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Unravelling the role of NFE2L1 in stress responses and related diseases

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ABSTRACT

The nuclear factor erythroid 2 (NF-E2)-related factor 1 (NFE2L1, also known as Nrf1) is a highly conserved transcription factor that belongs to the CNC-bZIP subfamily. Its significance lies in its control over redox balance, proteasome activity, and organ integrity. Stress responses encompass a series of compensatory adaptations utilized by cells and organisms to cope with extracellular or intracellular stress initiated by stressful stimuli. Recently, extensive evidence has demonstrated that NFE2L1 plays a crucial role in cellular stress adaptation by 1) responding to oxidative stress through the induction of antioxidative responses, and 2) addressing proteotoxic stress or endoplasmic reticulum (ER) stress by regulating the ubiquitin-proteasome system (UPS), unfolded protein response (UPR), and ER-associated degradation (ERAD). It is worth noting that NFE2L1 serves as a core factor in proteotoxic stress adaptation, which has been extensively studied in cancer and neurodegeneration associated with enhanced proteasomal stress. In these contexts, utilization of NFE2L1 inhibitors to attenuate proteasome "bounce-back" response holds tremendous potential for enhancing the efficacy of proteasome inhibitors. Additionally, abnormal stress adaptations of NFE2L1 and disturbances in redox and protein homeostasis contribute to the pathophysiological complications of cardiovascular diseases, inflammatory diseases, and autoimmune diseases. Therefore, a comprehensive exploration of the molecular basis of NFE2L1 and NFE2L1-mediated diseases related to stress responses would not only facilitate the identification of novel diagnostic and prognostic indicators but also enable the identification of specific therapeutic targets for NFE2L1-related diseases.

1. Introduction

Stress encompasses both intrinsic and extrinsic perturbations that are perceived by diverse cellular signalling processes, including oxidative stress, nutrient deprivation, heat shock, and DNA damage [1]. The biological stress response refers to a pervasive mechanism that enables mammalian cells to adapt to stress and reinstate homeostasis [2]. However, these adaptive responses, which are contingent upon the nature, duration, and magnitude of the stimulus, can also result in cumulative maladaptation or diseases if they fail to maintain homeostasis [3].

The nuclear factor erythroid 2 (NF-E2)-related factor 1 (NFE2L1, also known as Nrf1) is a highly conserved transcription factor found in mammals, with homologs present in *Caenorhabditis elegans* (referred to as SKN-1A) and in *Drosophila* (referred to as CnC-C) [4]. NFE2L1 belongs to the cap'n'collar (CNC)-basic region leucine zipper (bZIP) subfamily of transcription factors, which also includes the transcriptional activators p45 NF-E2, NFE2L2, and NFE2L3 [4]. Specifically, NFE2L1 and NFE2L2 are key regulators of AREs (antioxidant response elements)/EpREs (electrophile-response elements)-driven stress-responsive genes that are ubiquitously expressed [5]. NFE2L2 is well-known for controlling adaptive responses to electrophiles and oxidative stresses through the activation of antioxidant, detoxification, and cytoprotective genes [6]. Mice lacking NFE2L2 display increased susceptibility to chemical carcinogens and oxidative stress compared to wild-type mice [7]. Nonetheless, NFE2L2 is not essential for the basal expression of many ARE/EpRE-driven cytoprotective genes, and NFE2L2 knockout mice do not typically develop spontaneous cancer or other phenotypic manifestations [8]. Emerging evidence demonstrated that NFE2L1 has distinct physiobiological functions that cannot be compensated by NFE2L2 or other homologous factors [9]. Global knockout of NFE2L1 in mice leads to embryonic lethality [10,11]. Furthermore, tissue-specific

