

Nrf2 in Neurogenesis and Disease Development

Subjects: Physiology

Contributor: Linda Ines Zoungrana, Meredith Krause-Hauch, Hao Wang, Mohammad Kasim Fatmi, Lauryl Bates, Zehui Li, Parth Kulkarni, Di Ren, Ji Li

Neurogenesis occurs in the brain during embryonic development and throughout adulthood. Neurogenesis occurs in the hippocampus and under normal conditions and persists in two regions of the brain—the subgranular zone (SGZ) in the dentate gyrus of the hippocampus and the subventricular zone (SVZ) of the lateral ventricles. The transcription factor *Nrf2* (nuclear factor erythroid 2-related factor 2) is a major regulator of metabolism, protein quality control, and antioxidative defense, and is linked to neurogenesis.

Keywords: Nrf2 ; neurogenesis ; neurodegenerative diseases

1. Nrf2 Mechanism Pathway

One of the key regulators of cellular oxidation is nuclear factor erythroid 2-related factor 2 (*Nrf2*) which is a key transcriptional factor that regulates different genes in cells under both normal and stress conditions [1][2]. *Nrf2* maintains cellular homeostasis by activating the expression of cytoprotective, antioxidant, and anti-inflammatory genes [2]. *Nrf2* is a basic leucine zipper (bZip) transcription factor from the cap 'n' collar (CNC) family which includes p45 NF-E2, NRF1, NRF3, CNC homolog 1 (Bach 1) and Bach 2, broad-complex, tramtrack, and bric-a-brac (BTB) [1][3]. One difference between the members of this family of transcription factors is that *Nrf1* through 3 acts as a transcriptional activator, while Bach 1 and 2 serve as transcriptional repressors, and play a role in regulating *Nrf2* [1]. In the nucleus, *Nrf2* can heterodimerize with small MAF or JUN proteins. When *Nrf2* heterodimerizes with small MAF (sMaf), it enhances nucleotide sequences in the DNA called antioxidant response elements (ARE) or electrophile response elements (EpRE) [1][2]. Brain-derived neurotrophic factors show that *Nrf2* cellular function includes metabolic regulation, protein quality control, and antioxidative defense by initiating the transcription of cytoprotective genes, including anti-inflammatory interleukin (IL)-10, peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), and iron exporter ferroportin 1 [1][2]. The *Nrf2* molecular structure consists of seven *Nrf2*-erythroid-derived CNC homology (ECH; Neh) domains (Neh1-7), that are critical in *Nrf2* repression and activity [1]. For instance, Kelch-like ECH associated protein 1 (Keap1) is a negative regulator of *Nrf2* under unstressed cellular conditions [1]. Moreover, Neh6 is important for *Nrf2* degradation in stressed cells independent of Keap1 while on the other hand Neh3 interacts with other transcription factors through DNA binding and dimerization [1]. *Nrf2* is regulated in both the nucleus and the cytosol [1]. Glycogen synthase kinase 3 (GSK3) mediated proteasomal degradation of *Nrf2* in the nucleus while Keap1-mediated proteasomal degradation of *Nrf2* occurs in the cytosol with RBX1 and Cul3 [1]. *Nrf2* transcription factor is activated by Aryl hydrocarbon receptor (AhR), nuclear factor (NF)-κB (NF-κB), p53, myocyte-specific enhancer factor 2 D (MEF2D), breast cancer 1 (BRCA1), proliferator-activated receptor (PPAR)α or PPARγ, c-Jun, and c-Myc. All can activate *Nrf2* transcription, while the mechanistic target of rapamycin complex 1 (mTORC1), AMP-activated protein kinase (AMPK), as well as GSK3, all play a role in *Nrf2* stability and activity by directly or indirectly interacting with *Nrf2* [1]. With this interconnection of *Nrf2* with other genes and proteins, it is no surprise that *Nrf2* might be linked to neurogenesis and the development of neurodegenerative diseases. A summary of the *Nrf2* signaling pathways is presented in **Figure 1**. Although the *NRF2* pathway plays a protective role against regulating oxygen reactive species (ROS), some studies have suggested that both the suppression of the activity of the *Nrf2* transcription factor and priming are necessary for the upregulation of antioxidant molecules. However, there are contradictions among the literature regarding cell-generated memory mechanisms of activation [4][5].

