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The role of Nrf2 transcription factors in various physiological and pathological states

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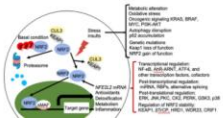

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REVIEW ARTICLE

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The role of Nrf2 transcription factors in various physiological and pathological states

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ABSTRACT

Since its first report in 1994, understanding of the nuclear factor erythroid 2-related factor 2 (Nrf2) has continued to grow. Initially recognized for its role in cellular response to oxidative stress, Nrf2 is now known to be involved in a variety of regulatory process, including metabolic regulation, autophagy, protein homeostasis (proteostasis), and mitochondrial biogenesis. The expression of Nrf2 target genes is highly dependent on stimulus activation and interactions with transcription factors, activators, and repressors. Nrf2 activation serves as a defense mechanism under physiological conditions, but in the context of cancer, it can trigger the development of cancer cells due to its complex roles. Nrf2 is strongly associated with the onset and development of many diseases, including those caused by metabolic disorders and inflammation. Understanding Nrf2's diverse functions offers valuable insights into disease pathogenesis and potential therapeutic approaches. This review explores the pleiotropic role of Nrf2 regulation.

Keywords: Nrf2, oxidative stress, metabolic regulation, proteostasis, transcription factor

Introduction

As a transcription factor, Nrf2 plays a major role in xenobiotic metabolism and the response to reactive oxygen species (ROS) [1,2]. Oxidative stress activates antioxidant genes via the antioxidant response element (ARE) [3,4]. Nrf2 was first reported in 1994 as an NF-E2-like transcription activator binding to the NF-E2/AP1 tandem repeat of the beta-globin locus control region [5,6], but its biological function is not yet clearly known. In 1996, studies in Nrf2 knockout mice revealed no aberrant phenotype, although the mice were more susceptible to stress [7]. In 1997, a study showed that knocking out enzymes such as glutathione S-transferase (GST) and NAD(P) H:quinone oxidoreductase-1 (NQO1), which are regulated by ARE, revealed that Nrf2 controls drug metabolism enzymes in vivo [8]. Recent findings revealed that Nrf2 regulates various processes through ARE and electrophile response elements (EpRE), which play a role in regulating endogenous responses to various intrinsic and extrinsic stresses [9–15].

Recent studies have further identified new roles of Nrf2 beyond its response to oxidative stress. Nrf2 is involved in regulating inflammation, autophagy, metabolism, protein homeostasis (proteostasis) and unfolded protein response (UPR), and mitochondrial biogenesis, as well as being associated with carcinogenesis [1,2,15,16]. These findings suggest that Nrf2 is a pleiotropic transcription factor. This review presents the role of Nrf2 in various processes inside the cell.

Structure of Nrf2

As a part of family of Cap'n'collar (CNC) proteins, Nrf2 has a unique CNC domain that binds to the basic leucine zipper (CNC-bZIP) motif [2,3]. The Nrf2 protein comprises seven functional domains, known as Nrf2-ECH homology domains (Neh1-

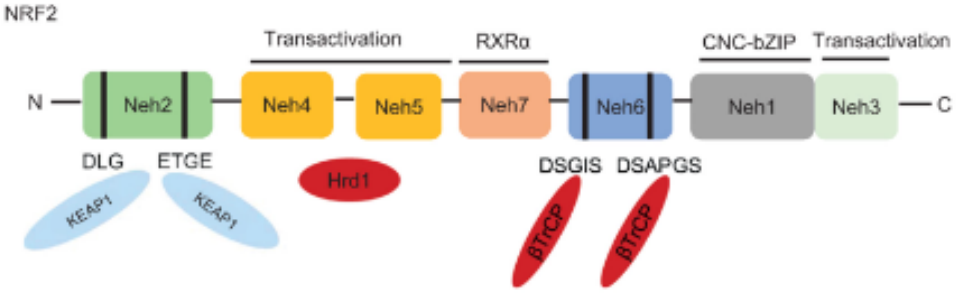

Figure 1. The structure of Nrf2. Nrf2 comprises seven domains, known as Nrf2-ECH homology domains (Neh1- Neh7)

Neh7), each with different functions in regulating Nrf2 transcription activity.

(a) Neh1 domain: comprises the CNC-bZIP region, enabling heterodimerization with the small musculoaponeurotic fibrosarcoma (sMAF) oncogenes. This interaction is crucial for recognizing ARE and/or EpRE. The CNC-bZIP region is conserved across various species, highlighting its importance for Nrf2 function [15].

(b) Neh2 domain: Features an N-terminal domain that binds to the negative regulatory domain of Kelch-like ECH-associated protein 1 (KEAP1). This domain contains ETGE and DLG motif, mainly interacting with the domain (KEAP1) for ubiquitination and subsequent NRF2 degradation [1,2].