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Abbreviations

NFE2L1/Nrf1 nuclear factor erythroid 2-related factor 1
NRF1/2 nuclear respiratory factor 1/2
6-OHDA 6-Hydroxydopamine
ACSL4 acyl-CoA synthetase long-chain family member 4
AD Alzheimer's disease
AKI acute kidney injury
ALL acute lymphoblastic leukemia
AMPK AMP-activated protein kinase
ARE antioxidant response elements
ARMC5 Armadillo repeat containing 5
Asn asparagine
Asp aspartates
ATF4/5/6 activating transcription factor 4/5/6
BAT brown adipose tissue
BiP/GRP78 ER chaperone 78-kilodalton glucose regulated protein
BTZ bortezomib
bZIP basic region leucine zipper
C/EBPα CCAAT enhancer binding protein alpha
CDK2 cyclin-dependent kinase 2
CFZ carfilzomib
CHOP C/EBP-Homologous Protein
CK2 casein kinase 2
CNC cap 'n' collar
CoA coenzyme A
CtBP2 C-terminal binding protein 2
DDI2 DNA-damage inducible 1 homolog 2
DEPTOR DEP domain-containing mTOR-interacting protein
DLBCL diffuse large B-cell lymphoma
DMT1 divalent metal transporter 1
ECT electron transport chain
eIF2α eukaryotic translation initiation factor 2 subunit alpha
EMT epithelial-mesenchymal transition
EpRE electrophile-response element
ER endoplasmic reticulum
ERAD ER-associated degradation
ERSE endoplasmic reticulum stress response elements
FGF21 fibroblast growth factor 21
GCL glutamate-cysteine ligase
GCN2 general control nonderepressible 2
GPX1/4 glutathione peroxidase 1/4
GSH glutathione
GSK3 glycogen synthase kinase 3
GSS glutathione synthetase
GST glutathione S-transferase
HC hypopharyngeal cancer
HCC hepatocellular carcinoma
HMOX1 heme oxygenase 1
HSP10/60/70 heat shock protein 10/60/70
IRE1α inositol-requiring enzyme 1alpha
JNK c-jun N-terminal kinase
KEAP1 Kelch like ECH associated protein 1
LOX lipoxygenase
LPCAT3 lysophosphatidylcholine acyltransferase 3
LPS lipopolysaccharide
LXRs liver X receptors
MIRI myocardial ischemia-reperfusion injury
MM multiple myeloma
MMP9 matrix metallopeptidase 9
MRTF-A myocardin-related transcription factor A
Mt-1/2 metallothionein-1/2
mTORC1 mechanistic target of rapamycin complex 1
mtROS mitochondrial reactive oxygen species
NASH non-alcoholic steatohepatitis
NDUFA9 NADH:Ubiquinone Oxidoreductase Subunit A9
NFV nelfinavir
NGLY1 peptide:N-glycanase
NST domain asparagine/serine/threonine-rich domain
OGT O-linked N-acetylglucosamine transferase
ox-LDL oxidized-low density lipoprotein
OXPHOS oxidative phosphorylation
OMI1/HTRA2 HtrA serine peptidase 2
PC prostate cancer
PGC1α peroxisome proliferator-activated receptor-gamma coactivator 1 alpha
PCK1/2 phosphoenolpyruvate carboxykinase 1/2
PD Parkinson's disease
PERK UPR mediator pancreatic ER kinase (PKR)-like ER kinase
PI3K phosphatidylinositol 3-kinase
PIMi PIM inhibitors
PIs proteasome inhibitors
PL-OOH phospholipid hydroperoxide
PL-PUFA polyunsaturated phospholipid
POMP proteasome maturation protein
POR cytochrome p450 oxidoreductase
PPARγ peroxisome proliferator-activated receptor γ
PRAAS proteasome-associated autoinflammatory syndromes
PRDX peroxiredoxins
PUFA polyunsaturated fatty acid
RIDD RE1alpha-dependent decay
ROS reactive oxygen species
RSK ribosomal S6 kinase
S1P/S2P Golgi-resident site-1/2 protease
SBMA spinal and bulbar muscular atrophy
SCF Skp1–Cullin1–F-box protein
Snail1 Snail family zinc finger 1
SOD1/2 superoxide dismutase 1/2
SREBP1 sterol regulatory element-binding protein 1
STAT3 signal transducer and activator of transcription 3
STEAP3 six-transmembrane epithelial antigen of prostate 3
STX12 syntaxin 12
T2D type 2 diabetes
tBHQ t-butyl hydroquinone
TfR1 transferrin receptor 1
TNBC triple-negative breast cancer
TRIM59 tripartite motif containing 59
TSC1/2 tuberous sclerosis complex 1/2
UPR unfolded protein response
UPRE unfolded protein response elements
UPRmt mitochondrial unfolded protein response
USP7 ubiquitin specific protease 7
XBP1s spliced x-box-binding protein 1