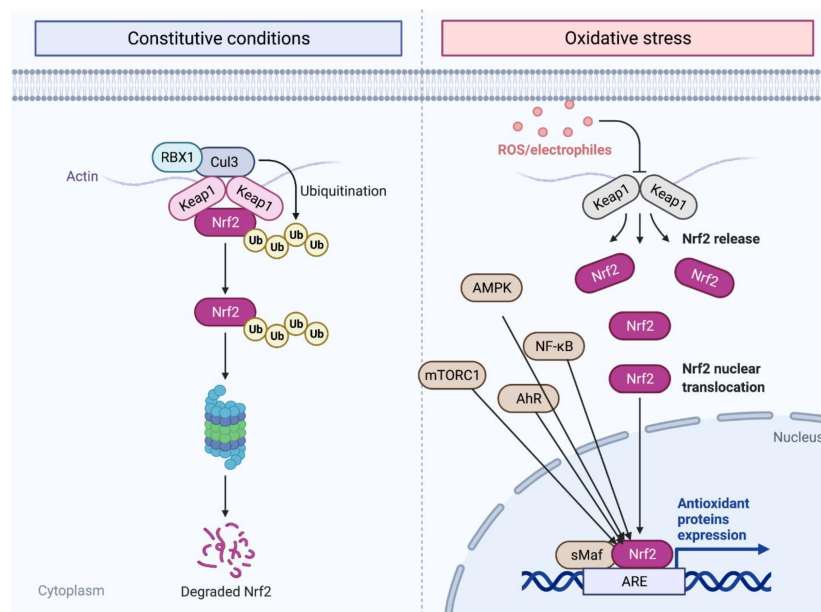


Figure 1. *Nrf2* mechanism pathway. *Nrf2* is released in the cytoplasm then migrates into the nucleus where it is transcribed during oxidative stress and degraded when it is no longer needed through ubiquitination (see text for more information). The figure was prepared by software provided by Biorender.com (accessed 3 March 2022).

2. Nrf2 in Neurogenesis

As previously mentioned, *Nrf2* controls cellular homeostasis linked to multiple stressors by regulating other genes involved in the anti-inflammatory response, metabolic reprogramming of tumor cells, antioxidant defense, autophagy, etc. [1][2]. The expression of those genes promote self-renewal, cell survival, differentiation, cell growth, proliferation, and increased lifespan [6]; all of which are important factors to the function of stem cells [6]. Some studies have explored the *Nrf2* association in neurogenesis and found that the decline in *Nrf2* expression during aging was linked to the reduction of neural stem cells in the SVZ [6][7]. Other studies have looked into the role of *Nrf2* in the homeostasis of the neurogenic niche in the SGZ and reported that the overexpression of *Nrf2* enhances neuronal differentiation. They have also found that an upregulation of *Nrf2* improves amyloid β -mediated neural stem cell death, and genetic change in *Nrf2* expression can either rejuvenate or suppress the neural stem cell niche in the SGZ [2][6][8].