(c) Neh3-5 domains: Serves as domains for transcriptional activation by interacting with transcriptional components [1,2].

(d) Neh6 domain: Involved in the degradation of Nrf2 independent of Keap1. It contains two redox-independent degrons, DSGIS and DSAPGS, which link to E3 ubiquitin ligase β-transducin repeat-containing protein (βTrCP) [1,2].

(e) Neh7 domain: Functions to suppress Nrf2 activity by interacting with retinoic X receptor alpha (RXRα).

All of these domains maintain the stability of Nrf2 and facilitate transcriptional activation of the target genes at a stratified level, encompassing transcriptional, post-transcriptional, and post-translational regulation in response to various stresses [1]. The structure of Nrf2 is illustrated in Figure 1.

Regulation of Nrf2

The regulation of Nrf2 generally occurs through the various stages shown in Figure 2 below.

Regulation of Nrf2 stability

Under basal conditions, Nrf2 is maintained at low levels within cells due to proteasomal degradation mediated by KEAP1 [1,17]. Nrf2 stability is strictly regulated through ubiquitination mediated by E3 ubiquitin ligase complexes and subsequent proteasomal degradation. The ubiquitin ligase complexes involved in this regulation include HRD1/Synoviolin, WD Repeat protein (WDR), βTrCP-S-phase kinase-associated protein-1 (SKP1)-CUL1-RBX1, KEAP1-Cullin (CUL) 3-RING-box protein (RBX)1, and 3-CUL4-damaged DNA binding protein (DDB)1. Each of these complexes plays a role under different cellular conditions [1].

Regulation of Nrf2 transcription

Nrf2 transcription is regulated through various mechanisms involving NF-κB binding sites, the aryl hydrocarbon receptor (AHR)-AHR nuclear translocator (ARNT) complex, other transcription factors, and cofactors [1]. The Nrf2 transcription factor binds to the ARE promoter region to activate gene transcription. The NFE2L2 gene contains the ARE promoter region, a xenobiotic responsive element (XRE), two additional promoters with XRE-like elements, and

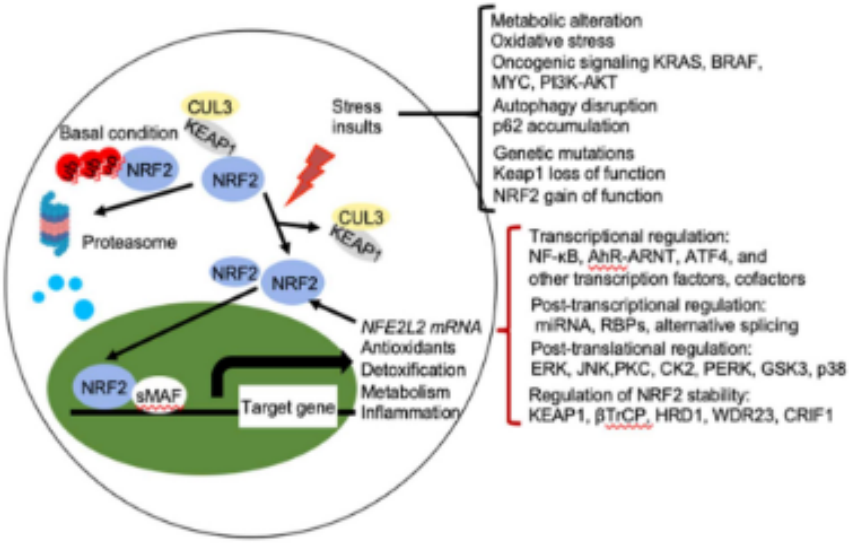

Figure 2. Stages of Nrf2 regulation. Nrf2 regulation involves multiple statges: stability, transcription, post-transcription, post-translation, metabolic changes, response to oxidative stress, oncogene signaling, autophagy regulation, and genetic mutations [1]

NF-κB binding site. The ARE region allows Nrf2 to directly activate the transcription process through a positive feedback mechanism that amplifies Nrf2's effect [1]. Additionally, transcription of NFE2L2 is regulated by various transcription factors, such as NF-κB and AHR. The AHR, in particular, activates the XRE [1,10].

Regulation of Nrf2 post-transcription

Post-transcription regulation of Nrf2 involves microRNAs (miRNAs), RNA-binding proteins (RBPs), and alternative splicing. MicroRNAs are non-coding RNAs, typically 22 nucleotides long, that can suppress gene expression by binding to mRNA molecules in a sequence-specific manner, thereby inhibiting protein translation and destabilizing mRNA. A decrease in Nrf2 transcription activity has been associated with an increase in miR-93, miR-144, miR-153, miR-28, and miR-34. However, the role of miRNAs regulation requires further study and validation [1,18].