knockout of NFE2L1 was clarified to result in 1) proteostasis-related diseases encompassing distinct cancers [12-15], inflammatory diseases [16-19], neurodegenerative diseases including Alzheimer's disease [20], and Parkinson's disease [21], 2) cellular redox-related disorders such as cardiovascular diseases (CVDs) [22]. Notably, NFE2L2 deficiency does not affect proteasome activity triggered under basal or proteotoxic stress [19], while NFE2L1 has been reported to provide greater cell protection and stress adaptation compared to NFE2L2 [22]. Indeed, NFE2L1 was recently reported to exhibit a potent role in cell stress adaptation towards oxidative stress, proteotoxic stress, and

endoplasmic reticulum stress, etc [23,24]. Therefore, this paper aims to review the emerging role and underlying molecular mechanism of NFE2L1 in stress responses and the related pathologies.

2. The molecular biology of NFE2L1

2.1. Functional isoforms and protein domains of NFE2L1

The expression of NFE2L1 gives rise to multiple mRNA transcripts ranging from 1.5 kb to 5.8 kb [25]. Further alternative splicing and the utilization of different translation initiation codons lead to diverse polypeptide isoforms varying from 140 kDa to 25 kDa [26-29]. The longest isoform, known as TCF11, comprises 772 amino acids and is notably absent in mice [30]. Another long isoform, termed NFE2L1α, consists of 742 amino acids and is generated from an alternatively spliced mRNA deleting exon 4 from TCF11 transcript [26]. These long isoforms (TCF11/NFE2L1α), weighing approximately 120-140 kDa, function as dominant active transcription factors. Shorter protein isoforms lacking one or more domains have also been identified. Functionally, the short isoform LCR-F1 generated from in-frame translation exhibits a weak transactivation ability, while the short isoform NFE2L1γ acts as a negative inhibitor to interfere the activity of long isoforms [31,32]. Notably, the origin of NFE2L1γ is speculated to be either in-frame translation or endoproteolysis of longer isoforms [25]. However, there is currently insufficient evidence regarding their specific expression patterns and functions [25]. In this review, the term NFE2L1 refers to TCF11/NFE2L1α collectively.

Multiple protein domains of NFE2L1 and their specific functions have been identified, as shown in Fig. 1 [33,34]. NFE2L1 contains a bZIP domain in close proximity to its carboxyl terminus, facilitating the formation of heterodimers with other bZIP proteins, primarily sMAf proteins [35]. The DNA binding ability of NFE2L1 relies on a highly conserved CNC domain situated adjacent to the bZIP domain, a distinctive feature absent in other bZIP proteins [36]. Additionally, several regions within NFE2L1 are crucial for its full transactivation capacity. These include the Neh6L domain, a serine-rich domain (SR), and two acidic domains (AD1 and AD2) separated by an asparagine/serine/threonine-rich domain (NST) [31,37,38]. Functionally, AD1 encompasses a putative cholesterol binding domain (CRAC), while the NST domain contains eight potential N-linked glycosylation motifs (N-X-S/T) [18,39,40]. At the N-terminal of NFE2L1, there is a transmembrane domain (TM) that directs newly synthesized NFE2L1 to the endoplasmic reticulum (ER) [41]. Notably, the TM domain undergoes proteolytic cleavage mediated by DDI2 (DNA damage inducible 1 homolog 2), liberating NFE2L1 from the ER [42].

2.2. Target genes of NFE2L1 and cofactors

NFE2L1 dimerizes with other bZIP proteins, mainly small-Maf proteins (Maf-F, Maf-G and Maf-K), to regulate gene transcription within the nucleus [28,35]. Besides, AP1 transcription factors (e.g. c-Jun, JunD, and c-Fos) [43–45], ATF4 [29,46], ATF6, CREBZF [47], and C/EBP-beta [48] have been reported to be potential partners of NFE2L1. NFE2L1 is of great importance in governing transcriptional regulation of ARE/EpRE-driven cytoprotective genes [5]. The typical target genes are involved in antioxidant metabolism, mitochondrial respiration, proteasome homeostasis, ER-related protein processing, genetic stability, glucose and lipid metabolism, and inflammation [9,49,50].

