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Nuclear factor erythroid 2-related factor 2 (Nrf2): As a therapeutic target for neurodegenerative diseases

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Abstract
Nuclear factor erythroid 2-related factor 2 (Nrf2) is a transcription factor that activates diverse array of proteins and is considered to be neuroprotective in nature. Neurodegenerative diseases such as Alzheimer, Amyotrophic lateral sclerosis and Parkinson's disease are becoming world's most alarming public health challenges. In fact, the mechanisms leading to neurodegeneration are not fully understood, so the diseases arising from it have no treatment so far. In this review, we introduce the structural features of Nrf2 and briefly depict its function in providing neuroprotection against different neurological diseases. The information presented here may be useful in the design of future experimental research and increase the likelihood of using Nrf2 as a therapeutic target for neurodegenerative diseases in the future.

Keywords: Nrf2, antioxidants, neurodegeration, reactive oxygen species, cytotoxicity

Introduction
Nrf2 belongs to the family of Cap'n'collar transcription factors and is considered as the master regulator of the anti-oxidant response [1]. It modulates the expression of a set of anti-oxidant genes encoding phase II enzymes and antioxidant enzymes such as glutathione S-transferase (GST), quinone oxidoreductases (NQOs), Heme oxygenase- 1 (HO-1), multidrug resistance-associated proteins (MRPs), the UDP-glucuronosyltransferase (UGT) family, cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) [23]. Considering the pivotal defensive role exerted by the Nrf2/ARE pathway, it is obvious that if dysregulation of Nrf2-regulated genes occurs, several neurodegenerative conditions will arise from unchecked oxidative stress. Thus targeting Nrf2 may be valuable in combating conditions with variable causes and etiologies including diverse neurodegenerative conditions.

Structure of Nrf2
Nrf2 is a member of the Cap'n'Collar (CNC) family of basic leucine zipper transcription factors. It is abundantly expressed in organs routinely engaged in detoxification reactions like lung, liver, intestine and kidney. Nrf2 is a central transcription factor and regulates expression of various anti-oxidant and phase II enzymes including heme oxygenase-1 (HO-1) and quinone oxidoreductase-1 (NQO-1), which provides cytoprotection against various stress conditions [4]. Nrf2 comprises of six regions or Neh (Nrf2-ECH homology) domains, which are highly conserved in different species [5] (as shown in figure 1). Neh 1 contains the CNC-basic leucine zipper region (CNC-bZIP) and is responsible for dimerization and provides specific DNA-binding ability. Neh2 domain consists of 100 amino acids and represents an N-terminal region of the protein. It contains DIDLID (amino acids 17–32) and the ETGE tetrapeptide motifs (amino acids 79–82) and negatively regulates Nrf2 function under homeostatic conditions [6]. The Neh4 and Neh5 domains bind co-operatively to the co-activator cAMP-response element-binding protein (CREB)/ATF4 and thereby activates transcription [7]. Neh6 domain (amino acids 329–379) contain two highly conserved regions (329-339 & 363-379) and is responsible for the degradation of Nrf2 in oxidatively stressed cells [8].

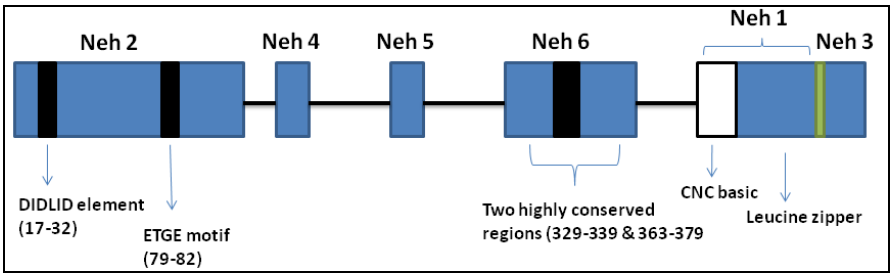

Fig 1: Schematic representation of conserved domains of Nrf2. The Neh2 domain contains the DIDLID element (ranging from amino acids 17-32 & ETGE motif 79-82). The Neh6 domain contains two highly conserved regions (329-339 & 363-379).

