apparent in urine before plaques are formed in brain.^{32,33} Oxidative stress occurs prior to A β deposition in a Tg2576 APP transgenic mice model.^{33,34} Evidence of oxidative stress also occurs in urine of AD patients.^{22,32} Moreover, increased levels of oxidative damage occur in individuals with Mild Cognitive Impairment (MCI), which is believed to often be one of the earliest stages of AD.³⁵ For example, the levels of HNE are elevated in MCI hippocampus and inferior parietal lobules compared to those of control brain.³⁶ Glial heme oxygenase-1 expression in the MCI temporal cortex and hippocampus is also significantly greater than in the non-demented group.³⁷ Together, these data support oxidative stress serving as an early event that leads to the development of cognitive disturbances and pathological features observed in AD.

An understanding of how reactive oxygen species may lead to AD requires an understanding the different kinds of radicals and their origin (Table 1) (for reviews^{38,39,40}). Superoxide is a normal product of metabolism that is short lived and can serve as a signaling molecule within molecules and perhaps between pathways. The primary ROS generated in mitochondria is superoxide ($O_2^{\bullet-}$), which is then converted to H_2O_2 by spontaneous dismutation or by superoxide dismutase. H_2O_2 can also be further transformed to $OH^{\bullet}$ in the presence of metal ions by Fenton chemistry. $NO^{\bullet}$ serves as signaling molecule, but its reaction with superoxide produces peroxynitrite which is very damaging to multiple macromolecules. Superoxide reacts with unsaturated lipids to produce lipid hydroperoxyl radicals and reactive aldehydes.

The origin of these reactive oxygen species is also critical to our understanding of how they might alter gene transcription. There are several major sites of ROS production in the cells including mitochondria. The major source of radicals during unstressed conditions is not clear, but during pathological conditions, mitochondria seem to be a major source. For example, monoamine oxidase (MAO) is located on the mitochondrial outer membrane, and participates in the degradation of neurotransmitters, which leads to generation of H_2O_2 .⁴¹ The up-regulation of MAO, and a consequent increase in H_2O_2 generation, has been implicated in several pathological conditions including Parkinson's disease.⁴² Arachidonate oxidation leads to isoprostane formation, which is an early change in AD and mouse models of plaque formation.^{43,44} Xanthine oxidase, NADPH oxidase, P450 enzymes and nitric oxide synthase all contribute to ROS formation. The relative contribution of these various sources is difficult to evaluate, and could all clearly contribute to AD through altered signaling pathways.

The relation of impaired energy metabolism in AD to oxidative stress

The brain depends heavily upon glucose metabolism, which is diminished in AD. Although not a part of the formal definition, AD does not occur without a reduction in cerebral blood flow and oxygen utilization. In rare genetic forms where the completely penetrant mutation always leads to AD, metabolism changes early in life and long before the physician would detect symptoms.^{45,46} Similarly, mildly cognitive impaired (MCI) patients, who will develop AD, have diminished metabolism.^{47,48,49} Production of ROS is a normal part of the electron transport chain, and impairment of the electron transport promotes free radical generation. For example, cytochrome oxidase (complex IV of the electron transport chain) is reduced in brains of AD patients.^{50,51,52} Inhibition of this enzyme increases the production of ROS.^{53,54,55} Furthermore, ROS production is also increased under hypoxia condition because there is no acceptor for the electrons available. These oxidants damage molecules but also serve as signaling molecules. In a chronic disease such as AD, it seems likely that free radicals are produced continuously. This would also promote changes in gene regulation.

In a simplistic way, brain metabolism can be divided into four distinct pathways: glycolysis, the pentose shunt, the tricarboxylic acid cycle and the electron transport chain [Figures 1 and 2]. As the brain is exposed to oxidative stress or increased production of reactive oxygen species, these pathways can be altered by direct modification of the enzymes or by changes at the level of gene expression. The pentose shunt and glycolysis do not utilize oxygen so that they do not produce reactive oxygen species. Nevertheless, they are involved in ROS production. The pentose shunt produces NADPH. The NADPH oxidase is activated during respiratory burst. It generates superoxide by transferring electrons from NADPH inside the cell across the membrane and coupling these to molecular oxygen to produce the superoxide. In addition, ROS can act directly on these proteins. For example, oxidants modify glyceraldehyde-3-phosphate dehydrogenase (GAPDH) in a way that promotes its migration to the nucleus. Alternatively, oxidants modify patterns of gene expression of these proteins through modification of transcription factors as described in more detail below.

Glycolysis and its alterations with AD

Glycolysis converts glucose to pyruvate and lactate with the production of relatively small amounts of NADH and ATP [Figure 1]. Acceleration of glycolysis occurs when mitochondrial function is impaired. Indeed, acceleration of glycolysis can keep cells from dying when mitochondrial function is impaired. The ROS signals that are produced in mitochondria serve this function by activating expression of glycolytic genes and inactivating the downstream pathways including the TCA cycle.⁵⁶

Mitochondrial glycerophosphate dehydrogenase (mGPDH) participates in the re-oxidation of cytosolic NADH by delivering reducing equivalents from this molecule into the electron transport chain, thus sustaining glycolysis. mGPDH is involved in maintaining a high rate of glycolysis and is an important site of electron leakage leading to ROS production in prostate cancer cell lines.⁵⁷ Whether mGPDH is a site for ROS generation in neurons or other cell types is unknown.

