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Review

Oxidative damage and the Nrf2-ARE pathway in neurodegenerative diseases ☆

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ABSTRACT

Oxidative damage contributes to pathogenesis in many neurodegenerative diseases. As the indicator and regulator of oxidative stress, the Nrf2-ARE pathway has been shown dynamic changes and examined for its neuroprotective role in many cases. In this review, we summarize the progress of the Nrf2-ARE pathway in combating toxicity induced from typical misfolded protein aggregates in neurodegenerative diseases, and specifically the effects on the clearance of protein aggregates. This article is part of a Special Issue entitled: Misfolded Proteins, Mitochondrial Dysfunction, and Neurodegenerative Diseases.

1. Introduction

Maintaining redox homeostasis is imperative for normal function of the brain. This process is tightly regulated by antioxidants, detoxifying proteins and other molecules. With age, genetic and environmental risk factors, the oxidative-redox system becomes imbalanced and oxidative stress ensues through increased levels of reactive oxygen species (ROS) and reactive nitrogen species (RNS). The rate of ROS/RNS production eventually overwhelms our endogenous antioxidant defenses leading to the accumulation of oxidative damage such as post-translational modifications of lipids, proteins and DNA/RNA, a common feature of many neurodegenerative diseases. The oxidative modifications affect the physiological functions of these cell components and cause abnormal deposits in neurons and/or glia in Parkinson's disease (PD), Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), and Huntington disease (HD). Although it is difficult to distinguish whether oxidative stress is a cause or effect of the disease because of the multifactorial nature of neuronal death and the progressive effects of oxidative stress on cells, the clear association between oxidative damage and the disease makes therapeutic targeting of the antioxidant systems an attractive option.

The nuclear factor erythroid 2-related factor 2 (Nrf2)-antioxidant response element (ARE) pathway is a primary sensor and a master regulator of oxidative stress via its ability to modulate the expression of hundreds of antioxidant and detoxifying genes [1–3]. Activation of the Nrf2-ARE pathway has shown benefits in animal models of many neurodegenerative disorders supporting the concept of developing pharmaceuticals to activate the Nrf2-ARE pathway in the brain. This review will summarize the commonality of oxidative damage in human neurodegenerative diseases and the potential neuroprotective effects of the Nrf2-ARE pathway especially against the toxicity from misfolded proteins.

2. Oxidative damage in neurodegenerative diseases

The generation of reactive species can arise through both spontaneous and enzymatic reactions. The sources and physiological functions of reactive species and human disease are explored in other reviews [4,5]. Overall, increased levels of oxidative markers and damaged cell components have been observed in the respective disease-affected regions of patients diagnosed with PD, AD, ALS, and HD. As shown in Table 1, markers of lipid peroxidation including 4-hydroxynonenol (4-HNE) are increased in PD [6–8], AD [9–11], ALS [12,13]. 4-HNE modified protein adducts have also been observed in the disease-related regions [14–16]. Protein carbonyl reflects protein oxidation and can be generated from direct free radical attack on amino acid side chains, glycation, and glycoxidation or from lipid oxidation products. Increased carbonyls have been observed in the substantia nigra (SN) of PD patients [17,18], and affected brain regions in other diseases

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Table 1
Elevated levels of oxidative stress in patients with neurodegenerative diseases.

	Lipid peroxidation	Oxidized protein	Post-translational modification	Oxidized DNA/RNA	Mitochondria disruption	Antioxidants
Parkinson's disease	MDA↑, HNE↑ [6–8]	Carbonyls↑ [17,18]	Nitrated, p-αsyn↑, [23,24] glycosaltaed -αsyn↑ [25]	8-OHDG↑ [30,31]	Complex I ↓ [149,150] Oxidized CoQ10↑ [151] mtDNA deletion↑[152]	glutathione↓[40,41]
Alzheimer's disease	HNE↑, acrole↑ [9–11] TBARS↑ [153]	HNE pyrrole adducts↑ [14,15], Carbonyls↑ [19–21] Nitrotyrosine/dityrosine↑ [28,29]	Nitrated, p-tau ↑ [26,27]	8-OHDG↑ [32,33]	Complex IV activity ↓ [154,155]	SOD1 activity↓ catalase↓ [153]
Amyotrophic lateral sclerosis	HNE↑ [12,13] Hydroxyl radical↑, ascorbate free radical↑ [34]	HNE-EAAT2↑ [16] glycoxidation↑, glycation↑ [36,130] Carbonyls↑ [22] Oxidized SOD1↑ [156]	AGEs-SOD1↑ [130] p-TDP-43 ↑ [131]	8-OHDG↑ [34–36]	Oxidized CoQ10↑ [35] Complex I activity (cortex)↑, (lymphocytes)↓ [22,157] Complex IV activity↓ [158] mtDNA4977 deletion↑ [159]	SOD/SOD1 protein/ activity↓ [34]
Huntington's disease	Plasma MDA↑ [37]	Carbonyls↑ [72,160] NADPH Oxidase↑ [161]	Extended polyQ-Htt [122]	8-OHDG↑ [37,38]	Energy failure [162], calcium↓ [148], mtDNA4977 deletion↑ [163], Complex II/III/IV↓, aconitase activity↓, citrate synthase↓ [164,165]	Plasma SOD1, GPX activity↓ [37]

[19–22]. In addition to oxidation, post-translational modifications have also been observed in patients, which can affect the structure and function of proteins. For example, nitrated, phosphorylated and glycosylated alpha-synuclein (αSyn) has been observed in different regions of patients with synucleinopathies including PD, and dementia with Lewy bodies (DLB) [23–25]. Nitration and phosphorylation of tau protein have been found in the hippocampus and neocortex of patients with AD, Down syndrome and in other tau pathologies [26,27]. Nitrotyrosine and dityrosine cross-linked proteins are elevated 8-fold and 3-fold, respectively, in hippocampus and neocortical regions of AD brain compared to age matched controls [28,29]. These disease-characteristic proteins are also ubiquitinated due to overwhelmed clearance systems. Besides lipids and proteins, oxidative damage to DNA/RNA has also increased in both central nervous and peripheral systems in many patients with different diseases as indicated by the marker 8-hydroxy-2-deoxyguanosine (8-OHDG) [30–38]. Nevertheless, typically the abnormal levels of oxidized and modified products correlate with oxidative stress.