Regulation of target gene activation

Nrf2 activation is strictly regulated, as only specific genes can interact with Nrf2 and its binding component (transcription factors, mediators, and cofactors) to achieve activation. Key transcription factors involved include sMAF transcription factors, BTB and CNC homology transcription factors 1 (BACH1), activating transcription factor 4 (ATF4), activator protein 1 (AP-1) subunit c-Jun, CREB-binding protein (CBP), p300 cofactors, activating transcription factor 3 (ATF3), and other co-activators [1,19].

Regulation of Nrf2 in oxidative stress response and drug detoxification

Nrf2 regulation oxidative stress response and drug detoxification involves the expression of cytoprotective genes that facilitates the synthesis of enzymes involved in drug detoxification and maintenance of cellular hemostasis [1–3].

a. Phase I enzymes: These enzymes participate in reduction, oxidation, and hydrolytic reactions of xenobiotics. Examples include aldehyde dehydrogenase 1 (ALDH1), NQO1, aldo-keto reductases (AKRs), carbonyl reductases (CBRs), and some cytochrome P450 oxidoreductases (CYPs) [3].
b. Phase II enzymes: These enzymes are involved

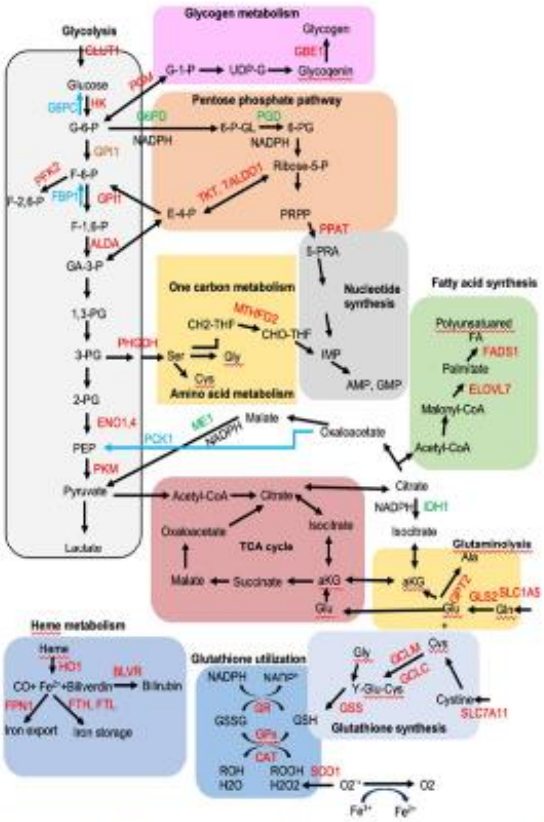

Figure 3. Regulation of Nrf2 on metabolism. Nrf2 enhances the expression of genes involved in glycolysis, glutaminolysis, glycogen metabolism, pentose phosphate pathway, amino acid metabolism, fatty acid synthesis, heme metabolism, glutathione synthesis, and nucleotide biosynthesis (red). Nrf2 decreases the expression of genes associated with gluconeogenesis (blue). Enzymes involved in NADPH production are highlighted in green [1]

in conjugation reactions, such as UDP-glucuronosyltransferase (UGT), glutathione S-transferase (GST), heme oxygenase-1 (HO-1), and UDP-glucuronate synthase [3,20].

c. Phase II enzymes: These drug transporters transport conjugated metabolites after phase II. Example include breast cancer resistant protein (BCRP), ATP-binding cassette G5 (ABCG5), multidrug resistance-associated proteins (MDR), and ATP-binding cassette G8 (ABCG8) [3].

Nrf2-targeted enzymes for ROS elimination include thioredoxin reductase, thioredoxin, catalase (CAT), superoxide dismutase 1 (SOD1), peroxiredoxin, glutathione peroxidase, and sulforedoxine, as well as some glutathione S-transferases [2,3,20]. The cytoprotective proteins encoded by Nrf2 are essential for protective mechanisms against various toxins and oxidants, particularly in diseases based on oxidative stress, such as cancer, coronary disease, metabolic syndrome, neurodegenerative diseases, and autoimmune diseases [2].

Regulation of Nrf2 on metabolism

Nrf2 improves the gene expression involved in glycolysis, the pentose phosphate pathways, glycogen metabolism, amino acid metabolism, glutaminolysis, fatty acid synthesis, heme metabolism, nucleotide biosynthesis, and glutathione synthesis. Conversely,

Nrf2 decreases the gene expression correlated with gluconeogenesis. Many studies support that Nrf2 is a major key in the reprogramming of cancer metabolism [2]. The regulatory mechanisms of Nrf2 are illustrated in Figure 3.