Reported changes in glycolytic enzymes in AD are controversial. Although early findings suggested large decreases, more recent reports show only moderate changes or increases. Measurements using optimal techniques reveal consistently higher activities of hexokinase, LDH and pyruvate kinase and consistently lower activities of glucose-6-phosphate dehydrogenase.^{58,59} Phosphofructokinase is significantly increased in frontal and temporal cortex and unchanged in the other brain areas studied when compared with control brains.⁶⁰ GAPDH is increased 74%.⁵⁹ The increased glycolysis may be an adaptive response. Clonal nerve cell lines and primary cortical neurons that are resistant to Abeta toxicity have enhanced flux of glucose through glycolysis.⁵⁹

Pentose shunt and its alterations in AD

The pentose shunt (hexose monophosphate shunt) is responsible for producing NADPH which is critical in the formation of glutathione and NO[•] [Figure 1]. The activities of transketolase are reduced more than 45% in AD brains compared to controls. Small but statistically significant abnormalities of transketolase also occur in red blood cells and cultured fibroblasts.⁶¹ Clonal nerve cell lines and primary cortical neurons that are resistant to Abeta toxicity have an enhanced flux of glucose through the hexose monophosphate shunt, which suggests this flux is protective.⁵⁹

TCA cycle and its alterations in AD

The tricarboxylic acid cycle (TCA) consists of eight enzymes that are encoded by 15 genes [see Figure 1]. The regulation of the transcription of these genes has not been studied very extensively. The TCA cycle is the major producer of reducing equivalents in the form of

NADH and FADH. These reducing equivalents are then used by the electron transport chain to produce ATP. As described in more detail below, relatively recent studies also indicate that some enzymes of the TCA cycle are major producers of H₂O₂ under reducing conditions.^{62,63}

Altered activities of the TCA cycle enzymes are likely associated with AD-related changes in metabolism. It has been known since 1988⁶¹ that the activities of the α -ketoglutarate dehydrogenase complex (KGDHC) are diminished in multiple brain areas and this has been reproduced multiple times. Diminished KGDHC activity also occurs in cells treated with oxidants⁶⁴ and thiamine deficient mice, an animal model with mild oxidative stress.^{65,66} More recent studies have shown that the dehydrogenases of the TCA cycle that are also decarboxylases are all diminished in AD brain. On the other hand, the enzymes that serve only as dehydrogenases are increased. The reduction in the activity of these enzymes is highly correlated to a clinical dementia rating score (CDR) before the patients die.⁶⁷ Whether the changes occur at the gene level or whether post-translational modifications are responsible is unknown. Further studies using cellular or animal models to address the mechanisms underlying these changes in relation to oxidative stress are necessary.

Electron transport chain and its alterations in AD

The electron transport chain converts the reducing equivalents from other aspects of metabolism to a hydrogen ion gradient. The final step, ATP synthase, converts the H⁺ gradient into ATP [Figure 2] (For detailed references see⁶⁸). Complex I contains fourteen central subunits that contain all the known redox cofactors of the complex. In mammals, these subunits are encoded by the mitochondrial DNA. Mammalian complex I contains up to 32 additional subunits that are all encoded by nuclear genes. Complex II (i.e., succinate dehydrogenase of the TCA cycle) contains four subunits and is bound to the inner mitochondrial membrane and participates in the citric acid cycle and the respiratory chain. An electron transferring flavoprotein accepts electrons from different substrate dehydrogenases and transfers them to the inner-membrane bound ubiquinone oxidoreductase. The electron transfer protein is a heterodimeric complex, which consists of two subunits, α and β that are both nuclear encoded. Complex III consists of a homodimer of two bc₁ complex monomers. The mammalian bc₁ complex is composed of eleven subunits. Cytochrome *b* is encoded by the mitochondrial genome, and all of the other subunits are encoded by nuclear genes. Complex IV includes three conserved subunits I, II and III, representing the minimal core of the enzyme. The mammalian aa₃ cytochrome c oxidase has three conserved subunits encoded by the mitochondrial DNA and ten nuclear encoded subunits.

A key feature of cellular respiration is the regulation of the functional capacity of respiratory chain complexes at the level of gene expression,⁶⁹ post-translational processing,⁷⁰ membrane traffic,⁷¹ membrane assembly⁷² and flux control processes.⁷³ There is also cross talk at the gene level between the TCA cycle and the proteins of the electron transport. A novel mRNA that is transcribed starting from intron 7 in the DLST gene (E2k protein of KGDHC of the TCA cycle) helps to regulate genes involved in electron transport. The truncated gene product (designated MIRTD) is localized to the intermembrane space of mitochondria. Cells deficient in this protein exhibit a marked decrease in the amounts of subunits of complexes I and IV of the mitochondrial respiratory chain, resulting in a decline of activity. The novel mRNA level in the brain of AD patients was significantly lower than that of controls. Thus, the DLST gene is bifunctional and MIRTD transcribed from the gene contributes to the biogenesis of the mitochondrial respiratory complexes.⁷⁴

Many groups have tested for changes in oxidative phosphorylation in AD, and the results are equivocal. The activities of mitochondrial respiratory chain enzyme complexes I+III,

complexes II+III, complex IV (cytochrome c oxidase, COX), succinate dehydrogenase, and citrate synthase in the frontal cortex, temporal cortex, hippocampus, and cerebellum have all been measured. The major finding is a decrease in COX activity in AD temporal cortex and hippocampus. The defect is confined to selected brain regions, suggesting anatomic specificity that is secondary to neurodegeneration.⁷⁵ Others found that compared with controls, COX activity is decreased significantly in platelets (–30%) and hippocampus (–35 to –40%), but not in motor cortex from the AD patients. F(1)F(0)-ATPase is not altered in the same samples.⁷⁶ Studies of mitochondria from patients with AD reveal a generalized depression of activity of all electron transport chain complexes, but the depression is most marked in COX activity ($p < 0.001$). Concentrations of cytochromes b, c1, and aa3 were similar in AD and controls.⁷⁷ However, others find Complex III core protein 1 is significantly reduced in the temporal cortex of AD patients.⁷⁸ Kish and colleagues find mean cytochrome oxidase (CO) activity in AD brain is reduced in frontal (–26%), temporal (–17%;), and parietal (–16%) cortices. In occipital cortex and putamen, mean CO levels are normal, whereas in hippocampus, CO activity, on average, is not significantly elevated (20%). The reduction of CO activity, which is tightly coupled to neuronal metabolic activity, could be explained by hypofunction of neurons, neuronal or mitochondrial loss, or possibly by a more primary, but region-specific, defect in the enzyme itself.⁷⁹