It is worth noting that the impaired function of the mitochondrial electron transport chain is a primary source of oxidative stress. Defects in this pathway result in increased free radicals and depleted ATP levels; both of which have been seen in numerous neurodegenerative diseases (Table 1). Increased free radical production can further damage mitochondria thereby forming a positive feedback loop. In addition, free radical levels are increased due to an imbalance between the rate of oxidant generation and the endogenous antioxidant capacity. Antioxidant systems, many of which are regulated by the Nrf2-ARE pathway, are responsible for the removal of free radicals. The failure of antioxidant defense systems has also been examined in postmortem brains of patients with neurodegenerative diseases. For instance, in accordance with the increased load of reactive species in disease, PD patients have lower reduced glutathione levels in the SN [39,40] and dopaminergic neurons [41] than in age-matched controls. This reduction is not evident in the blood plasma or other parts of the brain [39,42], implicating glutathione depletion as a secondary feature of increased oxidative stress in the SN of PD patients. Reduced levels of antioxidants result in further accumulation of free radicals. Although the animal models of diseases including genetic and toxin-inducing models may not totally recapitulate all the symptoms of human patients, similar changes in oxidative damage have been observed in many of animal models [43–46]. As activation of the Nrf2-ARE pathway can boost the ability to buffer free radical generation, it provides a valuable therapeutic target for the treatment of neurodegenerative diseases.

3. The Nrf2-ARE pathway and neuroprotection

3.1. The Nrf2-ARE pathway

Nrf2 is ubiquitously expressed in all human tissues including the brain, and is one of the cap'n'collar (CNC) transcription factors [47]. CNC proteins are a family of basic leucine zipper transcription factors that are conserved in vertebrates. They are defined by the presence of a conserved 43-amino acid CNC motif, which is located in the N-terminal of the DNA binding domain [48]. The ARE is an enhancer element with the consensus sequence RTGACnnnGC, located in the 5′ flanking region of many phase II detoxifying and antioxidant genes [49,50]. Nrf2 binds to the ARE through its DNA binding domain to regulate this pathway [47]. Under basal conditions, Nrf2 is negatively regulated in the cytoplasm by kelch-like ECH associating protein 1 (Keap1). Keap1 prevents the nuclear translocation of Nrf2 and functions as an adaptor protein to E3 ligase to promote the degradation of Nrf2 via the ubiquitin proteasome system (UPS) [51–56]. Upon disruption of Keap1-Nrf2 binding, Nrf2 translocates to the nucleus and binds with small Maf proteins. The formed heterodimer binds to the ARE and coordinates the transcription of genes involved in phase II detoxification and antioxidant defense [57]. Proteins expressed by these phase II detoxifying and antioxidant genes are responsible for maintaining redox balance. Some examples include superoxide dismutase 1 (SOD1), catalase, sulforedoxin, thioredoxin, and peroxiredoxin. Other proteins involved in glutathione synthesis and metabolism include glutathione peroxidase, glutathione reductase, gamma glutamine cysteine ligase, and gamma glutamine cysteine synthase. Additionally, there are proteins that prevent quinone recycling, and preserve iron homeostasis based on microarray analysis following Nrf2 activation [2,3,58].

3.2. Dynamic changes of the Nrf2-ARE pathway in neurodegenerative diseases

Dynamic changes are seen in the Nrf2-ARE pathway in patients and animal models of aging and disease demonstrating the accumulation of oxidative damage and the importance of this pathway in combating oxidative stress. Studies have established that Nrf2 nuclear translocation is induced in dopaminergic neurons in human PD cases, but is diminished in hippocampus neurons in AD cases [59]. mRNA and protein levels of Nrf2 are reduced in the motor cortex and spinal cord in ALS patients, and mRNA level of Keap1 is increased in the motor cortex [60]. Nrf2-dependent downstream genes have also been examined in postmortem

tissues from patients. As mentioned above, free radical scavengers regulated by Nrf2 such as SOD1 and catalase are reduced in patients (Table 1). Meanwhile, there are publications reporting upregulation of other Nrf2-dependent genes as discussed below. NAD(P)H:quinone oxidoreductase 1 (NQO1), an antioxidant enzyme catalyzing the two-electron reduction of quinones via NADH or NADPH, is upregulated in astrocytes, neurons and other cell types in human PD [61] and AD brain [62–64]. A similar pattern is observed with heme oxygenase 1 (HO-1) found in reactive astrocytes and neurons in the brain of human PD [65,66] and AD patients [67]. HO-1 catalyzes the degradation of heme to biliverdin, which is then degraded to bilirubin. Both biliverdin and bilirubin have antioxidant properties [68,69]. Peroxiredoxin, a thioredoxin dependent peroxidase that reduces hydrogen peroxide, is also upregulated in PD [70] and AD [71]. An oxidative stress analysis based on proteomic data reveals that antioxidant proteins including peroxiredoxins, glutathione peroxidases (GPX), SOD2 and catalase are induced in the striatum of HD patients [72]. However, it is currently impossible to track the status of the Nrf2-ARE pathway during the progression of the disease because the data have been collected from post-mortem brain tissue. Therefore, it is unclear whether the observed upregulation of Nrf2-ARE controlled proteins and Nrf2 nuclear translocation is a persistent feature of patients or a compensatory end-stage process in these diseases.