One of the main characteristics of Alzheimer's disease (AD) development is the extracellular deposits of amyloid β (A β) and the increase in oxidative stress associated with A β toxicity; so understanding the mechanism of *Nrf2* in this process could lead to a new therapeutic approach in AD [8][9]. Regulation of oxidative stress also has an impact on neural stem cell differentiation. *Nrf2* has an impact on neural stem cell survival, differentiation, and neurogenesis by ROS [2]. ROS, which is produced in the endoplasmic reticulum (ER), membrane-bound NADPH oxidase, and cellular mitochondria, is the main oxidative stressor that is constantly produced by cells during metabolic functions [2][10]. The amounts of ROS produced has been associated with cellular survival, proliferation, and differentiation [2][10]. The overproduction of ROS in the mitochondria of neural stem cell in the presence of glucose alters endogenous antioxidant homeostasis leading to oxidative stress [2][11]. A study of neural stem cell lines (i.e., C17.2) shows that high glucose-mediated oxidative stress induces endoplasmic reticulum (ER) stress, inhibiting C17.2 cell differentiation into glia or neuron cells [2][11]. Modulating physiological ROS signaling and stimulating *Nrf2*-dependent developmental genes, in primarily the mitochondria as well as the ER, determines the molecular metabolism and the fate of NSC is crucial [2][12]. Studies conducted on the *Nrf2* knockout rate in different ages show that *Nrf2* expression regulates the glial differentiation of NSC in the dentate gyrus as well as neurogenesis-related hippocampal behaviors [2][13]. Semkova et al. presented in their study that both *Nrf2* proteasomal activity and pathway response to oxidative stress was crucial to developing the nervous system, showing the importance of *Nrf2* in neurogenesis [14]. However, the stress that could be encountered during neurogenesis has not been fully explored, which can present limitations on *Nrf2* mechanistic pathways associated with neurogenesis. *Nrf2* is an important factor in NSC proliferation, differentiation, and survival, and could provide a further understanding of the fundamental aspects of NSC biology.

3. Nrf2 in AD

AD is one of the most common neurodegenerative diseases and its medical management is still a challenge [15]. AD pathology is associated with an aggregate of A β plaques as well as intracellular aggregations of neurofibrillary tangles

(NFTs), composed of hyperphosphorylated microtubule-associated τ and p-tau [16]. A β plaques develop and spread from the basal neocortex regions of the brain to the hippocampus, amygdala, and basal ganglia [16]. In patients with advanced AD, A β was found further in the cerebellar cortex and throughout the mesencephalon, while in the critical stage, it spread to the hippocampus and neocortex [16]. The abnormal concentration of A β causes a τ -tangle to form, which is mostly found in the locus coeruleus and transentorhinal and entorhinal areas of the brain [16].

In the aged population, *Nrf2* expression decreases. This phenomenon is also observed in AD patients [17]. The correlation between low *Nrf2* and AD can be explained due to *Nrf2* playing a role in inflammation, oxidative stress, and influencing autophagy directly or indirectly [18][19][20]. Rojo et al. (2017) and Joshi et al. (2015) demonstrated a decline in *Nrf2* in AD animal models and aggregate-like pathology enhancing *Nrf2* correlation to AD [20][21]. Some of the *Nrf2* target genes, Heme oxygenase-1 (HO-1), NADPH quinone oxidoreductase I (NQO1), and glutamate-cysteine ligase catalytic subunit (GCLC) have been observed in AD brains [19][22]. For instance, NQO1, which protects the plasma membrane from free radicals and lipid peroxidation, is upregulated in the AD frontal cortex region [19]. Bahn et al. (2019) in their study showed that high expression of NQO1 expression in 3xTg-AD mice leads to A β immunoreactivity [19][23]. Furthermore, Rojo et al. (2017) observed an increase in A β and p-tau expression in *Nrf2*-deficient mice [21]. Other studies implicate the link between *Nrf2* and chaperone-mediated autophagy [19]. Pajares et al. (2018) identified *Nrf2* binding sequences in lysosomal-associated membrane protein 2A (*LAMP2*) in both mouse models and humans. Moreover, an overexpression and under expression of *Nrf2* is linked to an increase or reduction in *LAMP2* [19][24]. *Nrf2* deletion has been associated with an increase in intracellular A β 42 and A β 40 [19][20]. Bahn et al.'s study of beta-site amyloid precursor protein cleaving enzyme 1 (BACE1) revealed that *Nrf2* inhibits BACE1, a rate-limiting enzyme for A β peptides in AD model mouse, by binding to the promoter of BACE1 [19][23]. Finally, *Nrf2* affects p-tau by inducing nuclear dot protein 52 (NDP52), an autophagy-associated protein linked in p-tau degradation and binding in its promoter [19][25]. This suggests that *Nrf2* could facilitate tau clearance [19][25]. Further study of the regulatory mechanism of *Nrf2* in AD could provide a better understanding of the disease development.