This section briefly summarized the association of oxidative stress with diminished energy metabolism in AD and the possible modifications of metabolic enzymes by oxidants. Although oxidative stress-induced alteration in mitochondria function appears to contribute to AD-related changes in metabolism, decreased metabolism in AD may reflect decreased synaptic activity.⁸⁰ Changes in synaptic structure and function in early stages of AD may lead to potentially reversible downregulation of oxidative phosphorylation (OXPHOS) within neuronal mitochondria.⁸⁰ Although decreased demand may underlie changes in oxidative phosphorylation enzymes, there is no evidence that the levels of TCA cycle enzymes are regulated by neuronal activity. This supports the suggestion that inactivation of these enzymes could underlie the decline in metabolic function which would lead to decline in mental function.

Major sites of ROS production

Electron transport chain

The metabolic sites for production of ROS in cells have been reviewed extensively recently^{38,81} and are shown in Figures 1 and 2. Traditionally, the primary source of ROS in the mitochondria is the electron transport chain. ROS can be produced at complex I, Complex II and complex III. Impairment of the electron transport chain beyond these reactions increases ROS formation. For example, azide blocks the final step of the electron transport and increases detectable ROS.⁵³ The main source of $O_2^{\bullet-}$ from the electron transport is believed to be the ubisemiquinone radical ($QH^{\bullet}$), formed at the complex III Q_O site, facing the inter-membrane space.^{82,83,84,85} A build-up of the mitochondrial membrane potential can increase ROS, while dissipation of the mitochondrial membrane potential can decrease ROS.^{86,87}

Dehydrogenases

Recent studies suggest that several dehydrogenases in the TCA cycle may generate ROS. Most notably, alpha-ketoglutarate dehydrogenase (KGDH) and pyruvate dehydrogenase (PDH) have been identified as sources of ROS.^{62,63,88} Both these enzymes contain miniature electron transport chains, including alpha-lipoic acid, NADH, and flavin binding sites. The precise site within these chains where electrons may interact with O_2 to generate ROS is not known. Interestingly, such inhibition of the TCA cycle dehydrogenases would

slow down the entry of electrons into the respiratory chain, by decreasing the generation of NADH, and this in turn would slow down ROS generation by complexes I and III. Such a feed-back loop would function as a safety valve, to prevent over-production of ROS by the respiratory chain.⁸⁹ This appears to have biological importance in aging. Replicative life span in *Saccharomyces cerevisiae* is increased by glucose limitation [calorie restriction (CR)] and increased NAD⁺. Strains defective in NAD⁺ synthesis and salvage pathways exhibit decreased oxygen consumption and increased mitochondrial H₂O₂ release, and this is reversed by CR. These mutant strains live shorter and this is rescued by CR. Furthermore, the changes in mitochondrial H₂O₂ release alter cellular redox state, as shown by reversal of changes in total, oxidized, and reduced glutathione. Deletion of the dihydrolipoyl-dehydrogenases gene prevents oxidative stress in the mutants. The results indicate that matrix-soluble dihydrolipoyl-dehydrogenases are an important source of CR-preventable mitochondrial ROS. Furthermore, pyruvate and alpha-ketoglutarate, substrates for dihydrolipoyl dehydrogenase-containing enzymes, promote pronounced reactive oxygen release in permeabilized wild-type mitochondria. Altogether, these results substantiate the concept that mitochondrial ROS can be limited by caloric restriction and play an important role in *S. cerevisiae* senescence. Furthermore, these findings suggest that dihydrolipoyl dehydrogenase is likely to be an important and novel source of ROS leading to life span limitation.⁹⁰

Amyloid β peptide

Although amyloid β peptide (A β) is the neurotoxic species implicated in the pathogenesis of AD, mechanisms through which intracellular A β impairs cellular properties and produces neuronal dysfunction remain to be clarified. Considerable evidence exists that A β can increase production of free radicals and this the radical may be generated by the A β molecule.^{91,92,93} Intracellular A β is present in mitochondria from brains of transgenic mice with targeted neuronal overexpression of mutant human amyloid precursor protein and AD patients. A β progressively accumulates in mitochondria and is associated with diminished enzymatic activity of respiratory chain complexes (III and IV) and a reduction in the rate of oxygen consumption. Importantly, mitochondria-associated A β , principally A β 42, was detected as early as 4 months, before extensive extracellular A β deposits.⁹⁴ Moreover, activation of NADPH oxidase by A β 42 results in ROS production in rat primary culture of microglial cells.^{95,96}

Microglial NADPH oxidase

Several lines of evidence suggest that one of the source of ROS is the microglial NADPH oxidase.^{95,97,98,99,100,101} The neuropathological hallmarks of Alzheimer's disease are the neurofibrillary tangles and the senile plaques. The latter are surrounded by activated microglia. Exposure of microglial cells to inflammatory stimuli activates the microglial NADPH oxidase which leads to generation of O₂⁻. Generation of O₂⁻ will further enhance the production of more potent free radicals such as peroxynitrite. The formation of peroxynitrite induces protein oxidation, lipid peroxidation and nucleic acid oxidation.¹⁰¹

Relation of oxidative stress and neuropathology

Increases in oxidative stress can lead to the classical neuropathology.¹⁰² Impairing oxidation can promote the formation of amyloidogenic fibrils of A β peptide.^{103,104,105,106,107} Further, oxidative stress and interruption of metabolism can promote hyperphosphorylation of tau in a manner that is reminiscent of tangles.^{108,109} If enough free radicals are generated to cause these pathological changes, it seems likely that these same free radicals could interact with gene expression.