Nrf2 regulation on unfolded protein response (UPR) and proteostasis

Misfolded protein accumulation triggers the production of ROS from the mitochondria and endoplasmic reticulum (ER), leading to an increase in activation of Nrf2 [17]. Nrf2 activates transcription of ATF4, which is related to amino acid metabolism. In *C. elegans,* the homologous Nrf2 protein SKN-1 activates various UPR target genes, including ATF6 and XBP1, thereby enhancing the UPR program by maintaining ER integrity and protein homeostasis (proteostasis) [21]. Additionally, Nrf2 promotes the expression of proteasome maturation proteins (POMP), which is crucial for proteostasis [22]. In summary, Nrf2 increases proteosome activity and antioxidants expression, aiding in stress adaptation.

Nrf2 regulation on autophagy

Nrf2 plays a significant role in autophagy by upregulating the expression of autophagy-related genes, including SQSTM1/P62, autophagy protein 5 (ATG5), calcium-binding and coiled-coil domain-containing protein 2 (CALCOCO2/NDP52), gamma-aminobutyric acid receptor-associated protein-like 1 (GABARAPL1), and unc-51-like kinase 1 (ULK1) [17]. Interestingly, the activation of Nrf2 can be stimulated by the accumulation of oxidized proteins or organelles due to impaired autophagy. This increase in Nrf2 is mediated by the accumulation of p62, a multifunctional receptor that stabilizes KEAP 1 and Nrf2, under autophagy-deficient conditions. In conclusion, a positive feedback loop by p62 and Nrf2 can regulate numerous cellular functions [23].

NRF2 regulation on mitochondrial biogenesis

Nrf2 is involved in enhancing the production and growth of new mitochondria within cells. This process is known as mitochondrial biogenesis. Nrf2 stimulates mitochondrial biogenesis by activating nuclear respiratory factor-1 (NRF-1), is a key regulator of mitochondrial transcription factor A (TFAM) and mitochondrial transcription factor B2 (TFBM2) [24]. TFAM is involved in the transcription and maintenance of mitochondrial DNA, while TFBM2 works alongside TFAM to regulate mitochondrial gene expression. Nrf2 also directly regulates the expression of peroxisome proliferator-activated receptor gamma co-activator 1 alpha (PGC-1α), a principal regulator of mitochondrial function and biogenesis. The cooperation between Nrf2 and PGC-1α regulates various aspects of mitochondrial function [24–26].

Conclusion

Nrf2 is a widely expressed transcription factor in mammalian cells, belonging to the Cap'n'collar (CNC) protein family. It features a unique CNC domain that binds to the basic leucine zipper (CNC-bZIP) motif. The Nrf2 protein contains seven functional domains, known as Nrf2-ECH homology domains (Neh1-Neh7). Nrf2 regulation occurs at multiple stages, including stability, transcription, post-transcription, post-translation, and target gene activation. This regulation is highly selective, with only specific genes capable of interacting with Nrf2 and its binding partners to achieve activation. Recent studies have highlighted the pleiotropic nature of Nrf2, demonstrating its roles not only in oxidative stress response and drug detoxification but also in metabolism, heme synthesis, proteostasis, unfolded protein response (UPR), autophagy, and mitochondrial biogenesis.

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Declaration of Interest

The authors declare no conflict of interest.

Author contributions

DY: Conceptualization, Writing – original draft; SWAJ: Supervision, Writing – review and editing.

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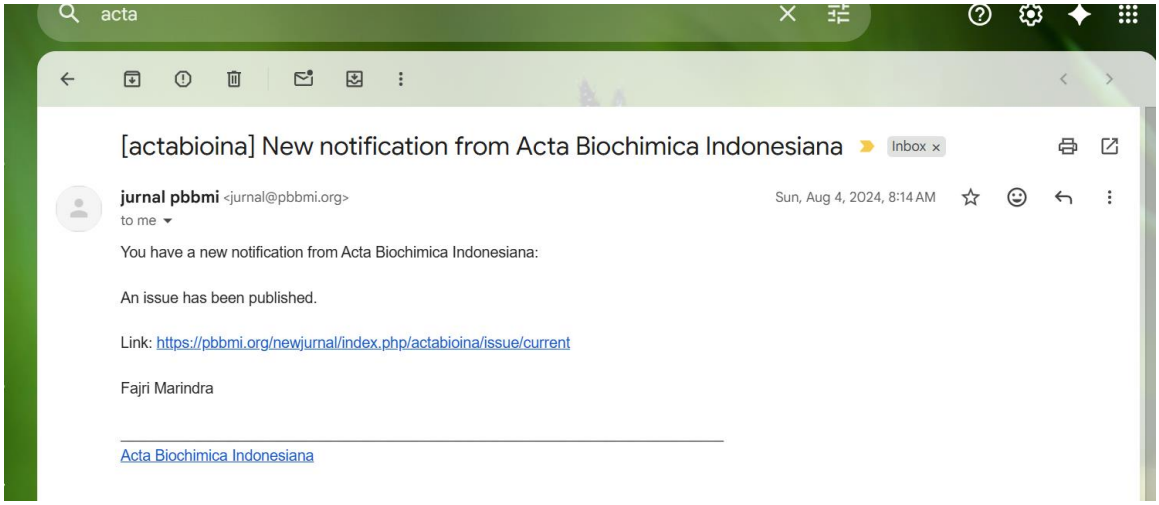

