Interplay between Nrf2 and NF-κB in Neuroinflammatory Diseases

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**Received date:** November 08, 2016; **Accepted date:** January 31, 2017; **Published date:** February 03, 2017

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**Keywords:** Nrf2; NF-kappaB; Antioxidant; Proinflammatory cytokine; Neuroinflammation

**Abbreviations**

AD: Alzheimer’s Disease; ALS: Amyotrophic Lateral Sclerosis; AREs: Antioxidant Response Elements; Bcl-3: B-cell lymphoma 3 protein; CAM: Cell Adhesion Molecule; CBP: CREB Binding Protein; COX-2: Cyclooxygenase-2; FTH: Ferritin Heavy Chain; FTLD: Ferritin Light Chain; GCLC: Glutamate-Cysteine Ligase Catalytic subunit; GCLM: Glutamate-Cysteine Ligase Modifier subunit; GSK3β: Glycogen Synthase Kinase 3 beta; GSTs: Glutathione-S-Transferases; HD: Huntington’s Disease; HDAC3: Histone Deacetylase 3; HMOX1: Heme Oxygenase 1; IkB: Inhibitor of κB; IKK, IκB Kinase: IL-1: Interleukin-1; IL-2: Interleukin-2; IL-6: Interleukin-6; IL-8: Interleukin-8; iNOS: Inducible Nitric Oxide Synthase; Keap1: Kelch-like ECH-associated protein; LPS: Lipopolysaccharide; MCP1: Monocyte Chemotactic Protein 1; MS: Multiple Sclerosis; NF-κB: Nuclear Factor-κB; NQO1: NAD(P)H dehydrogenase (quinone) 1; Nrf2: Nuclear factor erythroid 2-related factor 2 (Nrf2) and nuclear factor-κB (NF-κB) are key transcription factors regulating antioxidant and inflammatory pathways, respectively. These two opposing factors are inversely regulated, with activity of one most often accompanied by diminished activity of the other, giving rise to the oxidative stress and neuroinflammation evident in neurodegeneration. Emerging evidence is uncovering a complex interplay between Nrf2 and NF-κB, involving extensive interaction of regulatory mechanisms including cytosolic activators and repressors, transactivation partners and direct transcriptional crosstalk. Understanding these interactions may provide insight into the pathophysiology of neuroinflammatory diseases and facilitate discovery of novel therapeutic targets.

**Abstract**

Many neurodegenerative conditions involve redox imbalance and neuroinflammation. Nuclear factor erythroid 2-related factor 2 (Nrf2) and nuclear factor-κB (NF-κB) are key transcription factors regulating antioxidant and inflammatory pathways, respectively. These two opposing factors are inversely regulated, with activity of one most often accompanied by diminished activity of the other, giving rise to the oxidative stress and neuroinflammation evident in neurodegeneration. Emerging evidence is uncovering a complex interplay between Nrf2 and NF-κB, involving extensive interaction of regulatory mechanisms including cytosolic activators and repressors, transactivation partners and direct transcriptional crosstalk. Understanding these interactions may provide insight into the pathophysiology of neuroinflammatory diseases and facilitate discovery of novel therapeutic targets.

**Nrf2 Function and Activation**

Nrf2 is the master regulator of antioxidant pathways, responsible for promoting the transcription of hundreds of antioxidant and cytoprotective genes, and in the brain appears to be repressed in neurons and predominantly restricted to glia [1,2]. Nrf2 is a cap'n'collar basic leucine zipper transcription factor. Under normal conditions, Nrf2 is bound in the cytosol by its negative regulator Kelch-like ECH-associated protein (Keap1), a substrate adaptor protein of a Cullin3-dependent ubiquitin E3 ligase complex. Keap1 constitutively targets Nrf2 for proteasomal degradation. When activated, Nrf2 dissociates from Keap1 and can translocate to the nucleus where it forms heterodimers with small Maf proteins and binds to antioxidant response elements (AREs), promoting the transcription of a battery of antioxidant and cytoprotective genes [3]. Nrf2 targets include genes for glutathione synthesis and utilization (e.g. GCLM, GCLC, GSTs), the thioredoxin and peroxidized systems, NADPH generation, iron metabolism (HMOX1, FTLD, FTH) and quinone detoxification (NQO1) [4]. Nrf2 can be activated in response to oxidative stress and electrophiles via Keap1. Keap1 contains several highly sensitive cysteine residues that when oxidised cause Nrf2 to dissociate from Keap1, allowing Nrf2 to translocate to the nucleus. Thus Keap1 acts as a redox sensor [3]. Nrf2 activity is also regulated by kinases such as GSK3β [5].