Oxidative stress and altered gene expression in AD

Oxidative stress has been recently recognized to play an important role in signal transduction and transcription of specific genes through the activation of redox-sensitive transcription factors. Genes involved in several pathways that are associated with AD pathology are outlined and their intimate relations to oxidative stress are discussed.

Stress response and antioxidant genes

As described previously, overwhelming evidence suggests that oxidative stress is an early event in AD pathology and this is reflected at the gene level. Genes related to oxidative stress and antioxidant pathways are generally induced in AD [Table 2]. For example, heme oxygenase-1 is a 32-kDa stress protein that degrades pro-oxidant heme to antioxidant biliverdin, free iron and carbon monoxide.¹¹⁰ The induction of both mRNA and protein of heme oxygenase-1 in cerebral cortex and vessels of AD suggests an antioxidant defense in AD that is mediated at the level of transcription.^{111,112,113,114} Expression of genes for antioxidant enzymes are also elevated in AD. For example, the gene expression of Mn-, Cu, Zn-superoxide dismutases (Mn- and Cu, Zn-SOD), catalase (CAT), glutathione peroxidase (GSH-Px), and glutathione reductase (GSSG-R) are induced in brains from AD patients.¹¹⁵ These findings provide direct evidence that oxidative stress in AD increases relevant gene expression.

Inflammatory genes

Oxidative stress also leads to upregulation of inflammatory genes which have been implicated in AD [Table 2]. A DNA microarray study of hippocampal gene expression in control and AD individuals with varying severity reveals involvement of inflammatory processes in AD pathology.¹¹⁶ For example, gene expression of several inflammatory markers such as interferon gamma (IFN- γ), interleukin family (IL-6, 18), interleukin receptors and inducible nitric oxide synthase (iNOS) is up-regulated in incipient AD.^{116,117} ROS can stimulate production of these genes. Hydrogen peroxide synchronously promotes phospho-activation of several distinct protein kinase cascades including p38-mitogen activated protein kinase (p38-MAPK) and c-Jun amino terminal kinase (JNK) in primary rat astrocytes.^{118,119} p38-MAPK regulates expression of inflammatory cytokines including IL1 β ,¹¹⁹ inducible nitric oxide synthase (iNOS) and tumor necrosis factor α (TNF- α).^{120,121} In AD, increased levels of phospho-activated p38-MAPK are detected in neurons with plaques and neurofibrillary tangles.¹²² Elevated gene expression of MAPK family such as MAPK1 and MAPK12 also occur in brains of AD patients.¹¹⁶ Thus, oxidative stress induces inflammatory gene expression that is associated with AD possibly through MAPK pathways.

Genes of the TCA cycle

Mitochondrial dysfunction is a major cause of oxidative stress in AD. Increased oxidative stress, in turn, disrupts mitochondrial function. Several lines of evidence suggest that altered gene expression of mitochondrial enzymes may account for early mitochondrial dysfunction and oxidative stress in AD. Several genes involved in mitochondrial tricarboxylic acid (TCA) cycle are altered in autopsy brains of AD patients as determined by DNA array and/or real-time RT-PCR** [Table 2]. Decreased gene expression of mitochondrial aconitase, succinyl-CoA synthetase β , fumarase and mitochondrial malate dehydrogenase occurs in hippocampal samples from autopsy AD brains in two independent studies.^{116,123} Interestingly, oxoglutarate dehydrogenase, the gene encoding one of the subunits of KGDHC, shows increased and decreased gene expression in moderate and severe AD patients, respectively.¹¹⁶ KGDHC can be the rate-limiting enzyme of the TCA cycle. These findings suggest that altered expression of the TCA cycle genes in AD may represent an

early event that will later lead to mitochondrial dysfunction and further promote oxidative stress. Whether oxidative stress is a direct inducer of altered gene expression is not clear.

Genes of electron transport chain

Genes associated with oxidative phosphorylation (OXPHOS) are implicated in AD [Table 2]. Decreased mRNA levels of the mitochondrial-encoded cytochrome oxidase (COX) subunits I, II and III occur in brains of AD patients.^{123,124,125} Reduced expression of nuclear encoded subunits of mitochondrial enzymes of oxidative phosphorylation (OXPHOS) including subunit IV of COX and the beta-subunit of the F0F1-ATP synthase is also observed in vulnerable areas of AD brains.^{123,126} These data suggest that the decrease in mRNA involved in OXPHOS in affected brain regions may contribute to reduced brain oxidative metabolism in AD.