Notably, apart from well-established heterodimerization process, Kainoh et al. revealed that forming transcriptional complexes with C-terminal binding protein 2 (CtBP2) is a required step for NFE2L1 and NFE2L2 to promote the expression of antioxidant genes in response to oxidative insults [51]. CtBP2, exclusively localized in the nucleus, serves as a redox-sensing transcriptional cofactor that is activated by NADH [52]. Interestingly, a recent study using transcriptomics and metabolomics methods showed that decreased CtBP2 modulates the redox state, affecting ROS production and scavenging, and subsequently suppressing the proliferation of triple-negative breast cancer cells [53]. Although further validation is required, the reliance of NFE2L1/NFE2L2 on CtBP2 provides a reasonable explanation for this metabolic transformation. More importantly, the accessibility of redox-sensing CtBP2 may enable NFE2L1 to selectively respond to oxidative stress conditions. Besides, the TIP60 chromatin regulatory complex, along with its subunit AAA + ATPase RUVBL1, has been shown to be indispensable for NFE2L1 to upregulate expression of proteasome genes [54]. While the underlying mechanism for this TIP60 requirement has been hypothesized to involve chromatin remodeling at NFE2L1 target gene promoters, direct modulation of NFE2L1, or a combination of both, further research is needed to uncover the truth [54,55].

2.3. Regulation and activation

Cytokines, nutrients, and cellular stressors all contribute to the regulation and activation of NFE2L1 [14,56,57]. Upon activation, ER-associated NFE2L1 undergoes a series of molecular events including retrotranslocation, proteolytic cleavage, de-glycosylation and subsequent nuclear translocation to transactivate target genes. This multi-tiered hierarchical regulation governing NFE2L1 contributes to a finely orchestrated regulatory mechanism of defence systems, which holds paramount importance given its essential and conserved nature.

2.3.1. The transcriptional regulation of NFE2L1

NFE2L1 exhibits broad expression across various tissues and is subject to regulation by multiple factors. Wang et al. discovered that LncRNA DLGAP1-AS1 sponges miR-515-5p to block the expression of NFE2L1 and accelerate glioblastoma cell proliferation [58]. In 2014, Zhang et al. provided evidence of NFE2L1 transcriptional activation through the mTORC1/SREBP1/NFE2L1 axis [57]. Given that mTORC1 mediates a classic pathway for stimulating protein synthesis in response to nutrients/growth factors, NFE2L1 serves as a compensatory mechanism to enhance overall proteasome content, fulfilling the demand for protein turnover and quality control [59]. Nevertheless, the augmented degradation of NFE2L1 protein via ER-associated degradation (ERAD) raises the question of potential factors that stabilize NFE2L1 under these circumstances. More recently, Park et al. observed that LPS can upregulate the expression of NFE2L1 at the mRNA level [60]. Besides, NFE2L1 transcriptional upregulation is typically induced by a variety of mitochondrial defects, including inhibition of oxidative phosphorylation (OXPHOS) and depletion of mitochondrial DNA [56]. Mechanistically, Lee et al. identified ROS-mediated activation of STAT3 as a specific signalling pathway to stimulate NFE2L1 transcription in response to mitochondrial OXPHOS impairment, highlighting the involvement of NFE2L1 in mitochondrial retrograde signalling [14].

2.3.2. ER-targeted translation, ERAD-mediated retrotranslocation of NFE2L1 and potential regulation

The initial process of NFE2L1 translation involves its directed transport to the ER, where it emerges into the ER membrane through the N-terminal transmembrane domain [41]. Meanwhile, a series of N-X-S/T motifs in the NST domain undergo sequential N-glycosylation [39,40,61]. To release from ER into the cytoplasm, the retrotranslocation of NFE2L1 are mediated by ER-resident HRD1, which also serves as a E3 ubiquitin ligase to ubiquitinate NFE2L1 during this intricate process [62,63]. Notably, substantial evidence suggests that ER-associated NFE2L1 constantly senses the dynamic state of the ER and is subject to regulation. The electrophile *t*-butyl hydroquinone (t-BHQ) enhances NFE2L1 activity via an N-terminal domain-dependent mechanism, probably through influencing the topology of NFE2L1 in the ER [38]. Widenmaier et al. demonstrated that excessive cholesterol accumulation within the ER reduces ERAD-mediated retrotranslocation of NFE2L1 through direct binding [18]. Consequently, reduced NFE2L1 release alleviates the constant inhibition exerted by NFE2L1 on liver X