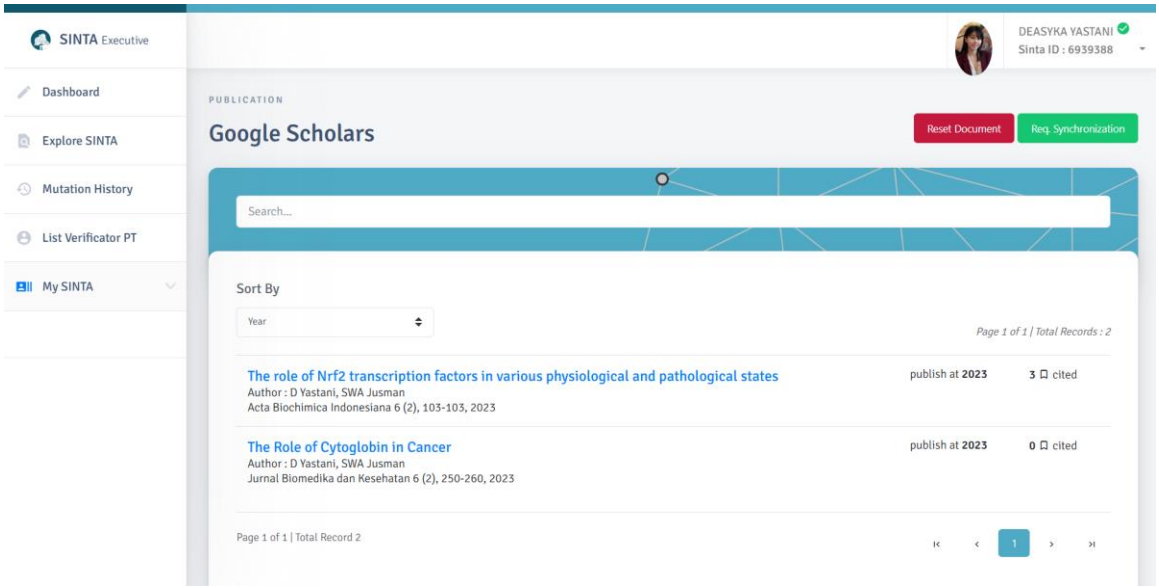

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The role of Nrf2 transcription factors in various physiological and pathological states

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REVIEW ARTICLE Open Access

The role of Nrf2 transcription factors in various physiological and pathological states

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ABSTRACT

Since its first report in 1994, understanding of the nuclear factor erythroid 2-related factor 2 (Nrf2) has continued to grow. Initially recognized for its role in cellular response to oxidative stress, Nrf2 is now known to be involved in a variety of regulatory process, including metabolic regulation, autophagy, protein homeostasis (proteostasis), and mitochondrial biogenesis. The expression of Nrf2 target genes is highly dependent on stimulus activation and interactions with transcription factors, activators, and repressors. Nrf2 activation serves as a defense mechanism under physiological conditions, but in the context of cancer, it can trigger the development of cancer cells due to its complex roles. Nrf2 is strongly associated with the onset and development of many diseases, including those caused by metabolic disorders and inflammation. Understanding Nrf2's diverse functions offers valuable insights into disease pathogenesis and potential therapeutic approaches. This review explores the pleiotropic role of Nrf2 regulation.

Keywords: Nrf2, oxidative stress, metabolic regulation, proteostasis, transcription factor

Introduction

As a transcription factor, Nrf2 plays a major role in xenobiotic metabolism and the response to reactive oxygen species (ROS) [1,2]. Oxidative stress activates antioxidant genes via the antioxidant response element (ARE) [3,4]. Nrf2 was first reported in 1994 as an NF-E2-like transcription activator binding to the NF-E2/AP1 tandem repeat of the beta-globin locus control region [5,6], but its biological function is not yet clearly known. In 1996, studies in Nrf2 knockout mice revealed no aberrant phenotype, although the mice were more susceptible to stress [7]. In 1997, a study showed that knocking out enzymes such as glutathione S-transferase (GST) and NAD(P)H:quinone oxidoreductase-1 (NQO1), which are regulated by ARE, revealed that Nrf2 controls drug metabolism enzymes in vivo [8]. Recent findings revealed that Nrf2 regulates various processes through ARE and electrophile response elements (EpRE), which play a role in regulating endogenous responses to various intrinsic and extrinsic stresses [9–15].