Oxidative stress and gene mutations that cause AD and the genes responsible for APP processing

Gene mutations of amyloid precursor protein (APP) and presenilin-1 (PS-1) that lead to familial AD (FAD) promote oxidative stress and/or reduced antioxidant defenses [Table 2]. Fibroblasts and lymphoblasts from FAD patients and frontal cortex of autopsy brains from FAD patients bearing APP and PS-1 mutations show elevated oxidative damage and decreased endogenous antioxidant capacity.^{28,127,128} Beta-secretase (BACE-1) together with γ secretase liberates A β from amyloid precursor protein (APP).^{4,129} The activity of BACE-1 increases in sporadic AD patients.^{130,131} Both BACE-1 mRNA and protein expression are elevated *in vivo* in the frontal cortex.¹³¹ The pathways regulating BACE have not been fully characterized. Oxidative stress is proposed to be one of the cause of elevated expression of BACE in AD.^{132,133} Thus, one reasonable hypothesis is that oxidative stress elevates BACE which increases A β deposit and that will further exaggerate oxidative stress. In addition, hypoxia also increases BACE1 expression and A β generation, and that is mediated by hypoxia-inducible factor 1 α (HIF-1 α).¹³⁴

Redox state and gene expression in cellular or animal models of AD

Growing evidence indicates that cellular reduction/oxidation (redox) status regulates various aspects of cellular function including gene expression. Oxidative stress can elicit positive responses such as cellular proliferation or activation, as well as negative responses such as growth inhibition or cell death. As reviewed in the previous section, genes altered in autopsy brains of AD patients and genetic mutations that lead to AD appear to be associated with oxidative stress. Numerous cell and animal models of AD have been developed and considerable effort has been exerted to identify mechanisms of redox state-mediated gene regulation in relation to AD pathology. Only a fraction of the studies that are related to oxidative stress-regulated gene expression will be covered in this section to further support that oxidative stress regulates the expression of genes that are implicated in AD.

Stress response and antioxidant genes

Elevated expression of stress and antioxidant defense genes occurs in AD and it is likely regulated by oxidative stress. H₂O₂ or menadione induces HO-1 expression (mRNA and protein) followed by mitochondrial iron deposition in rat primary astrocytes.¹³⁵ HO-1 and Mn-CuZn superoxide dismutase (SOD) are profoundly induced in aged AD transgenic mice and in PC-12 cells upon exposure of oxidative stress.^{136,137} Catalase is also induced in cortical neurons and astrocytes following oxidative stress induced by the redox-cycling compound paraquat.¹³⁸ Age-related increases in oxidative stress induce glutathione peroxidase in transgenic Tg2576 mice with AD-like pathology.¹³⁹ These findings provide

further and direct evidence that oxidative stress is a mediator of the induction of stress and antioxidant gene expression in affected brain regions of AD.

Inflammatory genes

Elevated expression of proinflammatory genes has been demonstrated in a number of neurodegenerative diseases including AD and the changes could plausibly result from oxidative stress. Oxidative stress regulates induction of proinflammatory genes through activation of JNK, p38 and MAPK.¹¹⁸ Induction of ROS in rat microglia and astrocytes by treatment of cells with lipopolysaccharide (LPS) and interferon (IFN)gamma increases the expression of inducible nitric oxide synthase (iNOS).¹⁴⁰ Moreover, primary astrocytes from NADPH oxidase-deficient mice have attenuated ROS production and diminished induction of iNOS in response to LPS/IFNgamma. These findings suggest that NADPH oxidase-derived ROS are crucial for proinflammatory gene expression in glial cells.¹⁴⁰ Oxidative stress is associated with selective neuronal loss during thiamine deficiency (TD).¹⁴¹ TD elevates expression of several inflammatory genes such as TNF- α , IL-1 β and IL6 in SmTN, the region most sensitive to TD and where oxidative stress is most profound.¹⁴²

Energy metabolism genes

Impaired energy metabolism occurs in a number of neurodegenerative diseases including AD. KGDHC can be a rate-limiting enzyme in the mitochondrial TCA cycle, a major oxidative energy pathway. Diminished KGDHC activity has been well documented in AD by several independent groups. Although a direct link between inactivation of KGDHC activity and various oxidants has been established in isolated enzymes, cell and animal models,^{64,143,144} whether oxidative stress regulates the gene expression of KGDHC has not been tested. Our studies on the gene expression of KGDHC in TD mice reveal a region and time-dependent profile.¹⁴⁵ Down-regulated gene expression of the three subunits of KGDHC occurs in the SmTN region where oxidative stress coexists with neuronal loss and microglial activation.

APP processing genes

β -secretase (BACE-1) is the key rate-limiting enzyme for the generation of A β peptide involved in the pathogenesis of AD.^{146,147,148} Although the mechanism of regulating BACE is not fully understood, oxidative stress is one plausible factor responsible for elevated expression of BACE in AD.¹³¹ In NT2 neurons, oxidative stress significantly increases expression and activity of BACE which leads to elevation of carboxy-terminal fragments of amyloid precursor protein.¹³² These cellular studies suggest that oxidative stress may be directly responsible for BACE activation and A β production in AD.

This section on redox state and gene expression in cellular or animal models of AD provides evidence that oxidative stress modulates the expression of genes that are associated with AD. Although the effects of specific redox perturbations can be similar in many organisms and tissues, some of them are likely to be cell or tissue-specific.¹⁴⁹ For example, heterogeneity in c-jun mRNA level occurs in a number of human fibroblast, leukemia, melanoma, sarcoma and carcinoma cell types exposed to H₂O₂.¹⁵⁰ The expression of genes involved in JNK/SAPK-c-Jun pathway is activated most strongly in astrocytes of amyotrophic lateral sclerosis patients, while motor neurons show unusually low expression of the pathway.¹⁵¹ Thus, studies on cell, tissue or region specific gene expression profile in response to oxidative stress would help to better understand the underlying mechanisms of tissue variations in AD.

Redox-regulated transcription factors in AD

ROS-mediated transcriptional regulation is relevant to altered gene expressions in AD. Several classic transcription factors, namely nuclear factor κ B (NF κ B), activator protein-1 (AP-1), specificity protein-1 (Sp-1) and hypoxia inducible factor (HIF) are known to modulate gene expression in response to cellular oxidative stress. These are summarized in Table 3. Recently, great interest has increased in co-factors of transcription factors due to their ability to modulate the activation or suppression of transcription factors. Peroxisome proliferator-activated receptor γ co-activator 1 α (PGC-1 α) is one of these co-activators that is particularly important for mitochondrial biogenesis.