**Regulation of NF-κB Activation**

NF-κB is a key regulator of the cellular inflammatory profile, promoting the transcription of inflammatory genes. In the brain, NF-κB signalling occurs predominantly in microglia, as well as astrocytes and oligodendrocytes, but not in neurons [6]. The NF-κB complex consists of homo- or heterodimers of p65, RelB, p50 and p52, the most abundant of which is p65/p50. The dimers are bound in the cytosol by a family of repressor proteins called inhibitor of κB (IκB), which include IκBa, IκBβ, IκBε, IκBγ and Bcl-3. IκB is phosphorylated by the IκB kinase (IKK) complex, consisting of IKKα, IKKβ and IKKγ subunits [7]. Upon activation by stimuli including TNFa, LPS and IL-1, IKK phosphorylates IκB, facilitating IκB degradation via the β-transducin repeat-containing protein (β-TRCP)-Skp1-Cullin1 ubiquitin ligase complex [8]. NF-κB homo- and heterodimers can then translocate to the nucleus and bind to κB motifs in the promoter region of proinflammatory target genes [9]. These include cytokines (e.g. IL-1, IL-6, TNFa), chemokines (e.g. IL-8, MCP1), adhesion molecules (e.g. CAM, VCAM) and inducible effector enzymes (e.g. iNOS, COX-2) [7].

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Inverse Regulation of Nrf2 and NF-κB in Neurodegeneration

Inflammation, with elevated pro-inflammatory mediators and oxidative stress, is common to many neurodegenerative diseases, as evidenced by the presence of activated astrocytes and microglia in the affected regions of the brain and/or spinal cord in diseases including Alzheimer’s disease (AD), Parkinson’s disease (PD), amyotrophic lateral sclerosis (ALS) and Huntington’s disease (HD), generally associated with degenerating neurons. Activated microglia are also found within and around amyloid plaques in AD, while activated astrocytes surround the plaques. Multiple sclerosis (MS), particularly the relapsing-remitting form, presents with transient localized sites of inflammation, whereby infiltrating peripheral T cells and microglia attack axonal myelin sheaths and oligodendrocytes. Stroke and traumatic brain injury (TBI) involve glial and peripheral immune cell activation at the site of injury that varies as the injury progresses. This extensive neuroinflammation and oxidative stress is consistent with elevated NF-xB activity concomitant with impaired Nrf2 activity [10,11], hence there is abundant evidence for inverse regulation of Nrf2 and NF-κB in neurodegenerative disease. Indeed, Nrf2 expression is diminished in human post-mortem tissue of AD and ALS patients [12,13]. Further evidence for the interplay between Nrf2 and NF-κB comes from experimental induction of inflammation. LPS-induced inflammation in the hippocampus is exacerbated in Nrf2-deficient mice [14], while induction of inflammation via α-synuclein in BV2 microglia is enhanced in the absence of Nrf2 [15]. Deletion of Nrf2 enhances inflammation and is associated with worsened outcomes in animal models of AD [16,17], PD [18], MS [19], and TBI [20]. These studies show that the absence of Nrf2 enhances NF-κB activity.

Conversely, inducing Nrf2 is associated with decreased inflammation. Nrf2 inducers such as synthetic triterpenoids and dimethyl fumarate decrease neuroinflammation and are protective in animal models of AD [21], PD [22,23], ALS [24], MS [25,26], HD [27,28] and stroke [29]. Other Nrf2 inducers also reduce neuroinflammation and are protective in animal models of AD [30], PD [31], ALS [32] and TBI [33], as does overexpression of Nrf2 in AD [34], ALS [35] and PD [18] animal models. That induction of Nrf2 suppresses inflammation and conversely inhibition of Nrf2 exacerbates inflammation across these diverse diseases and models, each with inflammatory pathology differing in localisation, extent and temporal pattern, supports the idea that Nrf2 and NF-κB are inversely regulated in a fundamental manner.

