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Review article

Modulation of proteostasis by transcription factor NRF2 and impact in neurodegenerative diseases

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ABSTRACT

Neurodegenerative diseases are linked to the accumulation of specific protein aggregates, suggesting an intimate connection between injured brain and loss of proteostasis. Proteostasis refers to all the processes by which cells control the abundance and folding of the proteome thanks to a wide network that integrates the regulation of signaling pathways, gene expression and protein degradation systems. This review attempts to summarize the most relevant findings about the transcriptional modulation of proteostasis exerted by the transcription factor NRF2 (nuclear factor (erythroid-derived 2)-like 2). NRF2 has been classically considered as the master regulator of the antioxidant cell response, although it is currently emerging as a key component of the transduction machinery to maintain proteostasis. As we will discuss, NRF2 could be envisioned as a hub that compiles emergency signals derived from misfolded protein accumulation in order to build a coordinated and perdurable transcriptional response. This is achieved by functions of NRF2 related to the control of genes involved in the maintenance of the endoplasmic reticulum physiology, the proteasome and autophagy.

1. Introduction

Nuclear Factor (erythroid-derived 2)-like 2 (NRF2) is a basic-leucine-zipper protein considered nowadays as a master regulator of cellular homeostasis. It controls the basal and stress-inducible expression of over 250 genes that share in common a cis-acting enhancer termed the antioxidant response element (ARE) [1–5]. These genes participate in phase I, II and III detoxification reactions, glutathione and peroxiredoxin/thioredoxin metabolism, NADPH production through the pentose phosphate pathway and malic enzyme, fatty acid oxidation, iron metabolism, and proteostasis [6]. Given these wide cytoprotective functions, it is possible that a single pharmacological hit in NRF2 might mitigate the effect of the main culprits of chronic diseases, including oxidative, inflammatory and proteotoxic stress. The role of NRF2 in the modulation of the antioxidant defense and resolution of inflammation have been addressed in numerous studies (reviewed in [7]). Here, we will focus on its role in proteostasis, i.e., the homeostatic control of protein synthesis, folding, trafficking and degradation. Examples will be provided in the context of neurodegenerative diseases.

Abbreviations: α-SYN, alpha synuclein; β-TrCP, β-transducin repeat containing E3 ubiquitin protein ligase; Aβ, amyloid beta; AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; AMPK, AMP-activated protein kinase; ARE, antioxidant response element; ASK1, apoptosis-signal-regulating kinase 1; ATF-6, activating transcription factor 6; APP, amyloid precursor protein; CG islands, cytosine guanine islands; ChIP, chromatin immunoprecipitation; CJD, Creutzfeldt Jakob disease; CSF, cerebrospinal fluid; D3T, 1,2-dithiole-3-thione; DMF, dimethyl fumarate; ER, endoplasmic reticulum; ERO1, sulfhydryl oxidase endoplasmic oxidoreductin 1; FOXO, forkhead box; GCLC, glutamate-cysteine ligase catalytic subunit; GCLM, glutamate-cysteine ligase modulatory subunit; GFP, green fluorescent protein; GLT-1, glutamate transporter 1; GPX, glutathione peroxidase; GR, GSR, glutathione reductase; GSH, glutathione (c-glutamyl-l-cysteinylglycine); GSK-3, glycogen synthase kinase-3; GSSG, glutathione disulfide; GST, glutathione S-transferase; HD, Huntington's disease; Htt, huntingtin; HMOX1, heme oxygenase-1; IRE1, inositol-requiring kinase 1; JNK, c-Jun N-terminal kinase; KEAP1, kelch-like ECH-associated protein 1; MAPKs, mitogen-activated protein kinases; MPTP, 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine; MEF, mouse embryonic fibroblasts; mTOR, mammalian target of rapamycin; NQO1, NAD(P)H:quinone oxidoreductase 1; NRF1, nuclear factor (erythroid-derived 2)-like 1; NRF2, nuclear factor (erythroid-derived 2)-like 2; LIR, LC3 interacting region; PERK, pancreatic ER eIF2α kinase; PD, Parkinson's disease; PDI, protein disulfide isomerase; PI3K, phosphatidyl inositol-3 kinase; PKA, protein kinase A; PKC, protein kinase C; PrP, prionic protein; PS1, presenilin 1; PRX, peroxiredoxin; ROS, reactive oxygen species; SFN, sulforaphane; SOD1, Cu/Zn-superoxide dismutase 1; TAK1, TGF-β-activated kinase 1; TFEB, transcription factor EB; UBA, ubiquitin associated domain; UPS, ubiquitin proteasome system; UPR, unfolded protein response; XBP1, X box-binding protein 1; γ-GCL, γ -glutamylcysteine synthetase; γGS, γ -glutamate cysteine synthetase; γGT, γ -glutamyl transpeptidase