Recent studies have further identified new roles of Nrf2 beyond its response to oxidative stress. Nrf2 is involved in regulating inflammation, autophagy, metabolism, protein homeostasis (proteostasis) and unfolded protein response (UPR), and mitochondrial biogenesis, as well as being associated with carcinogenesis [1,2,15,16]. These findings suggest that Nrf2 is a pleiotropic transcription factor. This review presents the role of Nrf2 in various processes inside the cell.

Structure of Nrf2

As a part of family of Cap'n'collar (CNC) proteins, Nrf2 has a unique CNC domain that binds to the basic leucine zipper (CNC-bZIP) motif [2,3]. The Nrf2 protein comprises seven functional domains, known as Nrf2-ECH homology domains (Neh1-

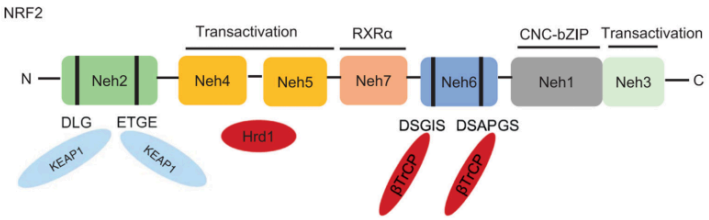

Figure 1. The structure of Nrf2. Nrf2 comprises seven domains, known as Nrf2-ECH homology domains (Neh1- Neh7)

Neh7), each with different functions in regulating Nrf2 transcription activity.

(a) Neh1 domain: comprises the CNC-bZIP region, enabling heterodimerization with the small musculoaponeurotic fibrosarcoma (sMAF) oncogenes. This interaction is crucial for recognizing ARE and/or EpRE. The CNC-bZIP region is conserved across various species, highlighting its importance for Nrf2 function [15].

(b) Neh2 domain: Features an N-terminal domain that binds to the negative regulatory domain of Kelch-like ECH-associated protein 1 (KEAP1). This domain contains ETGE and DLG motif, mainly interacting with the domain (KEAP1) for ubiquitination and subsequent NRF2 degradation [1,2].

(c) Neh3-5 domains: Serves as domains for transcriptional activation by interacting with transcriptional components [1,2].

(d) Neh6 domain: Involved in the degradation of Nrf2 independent of Keap1. It contains two redox-independent degrons, DSGIS and DSAPGS, which link to E3 ubiquitin ligase β-transducin repeat-containing protein (βTrCP) [1,2].

(e) Neh7 domain: Functions to suppress Nrf2 activity by interacting with retinoic X receptor alpha (RXRα).

All of these domains maintain the stability of Nrf2 and facilitate transcriptional activation of the target genes at a stratified level, encompassing transcriptional, post-transcriptional, and post-translational regulation in response to various stresses [1]. The structure of Nrf2 is illustrated in Figure 1.

Regulation of Nrf2

The regulation of Nrf2 generally occurs through the various stages shown in Figure 2 below.

Regulation of Nrf2 stability

Under basal conditions, Nrf2 is maintained at low levels within cells due to proteasomal degradation mediated by KEAP1 [1,17]. Nrf2 stability is strictly regulated through ubiquitination mediated by E3 ubiquitin ligase complexes and subsequent proteasomal degradation. The ubiquitin ligase complexes involved in this regulation include HRD1/Synoviolin, WD Repeat protein (WDR), βTrCP-S-phase kinase-associated protein-1 (SKP1)-CUL1-RBX1, KEAP1-Cullin (CUL) 3-RING-box protein (RBX)1, and 3-CUL4-damaged DNA binding protein (DDB)1. Each of these complexes plays a role under different cellular conditions [1].