In order to clarify these questions, studies on the perturbation of the Nrf2 pathway have been done using cell models from patients. Take PD as an example, pluripotent stem cells (iPSC)-derived neurons, which are generated from skin fibroblasts from PD patients carrying PARK2 mutations, show increased oxidative stress, dysfunctional mitochondria and enhanced activity of the Nrf2 pathway [73]. Another study profiling the gene expression of neurospheres obtained from the olfactory mucosa of PD patients and non-PD controls indicates that there is a significant dysregulation of the Nrf2-ARE pathway in PD patient cells relative to control patient cells [74]. These results suggest that the profile of Nrf2-ARE activation changes throughout the course of disease.

Similar changes are observed in animal models of PD. As shown in Fig. 1, the Nrf2-ARE pathway undergoes dynamic changes with the disease progression in the spinal cord in a αSyn mutant A53T transgenic mouse model of PD (hαSyn^{A53T}) [44]. Specifically, Nrf2 downstream genes related to glutathione synthesis increase at the early stage and decrease at the late stage disease with corresponding change in the total glutathione levels (Fig. 1A and B). Other genes such as GSTA4 and NQO1 have a similar trend, whereas Nrf2 itself increases at the late stage of the disease indicating the possibility of a compensatory response to the reduced glutathione and Nrf2-dependent gene levels. In another genetic αSyn mouse model driven by the tyrosine hydroxylase (TH) promoter, Nrf2 regulated genes including those involved in glutathione synthesis, metabolism and transportation and detoxification of hydrogen peroxide/quinones increase in the SN and striatum of 1-month-old αSyn mice [75]. However, these genes in the SN return to normal levels in 6- and 12-month old mice, whereas they continue to be upregulated until 6 month in the striatum. There is also upregulation of Nrf2-dependent genes in the SN but not in the striatum in a subchronic MPTP mouse model [76]. The Nrf2-ARE system is activated in cell culture systems as well in response to paraquat and maneb [77], and 6-hydroxydopamine [77,78].

Apparently, the extent of endogenous activation of the Nrf2-ARE pathway is insufficient to combat the overload of oxidative stress due to eventual mortality. Thus, the search for exogenous means to enhance the endogenous Nrf2-ARE activation has the potential to help the brain defend itself from oxidative damage. Proof-in-principle as to the benefit of this approach has been demonstrated in multiple animal models of neurodegenerative diseases [44,79–82].

3.3. Misfolded proteins in neurodegenerative diseases and neuroprotection of Nrf2-ARE pathway

Misfolded proteins and subsequent aggregate/inclusion formation are important contributors to pathology in many neurodegenerative

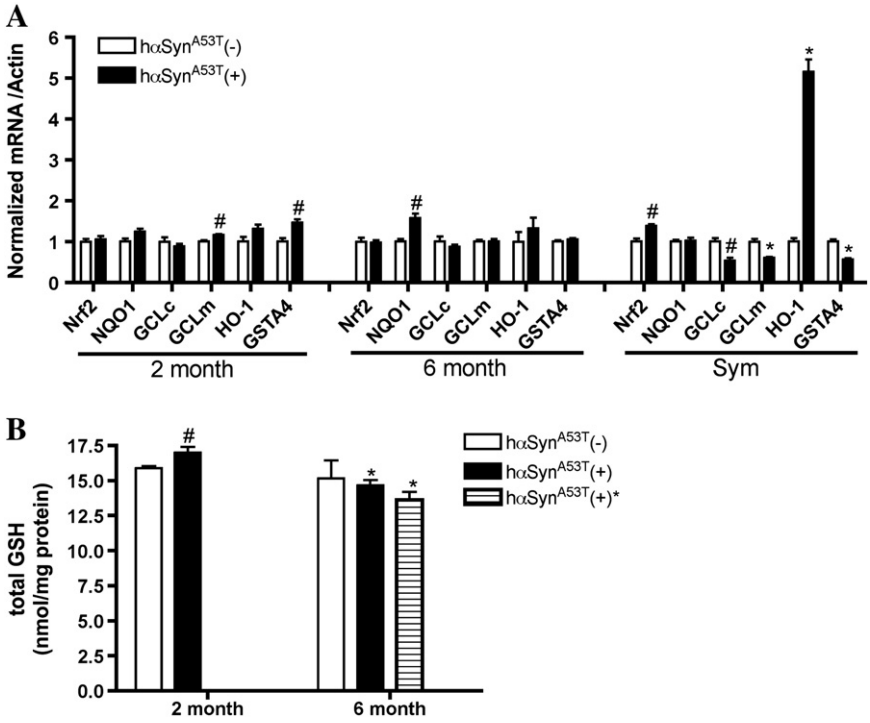

Fig. 1. Dynamic changes of Nrf2-ARE pathway in different ages of hαSyn^{A53T} transgenic mice. A, mRNA levels of Nrf2 and its regulated genes in spinal cord of 2- and 6-month-old nonsymptomatic hαSyn^{A53T} mice and sympmatic hαSyn^{A53T} mice (6–8 month old). $n = 4$. $^{\#}p < 0.01$, $^{*}p < 0.001$, hαSyn^{A53T}(+) versus age-matched hαSyn^{A53T}(−). B, Total GSH levels in spinal cord of 2- and 6-month-old nonsymptomatic hαSyn^{A53T} and 6-month-old sympmatic hαSyn^{A53T} mice. $n = 3$–5. $^{\#}p < 0.05$, 2-month old hαSyn^{A53T} (+) versus age-matched hαSyn^{A53T}(−), $^{*}p < 0.01$, 6-month old hαSyn^{A53T} (+) versus 2-month old hαSyn^{A53T}(−).