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2. Loss of proteostasis influences NRF2 activity in neurodegenerative diseases

A general hallmark of neurodegenerative diseases is the occurrence of aberrant aggregation of some proteins. Thus, misfolded protein aggregates of α-synuclein (α-SYN) are found in Parkinson's disease (PD), β-amyloid (Aβ) plaques and hyper-phosphorylated TAU neurofibrillary tangles in Alzheimer's disease (AD), huntingtin (Htt) in Huntington's disease (HD), superoxide dismutase 1 (SOD1) and TAR DNA binding protein 43 (TDP-43) in amyotrophic lateral sclerosis (ALS), prion protein (PrP) in spongiform encephalopathies, etc. Protein aggregates can have an impact on several cellular pathways, which in turn may affect NRF2 levels and activity.

2.1. Different layers of regulation tightly control NRF2 activity

Under physiological conditions, cells exhibit low NRF2 protein levels because of its rapid turnover. In response to different stimuli, NRF2 protein is accumulated, enters the nucleus and increases the transcription of ARE-containing genes. Therefore, management of NRF2 protein levels is a key point that should integrate positive and negative input signals. As we will discuss further, NRF2 is activated by diverse overlapping mechanisms to orchestrate a rapid and efficient response but on the other hand NRF2 could be inhibited, probably in a second phase, in order to switch off its response.

From the classic point of view, activation of NRF2 has been considered as a consequence of the cellular response to oxidant or electrophilic compounds. In this regard, the ubiquitin E3 ligase adaptor Kelch-like ECH-associated protein 1 (KEAP1) plays a crucial role. Molecular details will be further addressed in Section 4.1. In brief, KEAP1 acts as a redox sensor due to critical cysteine residues leading to NRF2 ubiquitination and proteasomal degradation. In addition to this classic modulation, NRF2 is profoundly regulated by signaling events. Indeed, different kinases have been shown to phosphorylate and regulate NRF2. For instance, NRF2 can be phosphorylated by mitogen activated protein kinases (MAPKs), although its contribution to NRF2 activity remains unclear [8–11]. PKA kinase as well as some PKC isozymes [12], CK2 [13] or Fyn [14] phosphorylate NRF2 modifying its stability. Previous work from our group reported that glycogen synthase kinse-3β (GSK-3β) inhibits NRF2 by nuclear exclusion and proteasomal degradation [15,25–30]. The molecular details will be discussed in the Section 4.1. Furthermore, NRF2 is submitted to other types of regulation. For instance, NRF2 acetylation by CBP/p300 increases its activity [17], while it is inhibited by miR153, miR27a, miR142-5p, and miR144 [16], or by methylation of cytosine-guanine (CG) islands within the NRF2 promoter [18].

2.2. Impact of protein aggregates on NRF2 regulatory mechanisms

In this section we will focus in how accumulation of misfolded protein could impact NRF2 activity providing some of the pathways mentioned above as illustrative examples. Firstly, we need to consider that protein accumulation has been tightly linked with oxidative damage. Indeed, misfolded protein accumulation and aggregation induce abnormal production of reactive oxygen species (ROS) from mitochondria and other sources [19]. As mentioned above, ROS will modify redox-sensitive cysteines of KEAP1 leading to the release, stabilization and nuclear localization of NRF2.