Activation of ARE-dependent genes

Nrf2 expression is regulated at several levels like transcription, translocation, degradation and post-translational modifications such as phosphorylation [9-14]. Under normal conditions, Nrf2 remain localized in the cytosol by a Kelch-like ECH-associated protein1 (KEAP1). Upon exposure to diverse stress stimuli, Nrf2 dissociates from KEAP1 and is subsequently translocated from the cytoplasm to the nucleus [15]. Dissociation of Nrf2 from KEAP1 upon stress may involve multiple mechanisms. One of the possible mechanisms involves phosphorylation of Nrf2-KEAP1 complex by various protein kinases like protein kinase C (PKC), mitogen-activated protein kinase (MAPK) cascades, and phosphatidylinositol 3-kinase (PI3K) (as shown in figure 2). Phosphorylation aid in the release of Nrf2 from KEAP1 (a cytoplasmic inhibitor of Nrf2), increase the stability of Nrf2 and lead its nuclear translocation [9]. All these three signal transduction pathways may possibly cooperate in the transcriptional regulation of antioxidant responsive elements (ARE's) due to the cross-reactions between them [16]. KEAP1 certain phosphorylation sites and therefore may also act as a potential target site for phosphorylation [17]. However, Nrf2 has been observed to be phosphorylated at Ser-40 in vitro by protein kinase C [10].

It has been reported that upon exposure to certain stress stimuli, Nrf2– KEAP1 complex gets activated through the direct phosphorylation of Nrf2 by KEAP1 [18] (figure 2). Diverse stress stimuli localize protein kinase RNA-like endoplasmic reticulum (PERK) kinase which senses the buildup of unfolded proteins in the ER and phosphorylates both Nrf2 and eukaryotic initiation factor 2a (eIF2a) kinase, promoting dissolution of the Nrf2–KEAP1 complex and the subsequent nuclear import of Nrf2, inducing the expression of pro-survival genes. This observation suggests that the Nrf2–KEAP1 system can be activated by signals other than oxidative stress, or that reactive oxygen species (ROS) are not always required [19].

Another model suggests that the Nrf2 transcription factor is a nuclear factor and not cytosolic one, before and during oxidative stress. Depending upon the external stimulus, a variety of tissues act like an oxidative stress sensor, modulate Nrf2 localization and activity differentially [20]. An alternate activation mechanism which has been proposed suggests a dissociation of the Nrf2–KEAP1 complex after chemopreventive agents and involves its direct interaction with the cysteine thiol (sulfhydryl) residues in either of the two proteins. Thus implying that the inducers will end up covalently bound to either KEAP1 or Nrf2 (most likely to KEAP1, as the Neh2 domain of Nrf2 does not contain cysteine residues) [21]. Other types of interactions are also suggested between the inducers and the reactive thiol groups of KEAP1, because of their extraordinary diverse chemical nature. Apart from their capacity of modification of sulfhydryl groups either by oxidation, alkylation or reduction, these inducers show few apparent similarities [21]. Furthermore, a positive feedback loop through an ARE-like element in the promoter has been shown to play a role in the regulation of transcription of Nrf2 gene in response to the anti-cancer agent 3H-1,2-dithiole- 3-thione [22].