diseases. Most diseases have characteristic misfolded protein aggregates such as αSyn in PD, beta-amyloid plaques (Aβ) and tau neurofilament tangles (NFTs) in AD, and Huntingtin (Htt) in Huntington's disease. Oxidative stress is a main source of protein modifications, and it affects their synthesis, folding and function. These post-translational modifications also cause organelle dysfunction. The Nrf2-ARE pathway modulates oxidative stress and thus protects against protein oxidation. This section will focus on neuroprotection via the Nrf2-ARE pathway in neurodegenerative diseases with an emphasis on misfolded proteins.

3.3.1. Nrf2-ARE pathway and Parkinson's disease

PD is the most common neurodegenerative movement disorder. The loss of dopaminergic neurons in SN causes a reduction of dopamine in the terminals in striatum. Intracellular inclusions [Lewy bodies (LBs)] are a hallmark of PD, and have been found in both familial and sporadic PD patients with αSyn as the main component of LB and Lewy neuritis [83,84]. Multiplication and three missense mutations (A53T, A30P, E64K) of αSyn gene have been associated with autosomal dominant PD [85–87]. αSyn is a small protein with 140 amino acids that is enriched in presynaptic nerve terminals, strongly suggesting a role in synaptic transmission [88]. αSyn has been reported to adjust dopamine levels through affecting TH phosphorylation and activity, and the amount of dopamine transporter on cell membrane [89–91]. It also binds with complex I and affects mitochondria function [92]. αSyn is natively unfolded and is prone to form fibrils under disease condition. Postranslational modifications, especially phosphorylated- (p-) and/or nitrated-αSyn positive-aggregates are present in areas of the central nervous system associated with pathology in early and late stages of PD patients [23,93,94]. Nitrated-, oxidized-, and 4-HNE-αSyn has been shown to promote oligomerization and prevent fibrilization in vitro. In particular, 4-HNE-αSyn induced toxic oligomers can be taken up by neuronal cells and function as seeds to accelerate the amyloidogenesis of monomeric αSyn. This is reflected by the studies that the treatment with 4-HNE increased the cell-to-cell transfer of αSyn protein [95–97]. Furthermore, oxidized-αSyn is more prone to form toxic aggregates and it has been reported that oxidized glutathione stimulates the amyloid formation of αSyn [98]. These data indicate that oxidative stress plays an important role in αSyn proteostasis. As the master regulator of the cellular antioxidant defense system, the Nrf2-ARE pathway is a logical target to examine for neuroprotection against misfolded proteins induced pathology.

Activation of the Nrf2-ARE pathway has been shown to be protective against the toxic forms of αSyn in several studies. In SK-N-SH neuroblastoma cells, ferrous iron promotes αSyn aggregation through inhibiting Nrf2 pathway [99]. αSyn aggregation exacerbates ferrous iron-induced oxidative damage, mitochondrial impairment and apoptosis. Overexpression of Nrf2 downstream gene HO-1 is able to reverse the toxicity. In a *Drosophila* model of PD with αSyn, it was found that transgenic activation of Nrf2 by overexpression of Nrf2 or Maf-S and knockdown of Keap1 could delay the αSyn-mediated dopaminergic neuron loss and motor dysfunction [100]. Correspondingly, genetic deletion of Nrf2 enhances αSyn toxicity delivered via an adeno-associated viral vector and exaggerates αSyn/p-αSyn accumulation in dopaminergic neurites and gliosis in vivo [101]. αSyn treatment activates the Nrf2 and NF-κB pathway and promotes proinflammatory cytokine production, as well as phagocytosis in vitro. Nrf2 deficiency enhances the inflammatory response and lowers the capability of phagocytosis in primary microglial cells. The authors speculate that the Nrf2 pathway may be involved in αSyn degradation through the UPS seeing that the basal mRNA levels of proteasome subunits PSMB7, PSMC3 and PSMC4 are slightly lower in the ventral midbrain of Nrf2 KO mice compared with Nrf2 WT mice, and PSMB7 only increases in Nrf2 WT mice, not in Nrf2 KO mice, after overexpression of αSyn [101].