NF κ B and AP-1

NF κ B, a redox-sensitive transcription factor, plays an important role in pro-inflammatory and protective pathways including transcription of cytokine genes and antioxidant genes.^{152,153} In neurons, the most common NF κ B consists of p50, p65/RelA and I- κ B subunits.^{154,155,156,157} Normally, NF κ B resides in the cytoplasm as an inactive form bound with the inhibitory subunit I- κ B. Upon stimuli such as oxidative stress, I- κ B is phosphorylated and proteolyzed, which leads to translocation of free NF κ B into the nucleus where it binds to promoter regions of its target genes. Age-related oxidative stress regulates the dissociation of I- κ B and nuclear translocation of NF κ B.¹⁵⁸ Treatment of a human T cell line with hydrogen peroxide rapidly activates NF κ B.¹⁵⁹ Stress response gene HO-1 exhibits several transcription factor binding sites including NF κ B¹⁶⁰ and is elevated in brains of AD patients. In addition to several altered NF κ B target genes, increased activation of NF κ B also occurs in neurons and astrocytes associated with A β plaques in brains of AD patients.¹⁶¹ Thus, oxidative stress activates NF κ B that will elevate expression of inflammatory and antioxidant genes in AD.

AP-1 is another transcription factor that is regulated by intracellular redox state. AP-1 is a dimeric transcription factor composed of the Jun and Fos gene families. AP-1 is induced by hydrogen peroxide, UV irradiation, depletion of intracellular glutathione by buthionine-(SR)-sulfoximine (BSO).¹⁶² AP-1 activates transcription of genes involved in both pro-inflammatory and antioxidant pathways through phosphorylation of JNK pathway. For example, oxidative stress modulates HO-1, IL-8 and ICAM-1 gene transcription by activation of NF κ B and/or AP-1.^{163,164,165,166} Thus, AP-1 together with NF κ B regulate expression of a wide range of genes that are involved in inflammatory and antioxidant defense pathways associated with AD pathology.

Specificity protein-1 (Sp-1)

Sp-1 is a redox sensitive transcription factor and its DNA-binding activity is modulated by the cellular redox state. SP-1 belongs to the zinc-finger family of DNA-binding proteins. It acts on transcription of both TATA-less and TATA-containing promoters. The DNA-binding activity of Sp-1 is decreased with age and the decline can be reversed by addition of high concentration of reducing agents.^{167,168} It has been shown that Sp-1 is essential for the constitutive expression of the human MnSOD gene.¹⁶⁹ p53 is a transcription regulator that suppresses tumor development. The expression of MnSOD is negatively regulated through the interaction of p53 with Sp-1.¹⁷⁰

Sp-1 is also likely to regulate genes that are involved in glucose metabolism such as the TCA cycle. Early studies on promoter analysis of DLST (gene encoding the E2k of KGDHC) and DLD (gene encoding the E3 of KGDHC) reveal a Sp-1 binding site in promoters of both genes.^{171,172} Similarly, MDH2 encoding one of the TCA cycle enzymes, malate dehydrogenase, shows a potential binding site for Sp-1.¹⁷³ However, further studies

on gene regulations have not followed. Considering altered mRNA levels of KGDHC and MDH2 in brains of AD patients and an animal model of AD, future studies on transcriptional regulations of these genes would provide new insights into impaired energy metabolism in relation to AD pathology.

Hypoxia inducible factor-1 α (HIF-1 α)

The hypoxia inducible factor (HIF) is a master regulator of genes of oxygen homeostasis. HIF belongs to the large family of basic-helix-loop-helix transcription factors. It binds DNA as a heterodimer of one oxygen-sensitive α -subunit (HIF-1 α , HIF-2 α or HIF-3 α) and one stable β -subunit (HIF-1 β) (for review see¹⁷⁴). Under normoxic conditions, prolyl-hydroxylase-domain proteins (PHDs) hydroxylate HIF-1 α , which initiates the degradation of HIF-1 α by the proteasome. Low oxygen levels decrease PHD activity and thus stabilize HIF-1 α , which induces expression of a series of HIF target genes including glycolysis-related genes (for review see¹⁷⁵). Oxidative stress also regulates HIF stability. Incubation of cells with H₂O₂ or other oxidative stressors leads to the stabilization of HIF-1 α and activation of HIF target genes.^{176,177,178,179}

HIF induces glycolysis-related genes including glucose-6-phosphate dehydrogenase and hexokinase 1, 2 (for review see¹⁷⁵). A recent study demonstrates that HIF-1 suppresses energy metabolism through the TCA cycle by directly trans-activating the gene encoding pyruvate dehydrogenase kinase 1 (PDK1).¹⁸⁰ PDK1 inhibits the pyruvate dehydrogenase complex (PDHC), the enzyme that provides acetyl-CoA to initiate the TCA cycle. Thus, the ability of ROS to activate HIF leads to activation of the genes of glycolysis and to inhibition of PDHC which together shunt glucose metabolism from the mitochondria to glycolysis. This provides cellular adaptation and protection in response to oxidative stress.