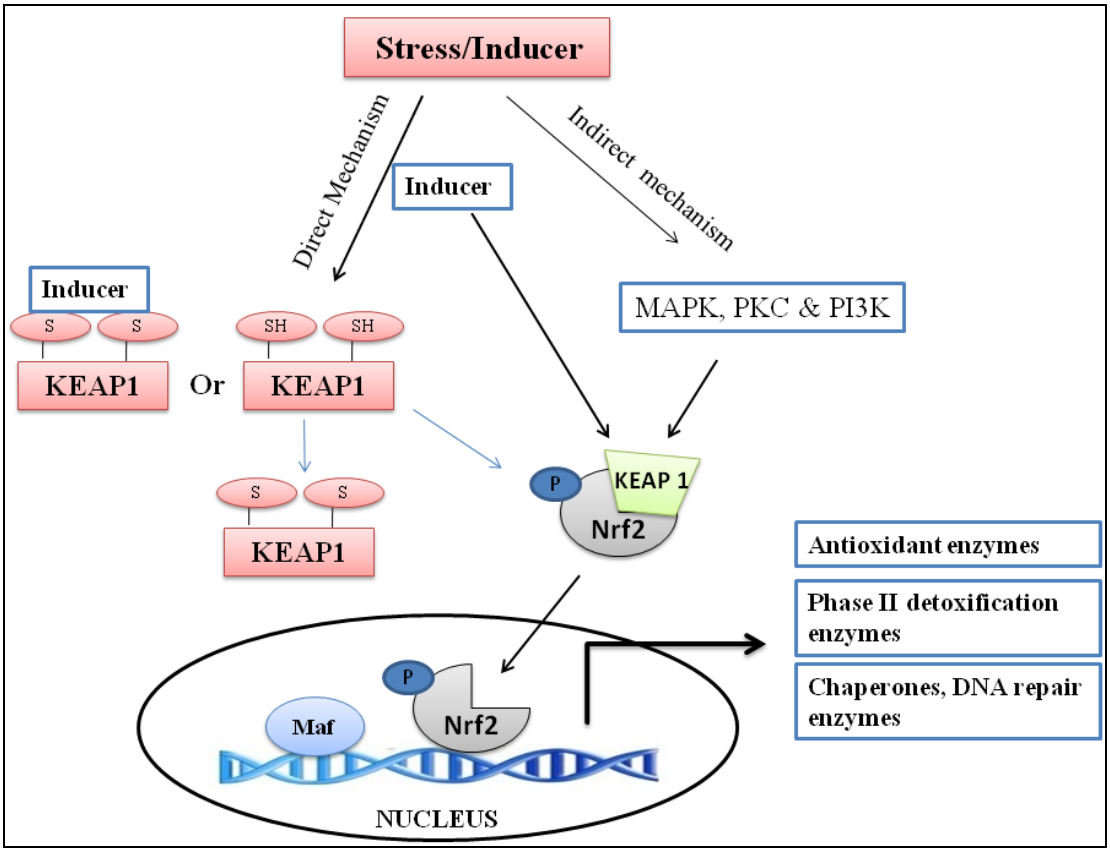

Fig 2: Different proposed pathways for the induction of Nrf2 associated cytoprotective genes

Role of Nrf2 in cytoprotection

Nrf2 is a major regulator of cellular defense mechanisms in various organs including the liver, lung, GI tract, bladder, kidney, brain, skin and ovary [23]. Additionally, Nrf2 has been implicated in a number of diseases including pulmonary fibrosis [24], drug-induced cellular toxicity [25], hepatic and gastrointestinal disease progression [26] and provides a potential therapeutic mechanism in the treatment of neurodegenerative diseases [27]. Downstream genes of Nrf2 support cellular redox homeostasis, mitochondrial biogenesis, cell growth and apoptosis, inflammatory functions and up-regulates phase II enzymes. A few phase II enzymes include HO-1, catalase (CAT), glutathione peroxidase (GPx), superoxide dismutase (SOD), thioredoxin, NQO-1, and GST [28]. The coordinated induction of Nrf2-mediated enzymes is crucial for cells to maintain redox homeostasis and avoid the adverse effects of oxidative stress. These cytoprotective proteins serve to directly or indirectly scavenge free radicals and as a result, decrease ROS toxicity. The ability of Nrf2 to regulate the transcription of antioxidant genes and detoxification enzymes was significantly blunted in Nrf2 deficient mice and such animals were more prone to carcinogenesis [29].