Recently, our laboratory has identified the importance of astrocytic Nrf2 regulating αSyn proteostasis. Astrocytic overexpression of Nrf2 (GFAP-Nrf2) can reduce αSyn aggregates in the central nervous system of a PD mouse model with neuronal overexpression of human αSyn mutant A53T (Thy1-hαSyn^{A53T}) (as shown in Figs. 2 and 3) [44]. These observations are not due to Nrf2-mediated down-regulation of the hαSyn^{A53T} transgene levels in the mice (Fig. 2A). The amount of hαSyn^{A53T} in the Triton-soluble fraction from the spinal cord decreases 60% in symptomatic mice [AN(+/−)*] (Fig. 2B, C). This is accompanied by a significant increase in hαSyn^{A53T} in the Triton-insoluble/SDS-soluble fraction. This movement of αSyn^{A53T} into Triton-insoluble/SDS-soluble aggregates is completely reversed by overexpression of Nrf2 in astrocytes [AN(+/+)] (Fig. 2B, C). Similar changes are observed for phosphorylated (Ser129) αSyn^{A53T} (p-hαSyn^{A53T}) in Triton soluble and Triton-insoluble/SDS-soluble fractions (Fig. 2B). Fluorescent staining of hαSyn^{A53T} also shows a dramatic increase in hαSyn^{A53T} aggregates that colocalized with p-hαSyn^{A53T} (Fig. 2D, E). Again, these changes are completely reversed by GFAP-Nrf2 [AN(+/+)] (Fig. 2D).

In addition, immunostaining shows increased density of p-hαSyn^{A53T} in the motor cortex, middle brain, and brain stem in symptomatic hαSyn^{A53T} mice (Fig. 3A, B). There is a striking increase of p-hαSyn^{A53T} staining in SN, especially in the pars reticulata (SNpr) (Fig. 3B middle panel). The GFAP-Nrf2 mice completely prevented or significantly reduced the p-hαSyn^{A53T} accumulation throughout these different brain regions (Fig. 3A, B).

The autophagy-lysosome pathway (ALP) is a highly conserved bulk protein degradation system responsible for the turnover of long-lived proteins, clearance of aggregate-prone proteins and disposal of damaged organelles. Inactivation of autophagy results in cytoplasmic protein inclusions composed of misfolded proteins and deformed organelles, leading to neurodegeneration and other diseases [102–104]. There is significant autophagic dysfunction observed in the αSyn^{A53T} mice with reduced macroautophagy as well as chaperone-mediated autophagy [44,105–107]. Indeed, the increased lifespan, delayed onset and reduced aggregation in αSyn^{A53T} mice are due to the GFAP-Nrf2-mediated prevention of macroautophagy and chaperone-mediated autophagy dysfunction in the αSyn^{A53T} transgenic mice [44].

3.3.2. Nrf2-ARE and Alzheimer's disease

AD is the most common progressive neurodegenerative disorder leading to the development of dementia and eventually death. It is characterized by degeneration of synapses and loss of neurons in the hippocampus and neocortex. The neuropathological hallmarks of this disease are extracellular senile plaques (SPs) and intracellular neurofibrillary tangles (NFTs). NFTs are composed of the microtubule-associated protein tau, which is hyperphosphorylated as well as oxidatively modified. SP is mainly composed of a small peptide Aβ (4 kDa), which is derived proteolytically from the beta-amyloid precursor protein (APP) [108–110].

A number of studies have shown that activation of Nrf2 can attenuate the toxicity mediated by Aβ. However, most studies focus on the neuroprotection by the Nrf2-ARE pathway against ROS generation and cell death induced by Aβ in vitro [111–114]. Unfortunately, the effects of the Nrf2 pathway on Aβ processing, clearance and aggregation in vivo is controversial. Terbutylhydroquinone (tBHQ), a prototypical Nrf2 activator, has been reported to reduce toxin-induced Aβ1-42 secretion in the NT2N cell line with increased cell viability [115]. However, it is difficult to make the conclusion that Nrf2 activation reduces the formation of Aβ aggregates or just simply prevents the release of monomer/oligomeric Aβ from dead cells. Another Nrf2 activator sulforaphane improves cognitive function in an acute mouse model of AD without shifting Aβ solubility [116]. Strikingly, overexpression of mitochondria catalase, one of the downstream genes regulated by Nrf2-ARE pathway, in APP (Tg2576) transgenic mice dramatically reduces full length APP and it's c-terminal fragment 99, lowers soluble and insoluble Aβ levels, extends lifespan and improves working memory [43]. A genetic approach through lentivirus-assisted overexpression of Nrf2 in the hippocampus of