PHD requires O₂, ferrous iron [Fe(II)] and α -ketoglutarate for full function.^{181,182} Thus, in addition to O₂ availability, changes in the other two co-factors would regulate PHD activity. Enhanced H₂O₂ levels promote the oxidation of Fe(II) to Fe(III) and limit the availability of Fe(II) for activation of PHD and lead to stabilization of HIF.¹⁸³ The TCA cycle intermediates such as pyruvate and oxaloacetate bind to the α -ketoglutarate site of PHD and inactivate HIF-1 α decay.¹⁸⁴ Thus, ROS and the TCA cycle intermediates are important modulators of PHD through acting on iron availability^{183,185,186,187} and α -ketoglutarate binding.¹⁸⁶ Interestingly, both substrate (α -ketoglutarate) and product (succinate) of PHD are intermediates of the TCA cycle. Accumulation of succinate as a result of mutation in succinate dehydrogenase inhibits PHD and stabilizes HIF.¹⁸⁸ Thus, accumulation of the TCA cycle intermediates due to inactivation of mitochondrial metabolic enzymes may represent both adaptive and protective response to oxidative stress associated with AD.

Peroxisome proliferators-activated receptor γ coactivator 1 α (PGC-1 α)

The peroxisome proliferators-activated receptors (PPARs) are members of a nuclear receptor superfamily that regulates transcription of genes involved in lipid, cholesterol, lipoprotein metabolism, glucose energy metabolism and immune response. The peroxisome proliferators-activated receptor γ (PPAR γ) plays a critical role in regulating adipogenesis (for review see^{189,190,191}). PGC-1 α is a co-activator of PPAR γ , and is strongly expressed in brown adipose tissue, heart, skeletal muscle, kidney and brain.^{192,193,194} PGC-1 α is a potent stimulator of mitochondrial biogenesis and respiration.^{192,195,196,197,198} The expression of PGC-1 α in 10T1/2 cells is increased significantly upon H₂O₂ treatment.¹⁹⁹ H₂O₂-induced gene expression of the ROS defense system including Cu/Zn-SOD (SOD1), Mn-SOD (SOD2), catalase and glutathione peroxidase is mediated by PGC-1 α .¹⁹⁹ An increased sensitivity to oxidative stress in the brain of PGC-1 α KO mice and protection of wild-type neural cells from oxidative stress through an increase in expression of ROS-detoxifying

genes by PGC-1 α supports an important role of PGC-1 α in suppressing ROS and neurodegeneration.

A number of transcription factor targets of PGC-1 α have been discovered (for review see²⁰⁰) [Table 3]. NRF-1, NRF-2, PPAR α , PPAR β , ERR α and TR are of particular interest because of their roles in regulating the expression of many nuclear-encoded mitochondrial genes such as cytochrome c, complex I–IV and ATP synthase subunits (for review see^{195,201}). Moreover, PPARs regulate inflammatory reactions.²⁰² For example, PPAR γ inhibits the transcription of pro-inflammatory molecules such as iNOS without direct binding to the gene promoter, and such inhibition is achieved in part through antagonizing the activities of the transcription factors AP-1, STAT and NF-kappaB.^{203,204,205} Interactions of PGC-1 α with other signal pathways may also be important in the response to oxidative stress and AD. Cre-binding protein (CREB) is an important regulator of PGC-1 α expression under normal physiological conditions and in response to oxidative stress.^{199,206,207} Nitric oxide induces PGC-1 α levels and triggers mitochondrial biogenesis through cGMP-dependent pathways.²⁰⁸ p38-MAPK activates PGC-1 α ^{209,210} and PPAR α .²¹¹ Understanding the integration of these signaling pathways in dynamic controlling of genes related to mitochondrial function and biogenesis in response to oxidative stress is a great challenge and will be beneficial to AD patients.

Transcription factors as therapeutic targets in AD

Currently, medications available for the treatment of AD patients are cholinesterase inhibitors including galantamine, donepezil and rivastigmine,^{212,213,214,215,216} and the NMDA-receptor antagonist, memantine.²¹⁷ Since these drugs produce very moderate symptomatic benefits, the development of novel drugs with strong disease modifying properties is a great need today. Development of new drugs that will initiate endogenous cytoprotective properties is one of the attractive therapeutic strategies (Figure 3). Acetyl-L-carnitine is proposed as a therapeutic agent for a number of neurodegenerative diseases. Treatment of senescent rats for 4 months with acetyl-L-carnitine induces HO-1, Hsp70 and SOD-2. Acetyl-L-carnitine also upregulates glutathione level, prevents age-related changes in mitochondrial respiratory chain complex expression and reduces protein carbonyls and HNE formation.²¹⁸

As discussed above, PPAR γ belongs to nuclear receptor family and is a ligand-activated transcription factor. This unique feature makes it a valuable target for new drug developments. PPAR γ agonists are shown to be efficacious in animal models of AD through their anti-inflammatory and neuroprotective effects (for review see²¹⁹). Long-term intake of non-steroidal anti-inflammatory drugs (NSAIDs) reduces the risk for AD and delays onset and progression of the disease.^{220,221} PPAR γ is a potent target of some NSAIDs,^{222,223} and the induction of PPAR γ by NSAIDs reduces A β levels in cell and animal models of AD.^{224,225,226}

The search of therapeutic strategies for AD has been recently expanded from targeting downstream pathways of amyloid cascade to upstream pathways that are associated with mitochondrial biogenesis. PGC-1 α has been established as the master regulator of mitochondrial function and oxidative metabolism. PGC-1 α naturally binds and responds to small lipophilic molecules. The search for both agonists and antagonists of PGC-1 α will make it as an attractive therapeutic target. Down-regulated expression of PGC-1 α has been implicated in Huntington's disease (HD) and in several HD animal models.^{227,228} Cui et al²²⁷ report that mutant huntingtin (htt) suppresses PGC-1 α transcription by associating with the promoter and interfering with the CREB/TAF4-dependent pathway. Expression of PGC-1 α in striatal neuronal progenitor cells expressing mutant htt protects against

mitochondrial dysfunction induced by mutant htt. Delivery of PGC-1 α by lentivirus in the striatum provides neuroprotection in the transgenic HD mice.²²⁷ These studies provide evidence of an important role of PGC-1 α in mitochondrial biogenesis. Thus, molecules that activate PGC-1 α and lead to stimulation of energy metabolism pathways may be potentially beneficial for HD and possibly for AD in which impaired mitochondrial function and oxidative stress are implicated.