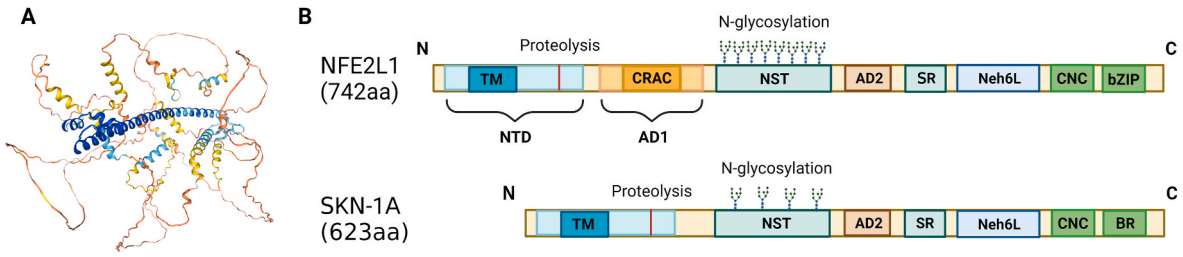

Fig. 1. The structure of NFE2L1.
A. Structural prediction was downloaded from the Alphafold project (https://alphafold.com/entry/A0A384A8U2) [33,34]. **B**. Functional domains of NFE2L1 in mouse (the top) and its homologus SKN-1A in C. elegans (the bottom) are illustrated. The sites subject to selective proteolysis or N-glycosylation are labelled. The sequences refer to the National Center for Biotechnology (NCBI) (www.ncbi.nlm.nih.gov). NTD = N-terminal domain, TM = transmembrane domain, AD = acidic domain, CRAC = cholesterol-recognition/amino acid consensus motif, NST = N-X-S/T-rich domain, SR = serine-repeat, Neh6L = Nrf2–ECH homology 6-like, CNC = Cap 'n' collar, bZIP = basic-region zipper, BR = basic region.

receptors (LXRs), facilitating cholesterol export to reinstate cholesterol homeostasis [18]. Interestingly, a recent study revealed that oleic acid (OA) promotes the extrusion of SKN-1A from the ER via impacting ER membrane conditions and in turn enhancing ERAD efficiency [16]. The increased nuclear SKN-1A accumulation decreases steatosis by modulating the lipid metabolism transcriptome and enhances lifespan [16]. These collective findings underscore the metabolic regulation of NFE2L1 within the ER and its role in restoring homeostasis.

2.3.3. Cytosolic activation of NFE2L1 and potential regulation

In cells with adequate proteasome capability, cytosolic ubiquitinated NFE2L1 swiftly undergoes recognition and degradation by proteasomes. This entire degradation process is executed through the ERAD pathway, which prominently targets misfolded proteins within the ER and mediates their degradation [64,65]. While the protein level of NFE2L1 remains undetectable under normal circumstances, in cells experiencing impaired or overwhelmed proteasome activity, cytosolic NFE2L1 may partially evade degradation and undergo selective proteolytic cleavage mediated by the protease DDI2 [63]. This cleavage event results in the loss of approximately 100 amino acids from the amino terminus of NFE2L1, including the transmembrane domain [63]. Additionally, prior to entering the nucleus, NFE2L1 is subject to de-glycosylation mediated by cytosolic peptide:N-glycanase (NGLY1) [66]. The sequential process of N-glycosylation and deglycosylation process serves as a mean to achieve post-translational asparagine (Asn, N) to aspartates (Asp, D) sequence editing, which is indispensable for the NFE2L1-dependent upregulation of proteasome subunit genes, but not for several other target genes, particularly those involved in response to oxidative stress [40,67]. Thus, Asn-Asp sequence editing operates to bias the transcriptional spectrum of NFE2L1 activation toward specific stress responses [4]. One proposed possibility for achieving this bias is that the edited sequence serves as a selector for recruiting other co-factors to facilitate the transcription of proteasome subunit genes [67]. Identifying such sequence-dependent interactors and elucidating their contribution to the adjustment of stress-responsive gene expression patterns mediated by SKN-1A/NFE2L1 holds significant interest.