In humans, dimethyl fumarate is approved for the treatment of relapsing-remitting MS under the trade name Tecfidera following two successful Phase III trials [36], while the Nrf2 inducer DL-3-n-butylphthalide has produced positive outcomes in phase II clinical trials for acute ischemic stroke (administered within 48h of stroke onset) and vascular cognitive impairment without dementia [37,38]. However, none of these trials specifically interrogated Nrf2 or NF-κB signalling. Interestingly, NF-κB is inhibited in B cells isolated from MS patients administered Tecfidera [39], and this inhibition seems to occur in cultured lymphocytes in a manner independent of Nrf2 [40]. Clearly Nrf2 and NF-κB activity are inversely related in neuroinflammatory diseases. The molecular mechanisms governing the interplay between Nrf2 and NF-κB will now be discussed (Figure 1).

Activation of Nrf2 and NF-κB Signalling by Oxidative Stress

Nrf2 is well known to be regulated by oxidative stress via oxidation of sensitive cysteine residues on Keap1, causing release of Nrf2 and subsequent nuclear translocation [3]. In addition to proinflammatory mediators, NF-κB is also believed to be regulated by oxidative stress. This stems from early investigations showing activation of NF-κB signalling by oxidants and inhibition of NF-κB signalling in the presence of antioxidants occurring at the level of NF-κB release from IκB [41-43]. This led to speculations that Nrf2 may impede NF-κB activity by eliminating oxidative stress. However, more subtle and specific interactions between antioxidants/antioxidants and NF-κB are emerging [44]. For instance, inhibition of NF-κB signalling by antioxidants has been shown to occur independent of their antioxidant activity, such as N-acetylcysteine inhibiting TNFα stimulation of NF-κB via interference with the TNFα receptor. In the case of pyrrolidine dithiocarbamate (PDTC), a well-known inhibitor of NF-κB that prevents the dissociation of NF-κB from IκB [45], its inhibitory action was originally ascribed to its antioxidant actions [42]. More recently, the mechanism by which PDTC inhibits NF-κB has been shown to be via disruption of IκB ubiquitin ligase activity [46]. However, PDTC also activates Nrf2 in brain and cultured astrocytes but not neurons [2], and improves cognition in the APP/PS1 AD mouse model [47]. Whether Nrf2 activation by PDTC is driven by NF-κB inhibition, or by other independent mechanisms remains to be elucidated.

Promiscuity of Nrf2 and NF-κB Activators and Repressors

There is considerable interaction between Nrf2 and NF-κB activators and repressors. For instance, Nrf2 binds to Keap1 via a conserved ETGE motif in Nrf2. IKK also contains an ETGE motif and can bind to Keap1 [48-50]. Keap1-mediated degradation of IKK is demonstrated by the elevation of IKK and NF-κB signalling when Keap1 is knocked down [48,50]. Furthermore, while Keap1 knockdown is well-known to induce Nrf2 signalling (due to lack of repression) [3], the influence of Nrf2 per se can be excluded as co-knockdown of Nrf2 has no effect [48]. In contrast to the proteasomal degradation of Nrf2, Keap1-dependent degradation of IKK likely occurs via an autophagy-dependent pathway [50], as per the degradation of Keap1 itself [51]. Importantly, the ETGE motif in IKK is conserved across human, chimpanzee, chicken and dog, but not mouse, rat, xenopus or medaka fish [48,50], which may influence investigations of this relationship in many in vitro and preclinical animal models. The relative extent and conditions governing the binding of Keap1 to IKK and Nrf2 remains unclear.