Regulation of Nrf2 transcription

Nrf2 transcription is regulated through various mechanisms involving NF-κB binding sites, the aryl hydrocarbon receptor (AHR)-AHR nuclear translocator (ARNT) complex, other transcription factors, and cofactors [1]. The Nrf2 transcription factor binds to the ARE promoter region to activate gene transcription. The NFE2L2 gene contains the ARE promoter region, a xenobiotic responsive element (XRE), two additional promoters with XRE-like elements, and

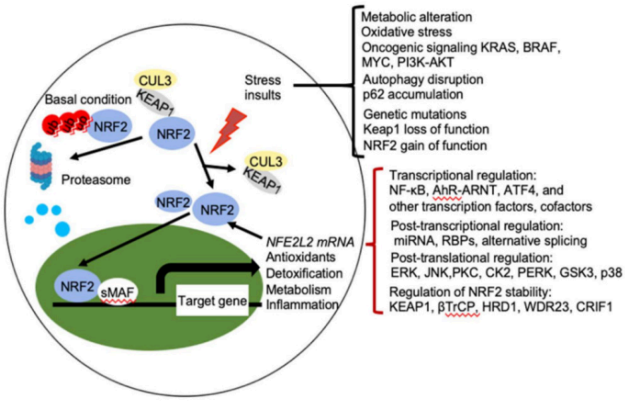

Figure 2. Stages of Nrf2 regulation. Nrf2 regulation involves multiple statges: stability, transcription, post-transcription, post-translation, metabolic changes, response to oxidative stress, oncogene signaling, autophagy regulation, and genetic mutations [1]

NF-κB binding site. The ARE region allows Nrf2 to directly activate the transcription process through a positive feedback mechanism that amplifies Nrf2's effect [1]. Additionally, transcription of NFE2L2 is regulated by various transcription factors, such as NF-κB and AHR. The AHR, in particular, activates the XRE [1,10].

Regulation of Nrf2 post-transcription

Post-transcription regulation of Nrf2 involves microRNAs (miRNAs), RNA-binding proteins (RBPs), and alternative splicing. MicroRNAs are non-coding RNAs, typically 22 nucleotides long, that can suppress gene expression by binding to mRNA molecules in a sequence-specific manner, thereby inhibiting protein translation and destabilizing mRNA. A decrease in Nrf2 transcription activity has been associated with an increase in miR-93, miR-144, miR-153, miR-28, and miR-34. However, the role of miRNAs regulation requires further study and validation [1,18].

Regulation of target gene activation

Nrf2 activation is strictly regulated, as only specific genes can interact with Nrf2 and its binding component (transcription factors, mediators, and cofactors) to achieve activation. Key transcription factors involved include sMAF transcription factors, BTB and CNC homology transcription factors 1 (BACH1), activating transcription factor 4 (ATF4), activator protein 1 (AP-1) subunit c-Jun, CREB-binding protein (CBP), p300 cofactors, activating transcription factor 3 (ATF3), and other co-activators [1,19].

Regulation of Nrf2 in oxidative stress response and drug detoxification

Nrf2 regulation oxidative stress response and drug detoxification involves the expression of cytoprotective genes that facilitates the synthesis of enzymes involved in drug detoxification and maintenance of cellular hemostasis [1–3].

a. Phase I enzymes: These enzymes participate in reduction, oxidation, and hydrolytic reactions of xenobiotics. Examples include aldehyde dehydrogenase 1 (ALDH1), NQO1, aldo-keto reductases (AKRs), carbonyl reductases (CBRs), and some cytochrome P450 oxidoreductases (CYPs) [3].
b. Phase II enzymes: These enzymes are involved

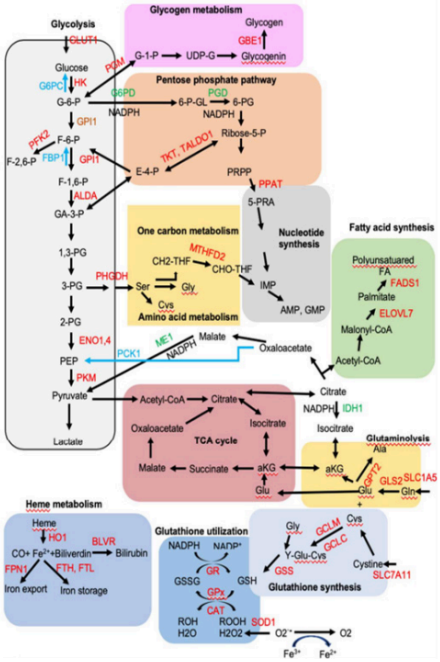

Figure 3. Regulation of Nrf2 on metabolism. Nrf2 enhances the expression of genes involved in glycolysis, glutaminolysis, glycogen metabolism, pentose phosphate pathway, amino acid metabolism, fatty acid synthesis, heme metabolism, glutathione synthesis, and nucleotide biosynthesis (red). Nrf2 decreases the expression of genes associated with gluconeogenesis (blue). Enzymes involved in NADPH production are highlighted in green [1]

in conjugation reactions, such as UDP-glucuronosyltransferase (UGT), glutathione S-transferase (GST), heme oxygenase-1 (HO-1), and UDP-glucuronate synthase [3,20].

c. Phase II enzymes: These drug transporters transport conjugated metabolites after phase II. Example include breast cancer resistant protein (BCRP), ATP-binding cassette G5 (ABCG5), multidrug resistance-associated proteins (MDR), and ATP-binding cassette G8 (ABCG8) [3].

