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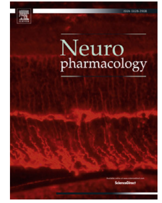

Review

NRF2-regulation in brain health and disease: Implication of cerebral inflammation

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ABSTRACT

The nuclear factor erythroid 2 related factor 2 (NRF2) is a key regulator of endogenous inducible defense systems in the body. Under physiological conditions NRF2 is mainly located in the cytoplasm. However, in response to oxidative stress, NRF2 translocates to the nucleus and binds to specific DNA sites termed "anti-oxidant response elements" or "electrophile response elements" to initiate transcription of cytoprotective genes. Acute oxidative stress to the brain, such as stroke and traumatic brain injury is increased in animals that are deficient in NRF2. Insufficient NRF2 activation in humans has been linked to chronic diseases such as Parkinson's disease, Alzheimer's disease and amyotrophic lateral sclerosis.

New findings have also linked activation of the NRF2 system to anti-inflammatory effects via interactions with NF-κB. Here we review literature on cellular mechanisms of NRF2 regulation, how to maintain and restore NRF2 function and the relationship between NRF2 regulation and brain damage. We bring forward the hypothesis that inflammation via prolonged activation of key kinases (p38 and GSK-3β) and activation of histone deacetylases gives rise to dysregulation of the NRF2 system in the brain, which contributes to oxidative stress and injury.

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1. Regulation of the NRF2 system

During evolution, cells have developed inducible defense systems against harmful endogenous and exogenous substances. Several transcription factors are involved in boosting the cell's defenses. The major regulator of the so-called phase II and some phase III genes is the nuclear factor erythroid 2 related factor 2 (NRF2) (Itoh et al., 1997; Moi et al., 1994). The principle of the NRF2 system is to keep NRF2 protein low under normal conditions with the possibility of rapid induction in case of a sudden increase in oxidation status in the cell. This is achieved by constitutive synthesis and degradation of NRF2 with the possibility of rapid redirection of NRF2 to the nucleus.

NRF2 is a member of the cap'n'collar (CNC) family of transcription factors, which also include NRF1, NRF3 and p45 NF-E2. NRF2 is a basic leucine zipper (bZIP) protein that in the nucleus heterodimerizes with small MAF or JUN proteins followed by binding to specific DNA sites termed anti-oxidant response elements (ARE) or electrophile response elements (EpRE) (Itoh et al., 1997; Venugopal and Jaiswal, 1998). NRF2-ARE binding can initiate transcription of hundreds of cytoprotective genes including enzymes in the glutathione defense system and proteasome subunits (Kwak et al., 2003a). New findings connect NRF2 not only to an elevated anti-oxidant capacity but also to expression of other types of protective proteins such as brain derived neurotrophic factor (Sakata et al., 2012), the anti-apoptotic B-cell lymphoma 2 (Niture and Jaiswal, 2012), the anti-inflammatory interleukin (IL)-10, the mitochondrial transcription (co)-factors NRF-1 and peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) (Piantadosi et al., 2011), the iron exporter ferroportin 1 (Harada et al., 2011), and the autophagic protein p62 (Komatsu et al., 2010).

1.1. Regulation of NRF2 by KEAP1

The NRF2 molecule contains six functional domains named NRF2-ECH homologies (Neh1–6). In the unstressed cell NRF2 is

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bound to Kelch-like ECH associated protein 1 (KEAP1) in the cytoplasm (Itoh et al., 1999) via its KEAP1 binding domain. KEAP1 is a homodimer with three major domains. Each C-terminal in the KEAP1 dimer, the so called DRG domain, binds to NRF2, while the N-terminal part of KEAP1 binds to an E3 ubiquitin ligase complex (Rbx-1) via an adaptor, cullin-3 (Kobayashi et al., 2004). This directs NRF2 to ubiqutination and constitutive degradation by the 26S proteasome (Dhakshinamoorthy and Jaiswal, 2001).

There are several theories on how NRF2 is released from KEAP1 in response to cellular stress. NRF2 binds to the DRG sites of each KEAP1 subunit via two different binding sites, one high affinity (hinge) and one low affinity (latch) (Kobayashi et al., 2006). One hypothesis is that NRF2 can still move freely when bound to the hinge site (high affinity), while the latch site restricts the movement of NRF2 and places the NRF2 lysins in the Neh2 regions for poly-ubiquitination via the cullin-3 E3 ligase. In this model, oxidative/electrophilic molecules modify cysteine residues of KEAP1, which activates NRF2 (Dinkova-Kostova et al., 2002). The KEAP1 protein contains relatively many cysteines, which are in the vicinity of basic amino acids. This configuration lowers the pKa values for many of the thiols and makes them extra reactive to oxidants/electrophiles. Modifications of (some of) these cysteines result in a different conformation of KEAP1, which then can dissociate from the latch (low-affinity) site. The result is that KEAP1 is bound to NRF2 at the hinge site and that "new" non-bound NRF2 can be phosphorylated by protein kinase C (PKC) (Niture et al., 2009) and possibly other kinases (see below), translocated to the nucleus and initiate transcription of cytoprotective genes. Alternative hypotheses on how NRF2 becomes free from KEAP1 include that oxidants/electrophiles can dissociate the NRF2-KEAP1 complex directly (Levonen et al., 2004) or that oxidants/electrophiles dissociate cullin-3 from KEAP1, which leads to blocking of further ubiquitination (Gao et al., 2007) and degradation of KEAP1 (Zhang et al., 2005). Recent studies also show that NRF2 activation can be achieved by autophagic degradation of KEAP1 (see more below).