Conversely, there is also crosstalk between the NF-κB-related E3 ligase adapter protein β-TrCP and Nrf2. Following phosphorylation by IKK, IκB releases NF-κB and is targeted for proteasomal degradation via the β-TrCP-Skp1-Cullin1 ubiquitin ligase complex in manner analogous to Nrf2 degradation via the Keap1-Cul3-Rbx1 complex [8]. Nrf2 can also be targeted for degradation in a Keap1-independent manner by β-TrCP, in a process mediated by GSK3β-induced phosphorylation of activated Nrf2, thereby shutting down Nrf2 activity [52,53]. As per IKK/Nrf2 interactions with Keap1, the relative competition of Nrf2 and IκB for β-TrCP requires further investigation.
Figure 1: Interplay between Nrf2 and NF-κB regulation. NF-κB (depicted as p65/p50 heterodimer) is bound in the cytoplasm by IκB. In response to external stimuli or possibly oxidative stress, IKK is activated and phosphorylates IκB, causing dissociation of NF-κB which subsequently translocates to the nucleus where it promotes the transcription of proinflammatory genes by binding to κB motifs. Phosphorylated IκB binds to β-TrCP and is targeted for proteasomal degradation. Under normal conditions, Nrf2 is bound by Keap1 in the cytosol and also targeted for proteasomal degradation. Upon activation by oxidative stress or electrophiles, Nrf2 is released from Keap1 and can translocate to the nucleus where it forms a heterodimer with small Maf proteins (sMaf) and binds to antioxidant response elements (ARE) to promote the transcription of antioxidant genes. Nrf2 can also bind to NF-κB target genes and repress their transcription, in a process possibly involving binding partners and not influenced by presence or absence of the ARE sequence or NF-κB binding. Both NF-κB and Nrf2 compete for CBP, which promotes DNA binding. Activated Nrf2 can be phosphorylated by GSK3β, which facilitates binding by β-TrCP and targeting for proteasomal degradation. Keap1 is degraded by autophagy, and can also bind and degrade IKK via autophagy.

Activation of toll-like receptors (TLR), well known to induce an NF-κB-dependent inflammatory response, has recently been shown to activate Nrf2 via autophagy-dependent degradation of Keap1 [54]. Another NF-κB activating protein, Rho family GTP-binding protein (RAC1) [55,56], has recently been shown to also activate Nrf2, which subsequently blocks RAC1-dependent NF-κB activation [57]. Conversely, the Nrf2 target heme oxygenase-1 per se inhibits NF-κB activation in ischemic and hemorrhagic stroke [58,59].

Interactions between Nrf2 and NF-κB Transactivational Activity

There is also extensive crosstalk between Nrf2 and NF-κB in the nucleus. NF-κB can directly promote Nrf2 transcription via the κB motif in the promoter region of the NFE2L2 gene encoding Nrf2 [60]. Both transcription factors also compete with CREB binding protein (CBP), which assists in binding of the transcription factors to their cognate DNA motifs [61,62]. Phosphorylated p65 appears to have a higher affinity for CBP than Nrf2, outcompeting the latter and diminishing Nrf2 target transcription [62]. On the other hand, Nrf2 activation in microglial-like BV2 cells by ethyl pyruvate competes with p65 for CBP, suppressing p65 transcriptional activity [63]. Activated p65 can also repress Nrf2 signalling by promoting hypoacetylation of histones via HDAC3, which also sequesters CBP and/or the small Maf protein MafK, all repressing Nrf2 activity [62].

In addition to these many and varied mechanisms of co-regulation, direct transcriptional repression of NF-κB proinflammatory targets by Nrf2 has recently been described. Kobayashi et al. [64] find that Nrf2 binds to the promoter region of proinflammatory targets of NF-κB,
repressing their transcription. This appears to occur regardless of NF-κB binding, and does not require the ARE sequence, to which Nrf2 binding typically results in promotion of transcription [64]. Nrf2 binding to NF-κB targets may involve binding partners, although their identity remains to be determined. The mechanism by which Nrf2 represses transcription appears to involve inhibition of RNA Pol II recruitment, thus preventing transcription [64]. This landmark study identifies for the first time a mechanism by which Nrf2 transcriptional activity directly represses proinflammatory cytokine production. The study focuses on peripheral macrophages, and it remains to be determined whether this mechanism is maintained in inflammatory cells of the central nervous system.