Nrf2-targeted enzymes for ROS elimination include thioredoxin reductase, thioredoxin, catalase (CAT), superoxide dismutase 1 (SOD1), peroxiredoxin, glutathione peroxidase, and sulforedoxine, as well as some glutathione S-transferases [2,3,20]. The cytoprotective proteins encoded by Nrf2 are essential for protective mechanisms against various toxins and oxidants, particularly in diseases based on oxidative stress, such as cancer, coronary disease, metabolic syndrome, neurodegenerative diseases, and autoimmune diseases [2].

Regulation of Nrf2 on metabolism

Nrf2 improves the gene expression involved in glycolysis, the pentose phosphate pathways, glycogen metabolism, amino acid metabolism, glutaminolysis, fatty acid synthesis, heme metabolism, nucleotide biosynthesis, and glutathione synthesis. Conversely,

Nrf2 decreases the gene expression correlated with gluconeogenesis. Many studies support that Nrf2 is a major key in the reprogramming of cancer metabolism [2]. The regulatory mechanisms of Nrf2 are illustrated in Figure 3.

Nrf2 regulation on unfolded protein response (UPR) and proteostasis

Misfolded protein accumulation triggers the production of ROS from the mitochondria and endoplasmic reticulum (ER), leading to an increase in activation of Nrf2 [17]. Nrf2 activates transcription of ATF4, which is related to amino acid metabolism. In *C. elegans,* the homologous Nrf2 protein SKN-1 activates various UPR target genes, including ATF6 and XBP1, thereby enhancing the UPR program by maintaining ER integrity and protein homeostasis (proteostasis) [21]. Additionally, Nrf2 promotes the expression of proteasome maturation proteins (POMP), which is crucial for proteostasis [22]. In summary, Nrf2 increases proteosome activity and antioxidants expression, aiding in stress adaptation.

Nrf2 regulation on autophagy

Nrf2 plays a significant role in autophagy by upregulating the expression of autophagy-related genes, including SQSTM1/P62, autophagy protein 5 (ATG5), calcium-binding and coiled-coil domain-containing protein 2 (CALCOCO2/NDP52), gamma-aminobutyric acid receptor-associated protein-like 1 (GABARAPL1), and unc-51-like kinase 1 (ULK1) [17]. Interestingly, the activation of Nrf2 can be stimulated by the accumulation of oxidized proteins or organelles due to impaired autophagy. This increase in Nrf2 is mediated by the accumulation of p62, a multifunctional receptor that stabilizes KEAP 1 and Nrf2, under autophagy-deficient conditions. In conclusion, a positive feedback loop by p62 and Nrf2 can regulate numerous cellular functions [23].

NRF2 regulation on mitochondrial biogenesis

Nrf2 is involved in enhancing the production and growth of new mitochondria within cells. This process is known as mitochondrial biogenesis. Nrf2 stimulates mitochondrial biogenesis by activating nuclear respiratory factor-1 (NRF-1), is a key regulator of mitochondrial transcription factor A (TFAM) and mitochondrial transcription factor B2 (TFBM2) [24]. TFAM is involved in the transcription and maintenance of mitochondrial DNA, while TFBM2 works alongside TFAM to regulate mitochondrial gene expression. Nrf2 also directly regulates the expression of peroxisome proliferator-activated receptor gamma co-activator 1 alpha (PGC-1α), a principal regulator of mitochondrial function and biogenesis. The cooperation between Nrf2 and PGC-1α regulates various aspects of mitochondrial function [24–26].

Conclusion

Nrf2 is a widely expressed transcription factor in mammalian cells, belonging to the Cap'n'collar (CNC) protein family. It features a unique CNC domain that binds to the basic leucine zipper (CNC-bZIP) motif. The Nrf2 protein contains seven functional domains, known as Nrf2-ECH homology domains (Neh1-Neh7). Nrf2 regulation occurs at multiple stages, including stability, transcription, post-transcription, post-translation, and target gene activation. This regulation is highly selective, with only specific genes capable of interacting with Nrf2 and its binding partners to achieve activation. Recent studies have highlighted the pleiotropic nature of Nrf2, demonstrating its roles not only in oxidative stress response and drug detoxification but also in metabolism, heme synthesis, proteostasis, unfolded protein response (UPR), autophagy, and mitochondrial biogenesis.

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Declaration of interest

The authors declare no conflict of interest.

Author contributions

DY: Conceptualization, Writing – original draft; SWAJ: Supervision, Writing – review and editing.

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