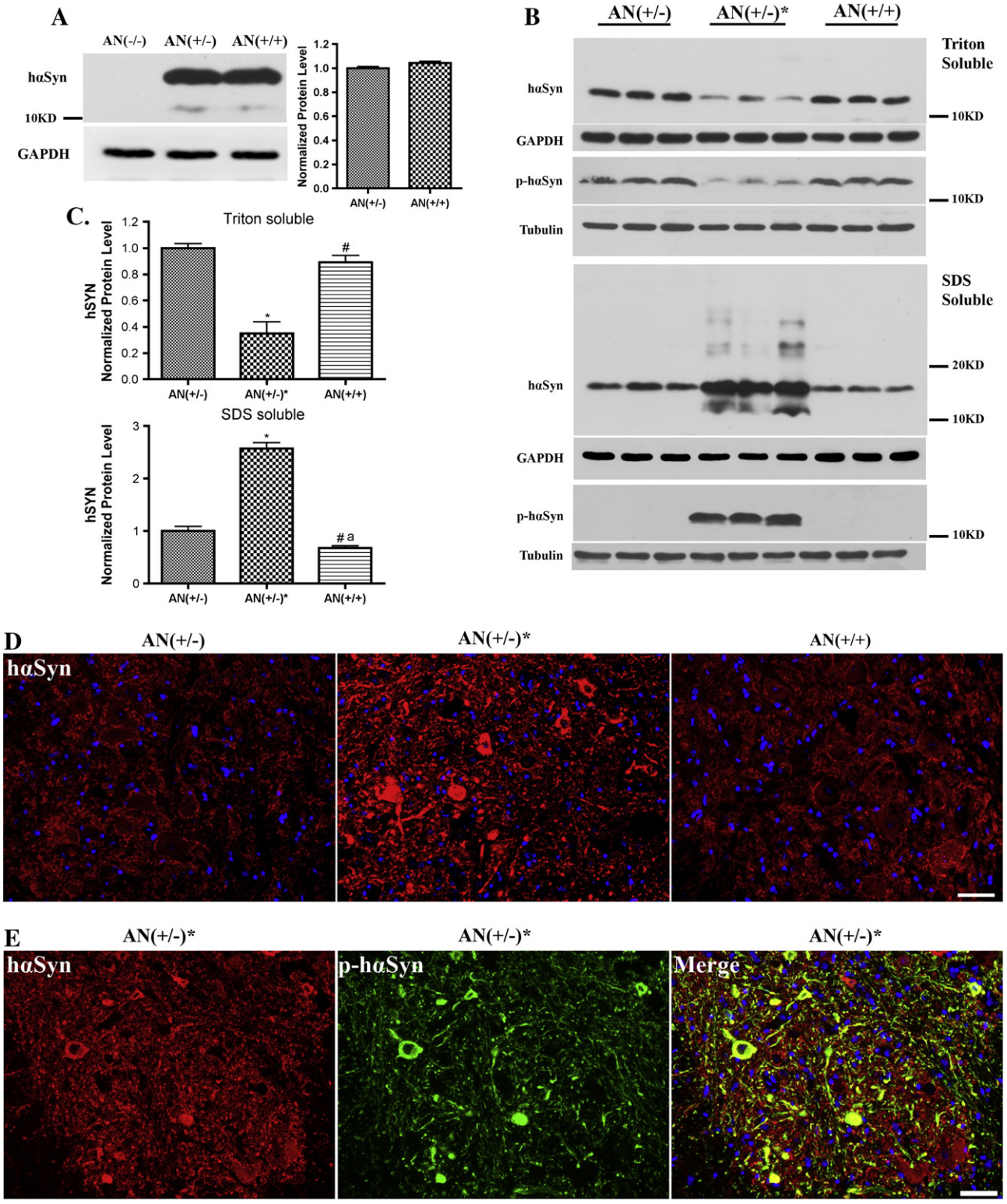

Fig. 2. Overexpression of Nrf2 in astrocytes decreases hαSyn^{A53T} and p-hαSyn^{A53T} aggregates in spinal cord. A, Western blotting of hαSyn^{A53T} for Triton-soluble fractions from spinal cords of 2-month-old hαSyn^{A53T} mice and age-matched littermates. Quantification is shown in the right, mean ± SEM; $n = 4$. B, Western blotting of hαSyn^{A53T} and p-hαSyn^{A53T} in Triton-soluble and -insoluble fractions (SDS-soluble fractions) from the spinal cord of 6-month-old hαSyn^{A53T} mice and age-matched littermates. C, Quantificative data for hαSyn^{A53T} protein level, mean ± SEM; $n = 3$. *$p < 0.001$, AN(+/−)* versus AN(−/−); #$p < 0.001$, AN(+/+) versus AN(+/−)*; $^{+}p < 0.05$, AN(+/+) versus AN(+/−). D–E, Fluorescent immunostaining of hαSyn^{A53T} and p-hαSyn^{A53T} aggregates with 80% formic acid pretreatment in spinal cord of 6-month-old mice. D, Staining for hαSyn^{A53T} in asymptomatic, symptomatic, and double transgenic mice. E, Colocalization of hαSyn^{A53T} and p-hαSyn^{A53T} in symptomatic mice; $n = 3$. Scale bars: 50 μm. Modified from Gan et al. [44].

APP/PS1 mice shifts the soluble/insoluble Aβ ratio toward the insoluble fraction without affecting the total Aβ burden, accompanied with improved spatial learning memory measured by the Morris Water Maze [117]. This agrees with the concept that soluble oligomer Aβ is the toxic form as opposed to the plaques [118,119]. A study from our laboratory suggests that APP/PS1 mice on an Nrf2 knockout background show an increased accumulation of insoluble APP fragments and Aβ (Joshi et al., manuscript submitted). This observation along with an