Conclusions

Nrf2 and NF-κB control the transcription of redox balance and inflammatory pathways. Given the opposing nature of these pathways, it is not surprising that there is extensive crosstalk between almost every level of Nrf2 and NF-κB regulation. The idea that NF-κB is regulated by redox status, which in turn is controlled by Nrf2, is too simplistic and a more complex picture is emerging. It is likely that the balance of Nrf2 and NF-κB signalling is dynamically governed by a combination of external stimuli and the prevailing cellular and environmental conditions, specific to given cell types and tissues. The mechanisms modulating Nrf2 and NF-κB in neuroinflammatory diseases require further investigation, which could uncover new therapeutic targets for their treatment.

Acknowledgements

JRL is supported by an NMHRC Peter Doherty fellowship.

References

1. Bell KF, Al-Mubarak B, Martel MA, McKay S, Wheelan N, et al. (2015) Neuronal development is promoted by weakened intrinsic antioxidant defences due to epigenetic repression of Nrf2. Nat Commun 6: 7066.
2. Liddell JR, Lehtonen S, Duncan C, Keksa-Goldsteine V, Levonen AL, et al. (2016) Pyrrolidine dithiocarbamate activates the Nrf2 pathway in astrocytes. J Neuroinflammation 13: 49.
3. Suzuki T, Yamamoto M (2015) Molecular basis of the Keap1-Nrf2 system. Free Radic Biol Med 88: 93-100.
4. Gorrini C, Harris IS, Mak TW (2013) Modulation of oxidative stress as an anticancer strategy. Nat Rev Drug Discov 12: 931-947.
5. Cuadrado A (2015) Structural and functional characterization of Nrf2 degradation by glycogen synthase kinase 3β-TrCP. Free Radic Biol Med 88: 147-157.
6. Hui CW, Zhang Y, Herrup K (2016) Non-Neuronal Cells Are Required to Mediate the Effects of Neuroinflammation: Results from a Neuron-Enriched Culture System. PLoS One 11: e0147134.
7. Ghosh S, Karin M (2002) Missing pieces in the NF-kappaB puzzle. Cell 109 Suppl: S81-96.
8. Winston JT, Strack P, Beer-Romero P, Chu CY, Elledge SJ et al. (1999) The SCFbeta-TRCP ubiquitin ligase complex associates specifically with phosphorylated destruction motifs in IkappaBalpha and beta-catenin and stimulates IkappaBalpha ubiquitination in vitro. Genes Dev 13: 270-283.
9. Chen FE, Huang DB, Chen YQ, Ghosh G (1998) Crystal structure of p50/p65 heterodimer of transcription factor NF-kappaB bound to DNA. Nature 391: 410-413.
10. Buendia I, Michalska P, Navarro E, Gameiro I, Ega J, et al. (2016) Nrf2-ARE pathway: An emerging target against oxidative stress and neuroinflammation in neurodegenerative diseases. Pharmacol Ther 157: 84-104.
and neurological function after stroke in rats. J Neuroinflammation 13: 269.
30. Peng Y, Sun J, Hon S, Nylander AN, Xia W et al. (2010) L-3-n-butylnaphthalide improves cognitive impairment and reduces amyloid-beta in a transgenic model of Alzheimer’s disease. J Neurosci 30: 8180-8189.
31. Jazwa A, Rojo AI, Innamorato NG, Hesse M, Fernandez-Ruiz J et al. (2011) Pharmacological targeting of the transcription factor Nrf2 at the basal ganglia provides disease modifying therapy for experimental parkinsonism. Antioxid Redox Signal 14: 2347-2360.
32. Feng X, Peng Y, Liu M, Cui L (2012) DL-3-n-butylnaphthalide extends survival by attenuating glial activation in a mouse model of amyotrophic lateral sclerosis. Neuropharmacology 62: 1004-1010.