Besides N-glycosylation and Asn-Asp sequence editing, numerous post-translational modifications have been proposed to affect the stability and activity of NFE2L1, including O-glycosylation, ubiquitination and phosphorylation. O-linked GlcNAcylation, catalysed by O-linked N-acetylglucosamine transferase (OGT), has the potential to either positively or negatively regulate NFE2L1 stability and activity, thereby modifying NFE2L1 function in accordance with the cellular metabolic state [68–70]. Deubiquitinating enzymes such as USP7 (Ubiquitin-Specific Protease 7), USP15 and USP19, remove ubiquitin moieties and potentially safeguard NFE2L1 from proteasomal degradation [71,72]. Intriguingly, along with NFE2L2, NFE2L1 has been shown to reciprocally upregulate the expression of USP19, USP14, and other USP/DUB proteins at distinct regulatory layers [72]. Conversely, β-TrCP and FBW7, two F-box proteins involved in the formation of SCF E3 ubiquitin ligase complexes, have been reported to ubiquitinate NFE2L1, thus exerting control over its nuclear level [73,74]. A recent study unveiled that ARMC5, a tumour suppressor gene, specifically targets NFE2L1 for ubiquitination in adrenocortical cells, although the precise molecular mechanism remains unclear [75]. Furthermore, the activity of NFE2L1 is also modulated by phosphorylation mediated by glycogen synthase kinase 3 (GSK3) or casein kinase 2 (CK2), which suppresses NFE2L1 function partly via targeting NFE2L1 to SCF^{FBW7}-mediated degradation as observed in the case of GSK3 [76,77].

3. NFE2L1 in stress responses

3.1. NFE2L1 in oxidative stress

Under normal physiological settings, reactive oxygen species (ROS) are continually produced from internal metabolism, including the mitochondria, ER, peroxisomes, and exposure to environmental toxins [78]. Correspondingly, robust antioxidant, detoxification, and cytoprotective defence systems are employed to achieve redox balance. The majority of genes involved in these defence systems are governed by ARE and encompass crucial components for glutathione (GSH) production and conjugation, ROS elimination, and phase 2 xenobiotic metabolism [79,80]. Oxidative stress arising from excessive ROS and insufficient antioxidant defence systems is associated with the pathogenesis of inflammatory diseases, metabolic diseases, neurodegenerative diseases, and even cancer. The indispensable role of NFE2L1 has been well-established, as several studies demonstrated that its loss results in severe oxidative stress and heightened susceptibility to cytotoxicity triggered by oxidative stress [11,81]. As described before, NFE2L1 activity is augmented upon oxidative stress induced by either hydrogen peroxide (H_2O_2), LPS, or mitochondrial defects, and ROS-STAT3 has been identified as a critical pathway to augment NFE2L1 expression in the case of mitochondrial defects [14,51,60]. Further research has revealed that NFE2L1 promotes the synthesis of glutathione (GSH), the primary small molecule antioxidant in the mammalian cell, through regulating the expression of glutamate-cysteine ligase (GCL) (including the catalytic GCLC subunit and regulatory GCLM subunit) and glutathione synthetase (GSS) [45,81–83]. In addition, other redox-related genes are regulated by NFE2L1, such as those encoding glutathione peroxidase 1 (GPX1), heme oxygenase 1 (HMOX1), and glutathione S-transferase (GST) [84,85]. Moreover, NFE2L1 promotes the expression of detoxification genes such as metallothionein-1 (Mt-1) and metallothionein-2 (Mt-2) to relieve cytotoxicity of toxic metals [86,87]. Collectively, NFE2L1 serves as an indispensable regulator to uphold the constitutive expression of cytoprotective genes driven by ARE, thereby preserving redox homeostasis.