The role of Nrf2 in cytoprotection has been suggested to be one of the most important pathways for the cell to respond to oxidative stress [30] and studies of Nrf2 knockout and over-expressed animals support this claim. Compared to wild-type cells, Nrf2 knockout cardiomyocytes have been reported to be more susceptible to H_2O_2 induced cell injury [31]. Nrf2 knockout mice are more susceptible to liver injury and die as a result of acetaminophen-induced oxidative stress sooner than wild-type animals [32]. Similarly, animals with over-expressed Nrf2 show enhanced cytoprotection, as demonstrated with adenoviral Nrf2 transfer and subsequent protection of endothelial cells from oxidant injury [33]. Chronic and prolonged activation of Nrf2 in the nucleus has been reported to be harmful, and also in mouse models, it results in post-natal death from malnutrition and hyperkeratosis, and increases the risk for tumorigenesis [34]. Because of this potentially pathogenic role, mechanisms exist within the cell to degrade the transcription factor shortly following its activation. After Nrf2 has been translocated and accumulated into the nucleus, nuclear degradation occurs to prevent constitutive activation. Prothymosin-α (PTMα) binds to KEAP1 (Kelch-like ECH-associated protein 1) and imports it into the nucleus in complex with CuI3 and Rbx1. Once KEAP1 enters the nucleus, it releases PTMα and binds to Nrf2 triggering its degradation to shut off downstream gene expression [35].

Role of Nrf2 in neuroprotection

Nrf2 activation provides the main role in neuroprotection. However, the site of Nrf2 activation is controversial. Some studies suggest that during stress conditions astrocytes predominantly express Nrf2 [36] [37] [38], whereas other studies suggest that Nrf2 could be induced in neurons *in vitro* [39] and *in vivo* [40]. Furthermore, Nrf2 activation has been observed in neuronal and glial cells [41-44]. Several studies suggest a role of the Nrf2-ARE pathway in neuroprotection. Firstly, tert-butylhydroquinone (tBHQ) has been observed to protect neuroblastoma cells from H_2O_2-induced apoptosis and oxidative glutamate toxicity by causing the activation of Nrf2-ARE pathway [45]. More sensitivity to oxidative damage, calcium disturbance, and mitochondrial toxins was reported in primary astrocytes and neurons derived from Nrf2 knockout mice than wild-type cells [46] [47]. In a central nervous system model, Nrf2 has been shown to be protective against oxidative stress and has been demonstrated to reduce ischemic brain injury, resulting from an attenuation of neuronal cell death [28], further supporting the role of Nrf2 in neuroprotection against oxidative stress

Furthermore, activation of the Nrf2-ARE pathway by small molecules and over-expression of Nrf2 in astrocytes increased the resistance of neurons to non-excitotoxic glutamate toxicity [36]. Likewise, in in-vitro NO-induced apoptosis model, dominant negative-Nrf2 stable cells were found to be more sensitive to apoptosis than wild-type cells, and knockdown of Nrf2 mediated by siRNA in sensitized neuroblastoma cells conferred more sensitivity to NO-induced apoptosis [48]. Moreover, Nrf2 knockout mice have been seen to be more susceptible to lesions produced by the mitochondrial complex II inhibitors, and transplantation of Nrf2-over-expressing astrocytes into the striatum has been reported to protect the striatum from malonate-induced lesions [49]. It has been recently found that

fucoxanthin activates Nrf2-ARE and Nrf2-autophagy pathways and thereby provides neuroprotection in traumatic brain injury models [50]. Similarly, mangiferin (a natural C-glucoside xanthine) mediate neuroprotection on early brain injury by acting via Nrf2/HO-1 pathway [51]. From this data, we can conclude that Nrf2-ARE pathway plays a pivotal role in protecting the nervous system from various disorders.

Conclusion

Despite the well-established role of oxidative stress in the etiology of neurological disorders, antioxidant intervention based on the administration of free radical scavengers and various antioxidants have met with limited success in clinical trials. This could be probably due to crosstalk between various inflammatory, non-inflammatory, oxidative stress and excitotoxicity mechanisms, which ultimately leads to diverse neurodegenerative conditions. The current review reported herein has shed light on some of the molecular mechanisms involved in the control of intrinsic anti-oxidant and neuroprotective pathways by Nrf2. Nrf2 signaling pathway confers neuroprotection in various neurological disorders. We believe, the comprehensive knowledge about the mechanisms involved in this pathway can prove valuable to the ongoing research for the treatment of neurodegenerative diseases.

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