33. Hong Y, Yan W, Chen S, Sun CR, Zhang JM (2010) The role of Nrf2 signaling in the regulation of antioxidants and detoxifying enzymes after traumatic brain injury in rats and mice. Acta Pharmacol Sin 31: 1421-1430.
34. Kanninen K, Heikkinen R, Malm T, Rolova T, Kuhmonen S, et al. (2009) Intrahippocampal injection of a lentiviral vector expressing Nrf2 improves spatial learning in a mouse model of Alzheimer’s disease. Proc Natl Acad Sci U S A 106: 16505-16510.
35. Vargas MR, Johnson DA, Sirkis DW, Messing A, Johnson JA (2008) Nrf2 activation in astrocytes protects against neurodegeneration in mouse models of familial amyotrophic lateral sclerosis. J Neurosci 28: 133574-133581.
36. Linker RA, Haghikia A (2016) Dimethyl fumarate in multiple sclerosis: latest developments, evidence and place in therapy. Ther Adv Chronic Dis 7: 198-207.
37. Jia J, Wei C, Liang J, Zhou A, Zuo X, et al. (2016) The effects of DL-3-n-butylnaphthalide in patients with vascular cognitive impairment without dementia caused by subcortical ischemic small vessel disease: A multicentre, randomized, double-blind, placebo-controlled trial. Alzheimers Dement 12: 89-99.
38. Cui LY, Zhu YC, Gao S, Wang JM, Peng B, et al. (2013) Ninety-day administration of DL-3-n-butylnaphthalide for acute ischemic stroke: a randomized, double-blind trial. Chin Med J (Engl) 126: 3405-3410.
39. Li R, Rezk A, Ghadiri M, Luessi F (2017) Dimethyl Fumarate Treatment Mediates an Anti-Inflammatory Shift in B Cell Subsets of Patients with Multiple Sclerosis. J Immunol 198: 691-698.
40. Gillard GO, Collette B, Anderson J, Chao J, Scannev RH, et al. (2015) DME, but not other fumarates, inhibits NF-kappaB activity in vitro in an NF-kappaB independent manner. J Neuroimmunol 283: 74-85.
41. Staal FJ, Roederer M, Herzenberg LA, Herzenberg LA (1990) Intracellular thiols regulate activation of nuclear factor kappa B and transcription of human immunodeficiency virus. Proc Natl Acad Sci U S A 87: 9943-9947.
42. Schreck R, Meier B, Männel DN, Dröge W, Baeuerle PA (1992) Dithiocarbamates as potent inhibitors of nuclear factor kappa B activation in intact cells. J Exp Med 175: 1181-1194.
43. Schreck R, Rieber P, Baeuerle PA (1991) Reactive oxygen intermediates as inducer to modulator. Antioxid Redox Signal 11: 2223-2243.
44. Oliveira-Marques V, Marinho HS, Cyme L, Antunes F (2009) Role of hydrogen peroxide in NF-kappaB activation: from inducer to modulator. Antioxid Redox Signal 11: 2223-2243.
45. Liu SE, Ye X, Malik AB (1999) Pyrroldine dithiocarbamate prevents I kappaB degradation and reduces microvascular injury induced by lipopolysaccharide in multiple organs. Mol Pharmacol 55: 658-667.
46. Hayakawa M, Miyashita H, Sakamoto I, Kitagawa M, Tanaka H, et al. (2003) Evidence that reactive oxygen species do not mediate NF-kappab activation. EMBO J 22: 3356-3366.
47. Malem TN, Izenen H, Goldsteins G, Keksa-Goldsteine V, Abtioniemi T et al. (2007) Pyrroldine dithiocarbamate activates Akt and improves spatial learning in APP/PS1 mice without affecting beta-amyloid burden. J Neurosci 27: 3712-3721.
48. Lee DE, Kuo HP, Liu M, Chou CK, Xia W, et al. (2009) KEAP1 E3 ligase-mediated downregulation of NF-kappaB signaling by targeting IKKbeta. Mol Cell 36: 131-140.