3.1.1. NFE2L1 in oxidative stress linked with mitochondrial homeostasis

The mitochondrial ROS (mtROS) typically accounts for about 90% of all ROS generated in eukaryotic cells, and their generation can escalate under conditions of damaged electron transport chains (ETCs) or uncoupled OXPHOS, leading to severe oxidative stress [88]. NFE2L2, a well-studied homolog of NFE2L1, has been proven to regulate mitochondrial biogenesis and mitophagy [89]. Recently, NFE2L1 was further identified as an essential redox-determining factor in maintaining mitochondrial homeostasis [90]. In response to various mitochondrial abnormalities, such as OXPHOS suppression and mitochondrial DNA defects, NFE2L1 transcription is commonly upregulated, partly through the ROS-STAT3 pathway [14]. Importantly, loss of NFE2L1 function results in elevated mtROS [91,92]. NFE2L1-silenced mBM-MSCs leads to increased mtROS with compromised antioxidative defence mediated by NFE2L2 under arsenite-exposed conditions, and the application of a specific mtROS scavenger (Mito-quinone) can alleviate induced apoptosis [91]. To reveal the molecular mechanism underlying the enhanced mtROS levels after NFE2L1 knockout, pathway analysis identified decreased expression of genes associated with mitochondrial respiratory function in NFE2L1-deficient mice livers [49]. This finding was further corroborated by Hu et al., as they discovered significant impairment of the mitochondrial oxidative respiratory chain and reduced expression of critical mitochondrial-related genes, including PGC-1α, αPal^{NRF1}, and GABP^{NRF2}, upon NFE2L1 loss [92]. However, the ChIP-sequencing analysis from the Encode database did not provide convictive evidence of NFE2L1 binding to the promoter regions of PGC1α, αPal^{NRF1} and GABPα^{NRF2}, leaving the precise pathways through which NFE2L1 regulates the expression of these important mitochondrial factors uncertain [92]. Moreover, NFE2L1 has been identified as an inducer of mitophagy-related gene transcription, thereby preventing the release of inflammatory mtDNA and/or ROS into the cytosol [50]. NFE2L1-deficient cells showed mitochondria fragmentation [50], decreased mitochondrial number and size, as well as reduced ridge-like structures [93]. Interestingly, it has been reported that dysregulated AMPK signalling following NFE2L1 knockout contributes partially to this phenotype, as AMPK can trigger mitochondrial division and mitophagy [93-95]. Mechanistically, NFE2L1 may interact with AMPK through its NTD region and inhibit AMPK phosphorylation by Serine/Threonine Kinase 11 (STK11/LKB1) via the Neh6L region [93]. Disruption of NFE2L1 reprograms glucose metabolism to aggravate the Warburg effect, concomitant with mitochondrial OXPHOS dysfunction, and the TCA cycle in the mitochondria was inhibited once NFE2L1 was knocked down [93]. Therefore, NFE2L1 was indicated to have a potential role in glucose metabolic disorders. Indeed, NFE2L1 was clarified to modulate glucose metabolic disorders such as type 2 diabetes (T2D) [96], and insulinomas [97], despite the lack of the detailed mechanisms.

3.1.2. Ferroptosis is regulated by NFE2L1 via oxidative stress

Ferroptosis driven by iron-dependent phospholipid peroxidation has emerged as a promising therapeutic approach for various diseases, particularly cancer and degenerative disorders [98] (Fig. 2). Assie et al. reported that NFE2L1-dependent expression of ROS scavengers, such as superoxide dismutase (SOD) and peroxiredoxins (PRDX), contributes to the decreased lipid peroxidation and ferroptosis resistance in