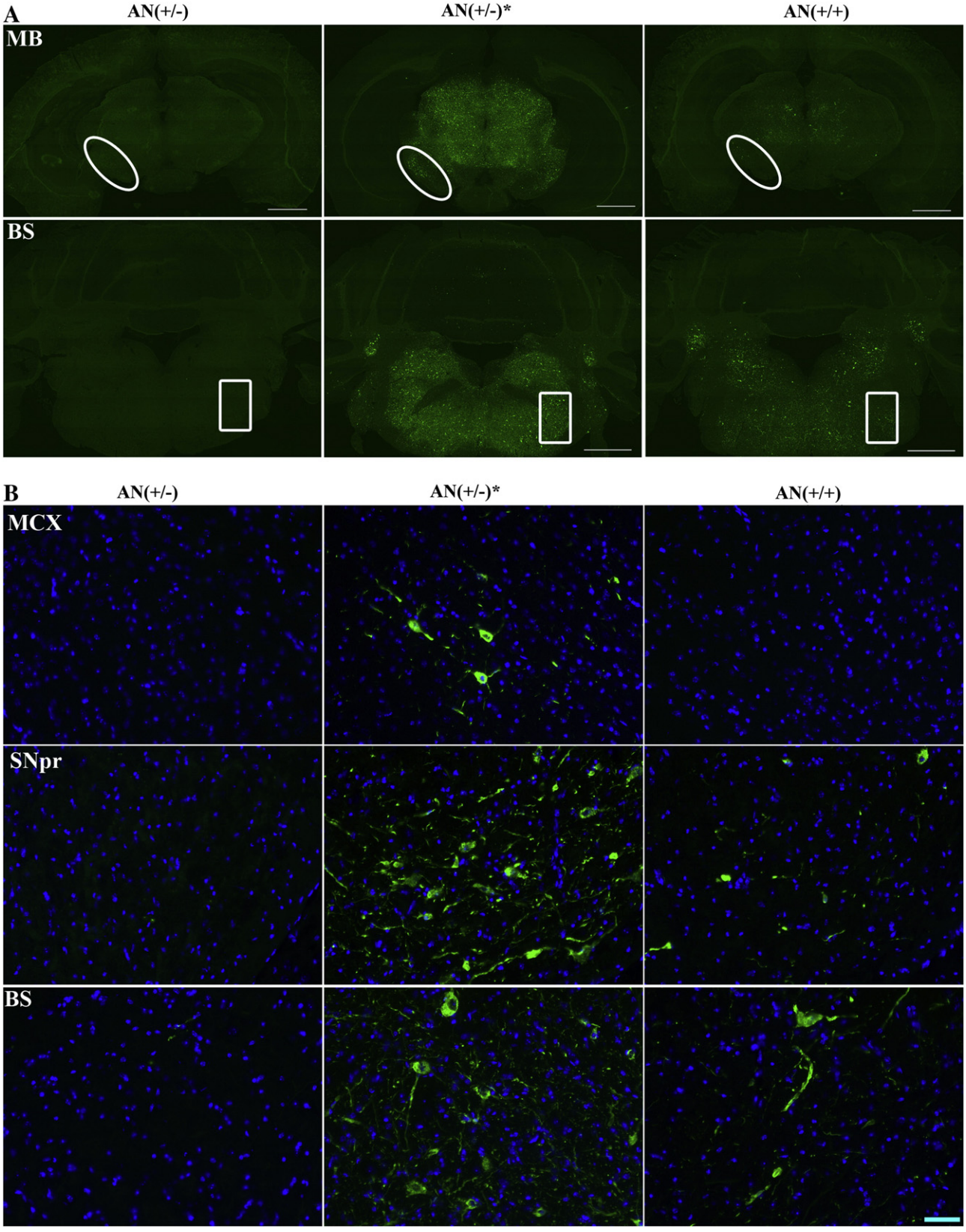

Fig. 3. Overexpression of Nrf2 in astrocytes decreases p-hαSyn^{A53T} aggregates in the brain. Representative fluorescent immunoimages of p-hαSyn^{A53T} [148] with 80% formic acid pretreatment in different brain areas of 6-month-old asymptomatic, symptomatic, and double transgenic mice. A, Middle Brain (MB) and brainstem (BS). Scale bar, 1000 μm. Higher magnification images of the oval and square areas are shown in B, middle and bottom, respectively. MCX, motor cortex. Blue: Hoechst; $n = 3$. Scale bar, 50 μm. Modified from Gan et al. [44]. Captions: AN(−/−): hαSyn^{A53T}(−)/GFAP-Nrf2(−) mice; AN(+/−): nonsymptomatic hαSyn^{A53T}(+)/GFAP-Nrf2(−) mice; AN(+/−)*: symptomatic hαSyn^{A53T}(+)/GFAP-Nrf2(−) mice; AN(+/+): hαSyn^{A53T}(+)/GFAP-Nrf2(+) mice; AN(−/+): hαSyn^{A53T}(−)/GFAP-Nrf2(+) mice.

increase in mTOR activity suggests that Nrf2 could mediate autophagy and alter processing/clearance of APP and/or Aβ.

3.3.3. Nrf2-ARE and Huntington's disease

HD is a neurodegenerative disease of genetic origin with an autosomal dominant inheritance pattern. The neuropathological characterization of the disease is the loss of medium-sized spiny neurons in the striatum. With disease progression, neuropathology is also observed in other brain regions including the cerebral cortex, the globus pallidus, the thalamus, and the cerebellum. The HD gene (huntingtin) was identified in 1993 and has an abnormal expansion of cytosine, adenine, and guanine (CAG) trinucleotide repeats [120,121]. The number of pathogenic CAG repeats correlates with the severity and age of onset of the disease. The abnormal CAG expansion results in the expression of an unusually long N-terminal poly-glutamine (polyQ) stretch in the huntingtin protein (Htt) [122]. N-terminal fragments of the mutant Htt (mHtt) proteins containing the polyQ repeat are aggregation-prone and form intracellular inclusion bodies.