49. Jiang ZY, Chu HX, Xi MY, Yang TT, Iia JM, et al. (2013) Insight into the intermolecular recognition mechanism between Keap1 and IKKp combining homology modelling, protein-protein docking, molecular dynamics simulations and virtual alanine mutation. PLoS One 8: e73076.
50. Kim JE, You DJ, Lee C, Ahn C, Seong JY, et al. (2010) Suppression of NF-kappab signaling by KEAP1 regulation of IKKbeta activity through autophagic degradation and inhibition of phosphorylation. Cell Signal 22: 1645-1654.
51. Taguchi K, Fujikawa N, Komatsu M, Ishii T, Unno M, et al. (2012) Keap1 degradation by autophagy for the maintenance of redox homeostasis. Proc Natl Acad Sci U S A 109: 15361-15366.
52. Chowdhry S, Zhang Y, McMahon M, Sutherland C, Cuadrado A, et al. (2013) Nrf2 is controlled by two distinct beta-TrCP recognition motifs in its Neh6 domain, one of which can be modulated by GSK-3 activity. Oncogene 32: 3765-3781.
53. Rada P, Rojo AI, Chowdhry S, McMahon M, Hayes JD, et al. (2011) SCF/[beta]-TrCP promotes glycogen synthase kinase 3-dependent degradation of the Nrf2 transcription factor in a Keap1-independent manner. Mol Cell Biol 31: 1121-1133.
54. Yin S, Cao W (2015) Toll-Like Receptor Signaling Induces Nrf2 Pathway Activation through p62/Triggered Keap1 Degradation. Mol Cell 35: 2673-2683.
55. Sanlioglu S, Williams CM, Samavati L, Butler NS, Wang G et al. (2001) Lipopolysaccharide induces Rac1-dependent reactive oxygen species formation and coordinates tumor necrosis factor-alpha secretion through IKK regulation of NF-kappaB. J Biol Chem 276: 30188-30198.
56. Arbibe L, Mira JP, Teusch N, Kline L, Guha M, et al. (2000) Toll-like receptor 2-mediated NF-kappaB activation requires a Rac1-dependent pathway. Nat Immunol 1: 533-540.
57. Cuadrado A, Martin-Moldes Z, Ye J, Lastres-Becker I (2014) Transcription factors Nrf2 and NF-kappab are coordinated effectors of the Rho family, GTP-binding protein RAC1 during inflammation. J Biol Chem 289: 15244-15258.
58. Yin XP, Wu D, Zhou J, Chen ZY, Bao B, et al. (2015) Heme oxygenase 1 plays a role of neuron-protection by regulating Nrf2-ARE signaling post intracerebral hemorrhage. Int J Clin Exp Pathol 8: 10156-10163.
59. Yeh CH, Chen TP, Wang YC, Lin YM, Lin PJ (2009) HO-1 activation can attenuate cardiomyocytic apoptosis via inhibition of NF-kappaB and AP-1 translocation following cardiac global ischemia and reperfusion. J Surg Res 155: 147-156.
60. Rushworth SA, Zaitseva L, Murray MY, Shah NM, Bowles KM, et al. (2012) The high Nrf2 expression in human acute myeloid leukemia is driven by NF-kappaB and underlies its chemo-resistance. Blood 120: 5188-5198.
61. Katoh Y, Itoh K, Yoshida E, Miyagishi M, Fukamizu A, et al. (2001) Two domains of Nfr2 cooperatively bind CBP, a CREB binding protein, and synergistically activate transcription. Genes Cells 6: 857-868.
62. Liu GH, Qu J, Shen X (2008) NF-kappab/p65 antagonizes Nrf2-ARE pathway by depriving CBP from Nrf2 and facilitating recruitment of HDAC3 to Mafx. Biochim Biophys Acta 1783: 713-727.
63. Kim SW, Lee HK, Shin JH, Lee JK (2013) Up-down regulation of HO-1 and iNOS gene expressions by ethyl pyruvate via recruiting p300 to Nrf2 and depriving It from p65. Free Radic Biol Med 65: 468-476.
64. Kobayashi EH, Suzuki T, Funayama R, Nagashima T, Hayashi M, et al. (2014) Nrf2 suppresses macrophage inflammatory response by blocking proinflammatory cytokine transcription. Nat Commun 7: 11624.