Summary

Oxidative stress is an early event in AD that precedes the formation of AD pathologies. Although numerous effects have been made to develop therapies based on antioxidants in the past years, the actual benefits to the patients have been very limited. It is likely due to lack of potency, late administration and poor penetration into the brain cells. Alternative strategies including searching for factors that initiate endogenous cytoprotection are necessary to improve the efficacy of treatment (Figure 3). ROS serve as subcellular messengers in gene regulation and signal transduction pathways, in addition to their deleterious effects on cellular biomolecules. Thus, understanding how oxidative stress modulates gene expressions that are critical to AD pathology might help to develop effective therapeutic strategies. This review summarized several aspects of oxidative stress and its relation to AD based on data collected from peripheral cells, AD autopsy brains, cellular and animal models. Oxidative stress-induced alterations that are associated with AD including impaired energy metabolism were discussed. In particular, the review highlighted current progress on the association of oxidative stress with altered gene expression and redox sensitive transcription factors that might contribute to AD pathophysiology. Possible therapeutic strategies to target redox sensitive transcription factors or their cofactors are suggested based on the updated view of redox-dependent gene regulation in AD.

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Figure 1.
Changes in Pentose Shunt, Glycolysis and the TCA cycle with Alzheimer's disease and
Sites of ROS Production of ROS by the TCA cycle

Figure 2.
Production of ROS by the Electron Transport Chain

Figure 3. Targeting transcription factors as a novel therapeutic strategy

Targeting transcription factors rather than downstream cellular events as a novel therapeutic strategy. Interaction of “activators” with classes of transcription factors (open circles) would enhance the bindings of transcription factors to promoters of protective genes and further initiate protective gene pathways that would promote normal cell functions (left section of the diagram). At the same time, interaction of suppressors with other transcription factors (filled circles) would interfere with bindings to promoters of “toxic genes” and suppress transcription of cytotoxic genes that would block production of gene products leading to cell dysfunction (right section of the diagram). We hypothesize this strategy would be more effective than just trying to fix the cellular abnormalities that result from harmful gene expression.

Table 1

Reactive oxygen species and closely related molecules

$O_2^{\bullet -}$	Superoxide anion
$OH^{\bullet}$	Hydroxyl radical
H_2O_2	Hydrogen peroxide
$NO^{\bullet}$	Nitric oxide
$ONOO^-$	Peroxynitrite
$LOO^{\bullet}$	Lipid hydroperoxyl radical

Table 2

Genes altered in AD and in cell/animal models of AD are associated with oxidative stress.

Genes	AD brain	Cell/animal model
Stress response/antioxidant defense		
Heme oxygenase (HO-1)	+ ^{107,108,109,110}	+ ^{132,156}
Mn-superoxide dismutase (Mn-SOD)	+ ¹¹¹	+ ¹³³
Cu,Zn- superoxide dismutase (Cu,Zn-SOD)	+ ¹¹¹	+ ¹³²
Catalase (CAT)	+ ¹¹¹	+ ¹³⁴
Glutathione peroxidase (GSH-Px)	+ ¹¹¹	+ ¹³⁵
Glutathione reductase (GSSG-R)	+ ¹¹¹	N/A
Inflammatory		
Interleukin 6 (IL-6)	+ ¹¹²	+ ¹³⁸
Interleukin 18 (IL-18)	+ ¹¹²	N/A
Interferon gamma (IFN- γ)	+ ¹¹²	N/A
Inducible nitric oxide synthase (iNOS)	+ ¹¹³	+ ¹³⁶
Glucose metabolism		
Aconitase (mitochondrial, ACO2)	– ^{112,119}	N/A
Succinyl-CoA synthetase β (SUCLA2)	– ^{112,119}	N/A
Fumarase (FH)	– ^{112,119}	N/A
Malate dehydrogenase (mitochondrial, MDH2)	– ^{112,119}	N/A
Ketoglutarate dehydrogenase (OGDH)	+/ ^{–112}	– ¹⁴¹
Cytochrome oxidase (COX) subunits I, II and III	– ^{119,120,121}	N/A
F0F1-ATP synthase β subunit	– ^{119,210}	N/A
APP processing		
BACE-1	+ ¹²⁷	+ ¹²⁸

Superscript numbers refer to references;

+ denotes up-regulated;

– denotes down-regulated;

+/[–] denotes up-regulation in moderate AD followed by down-regulation in severe AD;

N/A indicates regulation of a particular gene in cell/animal models of AD by oxidative stress is unknown.

Table 3

Redox-regulated transcription factors and co-activators that are implicated in AD.

Transcription factors	Target genes	Factors/pathways involved
NFκB	stress response, antioxidant defense, inflammation	Iκ-B kinase, E3RS ligase, Trx1, Ref1
AP-1	stress response, antioxidant defense, inflammation	p38-MAPK, JNK, Trx1, Ref1
Sp-1	antioxidant defense, inflammation, glucose metabolism	p53, NFκB.
HIF-1α	angiogenesis, ion metabolism, glucose metabolism	PHD hydroxylation, ubiquitin-proteasome pathway, Trx1, MEK/ERK pathway
PPARγ	Lipid metabolism, inflammation	AP-1, STAT, NFκB
Transcription factor co-activators		
PGC-1α	mitochondrial biogenesis and respiration, ROS metabolism	NRF-1, NRF-2, ERRα, CREB, cGMP-dependent pathway, P38-MAPK