The abundance of the proteins in the NRF2 system discussed above appears to be regulated by an autoregulatory loop. Thus NRF2 regulates the transcription of KEAP1, cullin-3 and Rbx-1 and, in turn, KEAP1/cullin-3/Rbx-1 degrades NRF2 (Kaspar and Jaiswal, 2010). The KEAP1 complex can also be imported into the nucleus and participate in the degradation of nuclear NRF2 (Niture et al., 2009). Further, feed back systems appear to exist where NRF2 activation induces an increase in proteasome expression and activity. In response to NRF2 activators, increased expression of genes coding for the proteasome subunits 20S and 19S have been observed (Kwak et al., 2003a,b; Kapeta et al., 2010). The NRF2-mediated induction of proteasome genes has been linked to increased resistance to oxidative stress (Kwak et al., 2007; Pickering et al., 2012).

Although KEAP1 is the main regulator of NRF2 activation others exist, including the transcription factor Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), as discussed below. Another regulator of NRF2 is Broad-complex, tramtrack and bric-a-brac and CNC homology 1 (BACH1). This is a transcription factor that competes with NRF2 for binding to ARE sites and thus functions as a repressor of NRF2 activation (Dhakshinamoorthy et al., 2005). Interestingly BACH1 appears to serve as a negative feedback regulator of NRF2 activation as it is regulated by NRF2-activating agents in an NRF2-dependent manner (Jyrkkanen et al., 2011).

1.2. Phosphorylation of NRF2

The transport to and from the nucleus is influenced by factors such as the phosphorylation of NRF2. Several kinases have been shown to affect NRF2 transport differently via specific phosphorylation sites. One of the best characterized include phosphorylation by PKC (Huang et al., 2000), which is necessary for liberating NRF2 from KEAP1 (Bloom and Jaiswal, 2003) and thus promoting transport to the nucleus. Protein kinase CK2 can also phosphorylate NRF2, which promotes transport of NRF2 into the nucleus (Pi et al., 2007). Similar activating effects on NRF2 translocation to the nucleus have been observed for phosphatidylinositide 3-kinases (PI3K) (Nakaso et al., 2003), c-Jun N-terminal kinase (JNK), extracellular regulated kinase (ERK) (Xu et al., 2006) and PERK (Cullinan et al., 2003). However, it has been suggested that mitogen-activated protein kinases (MAPKs)-induced phosphorylation of NRF2 does not directly affect KEAP1-NRF2 protein interaction, but rather acts through indirect mechanisms (Sun et al., 2009a).

Phosphorylation catalyzed by kinases can also increase NRF2 breakdown. The MAPK p38 has been shown to stabilize the interaction between KEAP1 and NRF2 thereby elevating the breakdown of NRF2 (Keum et al., 2006). Activation of glycogen synthase kinase 3-beta (GSK-3β) can cause degradation of NRF2 by the proteasome that is independent of KEAP1. Phosphorylation of the Neh6 domain in NRF2 by GSK-3β leads to recognition by an E3 ubiquitin ligase (beta-TrCP) (Chowdhry et al., 2013). Binding of beta-TrCP couples NRF2 to the cullin-3/Rbx1 ubiqutination complex (Rada et al., 2012), directing NRF2 to proteasomal degradation. GSK3β activation acts upstream and phosphorylates Src kinases, leading to their nuclear localization and NRF2 phosphorylation (Niture et al., 2011; Jain and Jaiswal, 2007). Ultimately this will lead to export, with or without KEAP1, followed by proteasomal degradation of NRF2. Several Src kinases (FYN, SRC, YES, and FGR) in the nucleus can regulate NRF2 via phosphorylation of NRF2 Tyr568 that triggers nuclear export and degradation of NRF2. Thus, kinase activation is of utmost importance in regulation of the NRF2-system.

1.3. Autophagic regulation of NRF2

The protein p62, which represents both a selective autophagy substrate and a cargo receptor for autophagic degradation of misfolded proteins, has been reported to activate NRF2 in response to oxidative stress (Komatsu et al., 2010; Bjorkoy et al., 2005; Komatsu et al., 2007; Lamark et al., 2009). The promoter/enhancer region of the p62 gene contains ARE sites (Jain et al., 2010) and autophagy defects induce an excessive accumulation of p62 and oxidative stress (Komatsu et al., 2007; White et al., 2010). An increase in endogenous p62, either due to a defect in autophagy or as a result of its ectopic expression, sequesters KEAP1 into aggregates, hence causing inhibition of KEAP1-mediated NRF2 ubiquitination and degradation (Lau et al., 2010). Thus, when autophagy is impaired, p62 accumulates and activates NRF2 by sequestering KEAP1 in inclusion bodies. In turn NRF2 promotes new p62 products creating a positive loop of NRF2 activation. With regard to the brain, recent findings demonstrate that interactions between p62 and the KEAP1-NRF2 signaling pathway play a key role in preventing oxidative injury and alleviate endoplasmic reticulum stress during cerebral ischemia/reperfusion (Wang et al., 2013).

1.4. Epigenetic regulation of NRF2

Histone acetylation and phosphorylation, methylation of CpG islands and synthesis of specific miRNAs are additional means by which cells can regulate the levels of NRF2. This field of NRF2 regulation is just beginning to be explored but it contains interesting targets for future therapeutic activation of the NRF2 system, including in the brain. We have shown that factors released from activated microglia activate histone deacetylases (HDACs), reduce the overall acetylation level of histone 3 and decrease the activation

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