Regarding proteinopathies, an example of dysregulated signaling events that may affect NRF2 is provided by the hyperactivation of GSK-3β in AD. GSK-3β, also known as TAU kinase, participates in the phosphorylation of this microtubule-associated protein, resulting in its aggregation, formation of neurofibrillary tangles and interruption of axonal transport (reviewed in [20]). On the other hand, GSK-3β dramatically reduces NRF2 levels and activity as mentioned above. Although not widely accepted, the amyloid cascade proposes that toxic Aβ oligomers increase GSK-3β activity together with TAU hyperphosphorylation and neuron death [21,22]. There are different models to explain how Aβ favors GSK3-β activity. For instance, Aβ binds to the insulin receptor and inhibits PI3K and AKT signaling pathways, which are crucial to maintain GSK-3β inactivated by phosphorylation at its N-terminal Ser9 residue [23]. On the other hand, extracellular Aβ interacts with Frizzled receptors, blocking WNT signaling [24] and again resulting in release of active GSK-3β. In summary, Aβ accumulation leads to abnormal hyperactivation of GSK-3β, thus impairing an appropriate NRF2 response.

As discussed in the following section, misfolded proteins lead to activation of PERK and MAPKs, which in turn up-regulate NRF2 [31,8–11]. Moreover, dysregulated CBP/p300 activity has been reported in several proteinopathies [32] and a global decrease in DNA methylation in AD brains was also shown [33], therefore providing grounds to explore the relevance of these findings in NRF2 regulation.

We and others have observed in necropsies of PD and AD patients an increase in NRF2 protein levels and some of its targets, such as heme oxygenase 1 (HMOX1), NADPH quinone oxidase 1 (NQO1), p62, etc., both by immunoblot and by immunohistochemistry [34–39]. The up-regulation of NRF2 in these diseases is interpreted as an unsuccessful attempt of the diseased brain to recover homeostatic values. However, another study indicated that NRF2 is predominantly localized in the cytoplasm of AD hippocampal neurons, suggesting reduced NRF2 transcriptional activity in the brain [40]. It is conceivable that the disparity of these observations is related to changes in the factors that control NRF2 along the progressive stages of neurodegeneration.

Three major systems contribute to proteostasis, namely the unfolded protein response (UPR), the ubiquitin proteasome system (UPS) and autophagy. Next, we present evidence to envision NRF2 as a hub connecting emergency signals activated by protein aggregates with the protein derivative machinery.

3. NRF2 participates in the unfolded protein response (UPR)

3.1. NRF2 activation in response to the UPR

Oxidative protein folding in the ER is driven by a number of distinct pathways, the most conserved of which involves the protein disulfide-isomerase (PDI) and the sulfhydryl oxidase endoplasmic oxidoreductin 1 (ERO1α and ERO1β in mammals) as disulfide donor. Briefly, PDI catalyzes the formation and breakage of disulfide bonds between cysteine residues within proteins, as they fold, due to the reduction and oxidation of its own cysteine aminoacids. PDI is recycled by the action of the housekeeping enzyme ERO1, which reintroduces disulfide bonds into PDI [41]. Molecular oxygen is the terminal electron acceptor of ERO1, which generates stoichiometric amounts of hydrogen peroxide for every disulfide bond produced [42]. Peroxidases (PRX4) and glutathione peroxidases (GPX7 and GPX8) are key enzymes to reduce hydrogen peroxide in the ER. When this oxidoreductive system does not work properly, abnormal accumulation of misfolded proteins occurs in the ER and a set of signals named the unfolded protein response (UPR) is transmitted to the cytoplasm and nucleus to reestablish the ER homeostasis [43]. Three membrane-associated proteins have been identified for sensing ER stress in eukaryotes: activating transcription factor 6 (ATF6), pancreatic ER eIF2α kinase (PERK, also double-stranded RNA-activated protein kinase-like ER kinase), and inositol-requiring kinase1 (IRE1). The luminal domain of each sensor is bound to a 78 kDa chaperone termed glucose-regulated protein (GRP78/BIP). BIP dissociates upon ER stress to bind unfolded proteins, leading to the activation of the three sensors [44].

NRF2 and its homologue NRF1, also related to the antioxidant response, participate in the transduction of the UPR to the nucleus. In the case of NRF1, this protein is located at the ER membrane and undergoes nuclear translocation upon deglycosylation or cleavage.