Our lab and others have shown that activation of the Nrf2-ARE pathway can protect against toxicity from mHtt [79,81,123]. Nrf2 signaling is severely compromised by the presence of mHtt in the striatal cell line STHdh$^{Q111/Q111}$ compared to wildtype (wt) Htt expressing cell line STHdh$^{Q7/Q7}$ [124]. STHdh$^{Q111/Q111}$ cells fail to activate Nrf2 in response to oxidative stress and activators. The investigators reason that this impaired Nrf2 pathway may be partially due to activated autophagy pathway because mRNA and protein levels Nrf2 itself are not changed but protein levels of Nrf2 modulators, Keap1 and p62, are reduced. Keap1 and p62 are substrates of autophagy [125,126], and reduction of Keap1 and/or induction of p62 are known to activate the Nrf2 pathway [127]. In view of this, the exact cause requires further investigation. Nevertheless, coexpression of Nrf2 attenuates the fragmentation of mitochondria in STHdh$^{Q111/Q111}$ cells. A microarray analysis shows that there is an induction of the Nrf2-ARE pathway in an inducible rat PC12 cell line expressing an exon 1 fragment of huntingtin with Q74 glutamine repeats [128]. Following 5 days of doxycycline-mediated induction there are extensive aggregation as well as increases in detoxifying and antioxidant genes including NQO1, GSTA4, GSTP2, catalase, SOD1, SOD2, metallothionein 3, glutathione peroxidase and glutathione biosynthesis genes including GCLm, GCLc. These increases are not seen in cells expressing Q23 glutamine repeats or after 1-day doxycycline induction. These results indicate that activation of the Nrf2-ARE pathway is a compensatory response and the cells attempt to prevent the oxidative stress induced by aggregate formation. Although direct evidence of Nrf2 modulating Htt aggregates remains elusive, cotransfection of Nrf2 with mHtt in primary striatal neurons shortens the mean lifetime of mHtt N-terminal fragments and improves cell viability [129]. This strongly suggests that Nrf2 has the potential to alter mHtt levels thereby altering the extent of aggregation.

3.3.4. Nrf2-ARE and amyotrophic lateral sclerosis

ALS is a progressive fatal disease caused by degeneration of lower motor neurons in the ventral horn of the spinal cord and the upper motor neurons of the motor cortex, resulting in progressive motor weakness. Ubiquitinated aggregates are present in patient brains. For almost 15 years, the only gene clearly associated with familiar ALS was the Cu–Zn superoxide dismutase 1 (SOD1). Advanced glycation endproduct-modified SOD1-positive inclusions are common to familial ALS patients with SOD1 gene mutations and transgenic mice expressing human SOD1 with a G85R mutation [130]. SOD1 aggregates are not usually detected in sporadic cases. Recently, RNA/DNA-binding proteins, 43-kDa transactive response (TAR) DNA-binding protein (TDP-43) and fused in sarcoma/translocated in liposarcoma (FUS/TLS) were identified to associate with sporadic and non-SOD1 familial ALS [131–135]. Both TDP-43 and FUS are predominantly nuclear proteins involved in diverse aspects of RNA metabolism, however, both are observed as aggregates in the cytosol of affected neurons in ALS disease. This finding suggests that aberrant neuronal cytoplasmic protein aggregation and defective RNA metabolism appear to be common pathogenic mechanisms involved in ALS and possibly in other neurodegenerative disorders. Interestingly, both TDP-43 and FUS contain "glycine-rich" domains and most of the disease-related mutations occur in this region [136].

Nrf2 activators have been shown to protect against oxidative stress and cell death induced by SOD1 mutant protein [137,138]. Astrocytic expression of Nrf2 extends lifespan and enhances motor neuron survival in the spinal cord of SOD^{G93A} and SOD$^{H46R/H48Q}$ transgenic mouse model of ALS [82]. Cocultures of motor neurons derived from wild-type mice and astrocytes derived from SOD^{G93A} mice lead to motor neuron death. Overexpression of Nrf2 in the SOD^{G93A} astrocytes is sufficient to mitigate the toxicity. Interestingly, specific overexpression of Nrf2 in neurons or muscle does not affect the lifespan in SOD^{G93A} and SOD^{G85R} mice, and genetic deletion of Nrf2 has no impact on the disease progression and pathology of SOD^{G93A} mice [139–141].

Recently, NSC34 motor neuronal cell lines expressing TDP-43 mutants exhibit shortened neurites, increased oxidative stress and decreased HO-1 level. These effects are reversed by the UPS inhibitor MG132, but not by the Nrf2 activator sulforaphane [142,143]. This is attributed to an increase in HO-1 following MG132 treatment that appeared to be independent of Nrf2 activation. The question as to how mutant TDP-43 reduces expression of HO-1 and prevents sulforaphane from activating Nrf2 signaling remains to be determined. While the role of Nrf2 in protection against SOD1 mutant neuronal toxicity is clear, its effect on other ALS-associated gene mutations particularly TDP43 and FUS needs to be clarified by future studies.

4. Conclusions

Oxidative stress and misfolded proteins act synergistically to contribute to the pathogenesis of multiple neurodegenerative diseases. Oxidative modification of proteins can affect protein structure and biological functions. In many diseases, proteins with abnormal modifications have increased potential to form aggregates. In addition, misfolded proteins sequester other proteins into the forming aggregates, cause functional failure of organelles, and enhanced oxidative stress. Neuroprotection by the Nrf2-ARE pathway against oxidative damage and cell death has been the primary focus of research surrounding Nrf2 for many years. However, gathering evidence supports the concept that the Nrf2-ARE pathway may modulate the formation and degradation of misfolded protein aggregates in neurodegenerative diseases. The detailed mechanism as to how activation of the Nrf2-ARE pathway alters cellular proteostasis is still obscure. Is it by decreasing the overload of oxidative stress? Is it due to some as of yet unidentified downstream pathway regulated via Nrf2? Or is it a combination of both concepts? Current data suggest that Nrf2 affects both primary protein degradation pathways, the UPS and ALP, which are both altered in neurodegenerative diseases [144–147]. Since the research progression sheds light on the importance of the Nrf2-ARE pathway in the clearance of misfolded protein aggregates, more efforts should be put forth in elucidating how Nrf2 could maintain/enhance proteostasis so that it may lead to discovery of new targets for the treatment of neurodegenerative diseases.

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