4. *Nrf2* in PD

PD is one of the most common neurodegenerative diseases that affect individual movements. The pathogenesis of PD is characterized by the degeneration of dopamine neurons in the midbrain leading to the loss of dopamine neurotransmitters, the primary motor neurons [19][26]. This results in symptoms such as ataxia, bradykinesia, and rigidity [26]. In addition to the loss of dopamine, the presence of protein inclusions such as Lewy bodies have been observed in PD [26]. Further, the upregulation of free radical-generating enzymes is another attribute that has been observed in PD [19][27]. Guo et al. observed that *Nrf2* activity was reduced in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model of PD, which enhances the PD phenotype and MPTP has been associated with iron deposit and astroglia HO-1 expression [19][28][29]. Furthermore, studies have shown that NQO1 expression in PD links *Nrf2* to its neuroprotective effect [19][30]. An increase in proinflammatory cytokines released by activated microglia was observed in the cerebrospinal fluid of PD patients [19][31]. Another study by Rojo et al. has shown that *Nrf2* decreases microglial activation in PD progression [32].

Moreover, studies have shown that the PI3K/AKT/GSK3 β signaling axis is involved in PD neuroprotection, and a decline in AKT is associated with sporadic PD [19]. In addition, elevated expression of GSK3 β expression and activity has been reported in PD, and inhibition of GSK3 β is known to increase antioxidant genes as well as *Nrf2* activity [19]. In summary, *Nrf2* has potential neuroprotective effects in PD.

5. *Nrf2* in HD

HD is a rare hereditary neuronal disease contrary to AD and PD, which are caused by mutations or protein misfolding. HD autosomal hereditary disease is caused by CAG trinucleotide repeat expansion in the huntingtin (*HTT*) gene leading to an expansion of polyglutamine repeats in the huntingtin protein (mHtt) [33][34]. This mutation causes progressive degeneration of nerve cells in the brain and leads to a lack of movement coordination along with motor impairments [33]. Even though there is a lot to learn about HD, studies have shown that cellular antioxidants, as well as mitochondrial dysfunction, play a role in HD pathology connecting *Nrf2* to HD [33]. Enhanced lipid peroxidation has been observed in HD mice. Impairment in this antioxidant mechanism can lead to the inhibition of *Nrf2* activity by mHtt [33]. mHtt interacts with the CBP/p300 dimer, preventing its acetylation and function, which then blocks *Nrf2* cellular localization and stability [33][35]. The mechanism by which *Nrf2* affects the formation and aggregation of huntingtin protein is not fully understood. However, studies have found that *Nrf2* activation in certain parts of the brain have a neuroprotective effect and extends the lifespan in HD animal models [33][36]. Furthermore, Saito et al. (2020) observed that *Nrf2* induced the expression of p62 autophagy-related proteins and microtubule-associated protein 1A/1B-light chain 3 (LC3) [37]. Both aid in the rapid clearance of toxic of mHtt aggregates by forming a shell around it [37].

The deposit of toxic mtHtt aggregate, astrocyte, and microglia activation all contribute to HD pathology and progression. This deposit triggers the release of cytokines and pro-inflammatory mediators [33]. The connection between NF-κB and the *Nrf2* pathway is well documented and shows the activated *Nrf2* upregulation of HO-1. This upregulation decreases the expression of pro-inflammatory cytokines and reduces inflammatory mediator levels [33][38][39]. The *Nrf2/ARE* pathway assists in the neuroinflammation caused by mtHtt accumulation [33][38][39]. The interaction between NF-κB and the *Nrf2* pathway could be the target of new treatment therapies for HD.

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