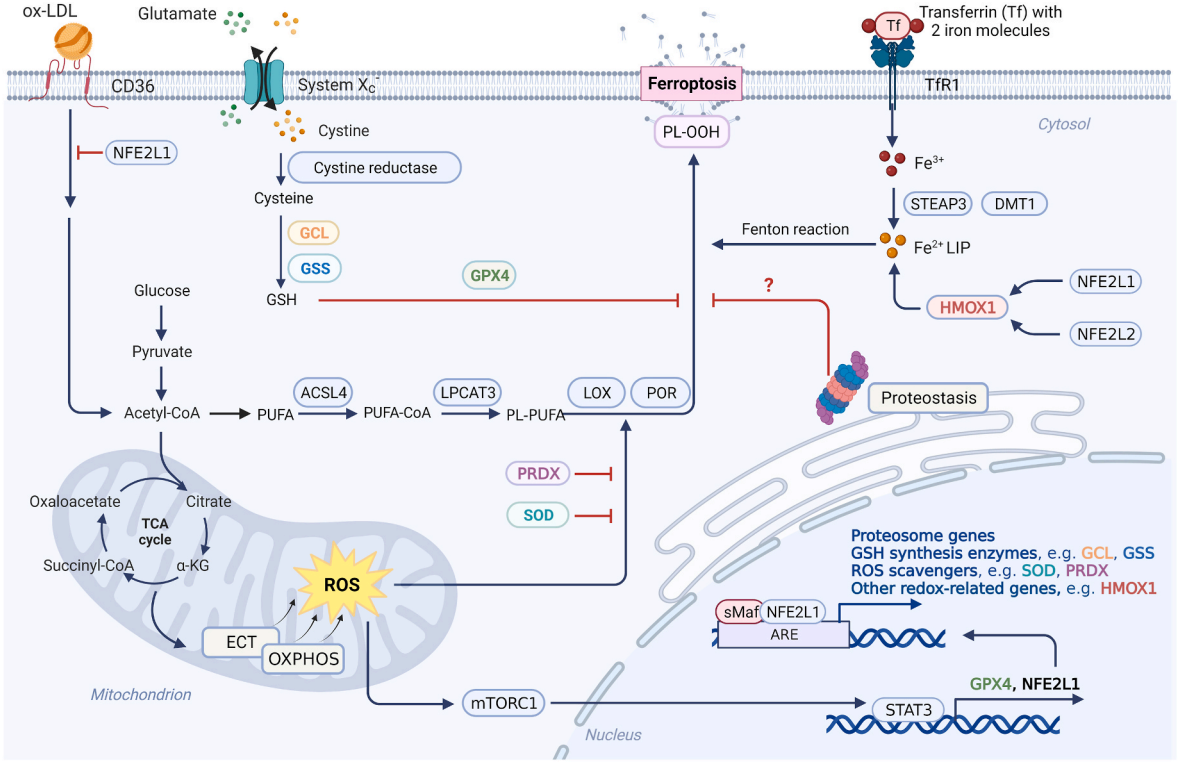

Fig. 2. NFE2L1-mediated resistance to ferroptosis.
GSH biosynthesis is critical for protecting cells from oxidative damage and ferroptosis, the biogenesis of which is catalysed by a series of enzymes regulated by NFE2L1. NFE2L1 also induces the expression of ROS scavengers, such as SOD and PRDX, to inhibits lipid peroxidation. Besides, NFE2L1 can promote ferroptosis resistance by maintaining the protein level of GPX4 in a transcription-independent way. Moreover, the ability of NFE2L1 to maintain normal proteosome activity and proteostasis has been attached great importance in mediating resistance to ferroptosis, although the detailed mechanism remains unclarified. ox-LDL = oxidized-low density lipoprotein, CoA = coenzyme A, PUFA = polyunsaturated fatty acid, PL-PUFA = polyunsaturated phospholipid, PL-OOH = phospholipid hydroperoxide, ECT = electron transport chain, OXPHOS = oxidative phosphorylation, ROS = reactive oxygen species, SOD = superoxide dismutases, PRDX = peroxiredoxins, GCL = glutamate-cysteine ligase, GSS = glutathione synthetase, GSH = glutathione, GPX4 = glutathione peroxidase 4, ACSL4 = acyl-CoA synthetase long-chain family member 4, LPCAT3 = lysophosphatidylcholine acyltransferase 3, LOX = lipoxygenase, POR = cytochrome p450 oxidoreductase, TfR1 = transferrin receptor 1, DMT1 = divalent metal transporter 1, STEAP3 = six-transmembrane epithelial antigen of prostate 3.

adrenocortical cells [75]. Subsequent research revealed that NFE2L1 can promote ferroptosis resistance by maintaining the protein level of glutathione peroxidase 4 (GPX4) in a transcription-independent way, a key protein that prevents lethal lipid peroxidation [99]. However, Kotschi et al. found that NFE2L1-mediated ferroptosis resistance is not dependent on GPX4 but rather relies on normal proteosome activity, as evidenced by the presence of multiple ferroptosis hallmarks, including hyper-ubiquitination of ferroptosis regulators, in NFE2L1-deficient mouse models [98]. As mentioned earlier, NFE2L1 activation is induced through STAT3 signalling, which is also reported to promote GPX4 expression [100]. Intriguingly, existing evidence suggests that STAT3 can negatively regulate ferroptosis in various diseases such as ulcerative colitis [101], pancreatic cancer [100], and gastric cancer [102]. Therefore, NFE2L1 and GPX4 may synergistically contribute to STAT3-dependent ferroptosis resistance. Overall, controlling NFE2L1 activity holds promise for improving cancer treatments utilizing ferroptosis and providing protection against abnormal ferroptosis in conditions including neurodegeneration, vascular disorders, and other diseases.

3.2. NFE2L1 in proteotoxic stress

Ubiquitin-proteosome system (UPS) is an essential mechanism in protecting cells from proteotoxic stress through controlling protein turnover. When the proteasome's capability is overwhelmed, either by an excess of misfolded proteins or chemical inhibitors, NFE2L1 can escape proteasomal degradation and undergo maturation. In its mature form, it translocates to the nucleus and upregulate genes encoding proteasome and POMP (a 20S assembly chaperone) [62,103]. This well-established process is known as the proteasome "bounce-back" response, wherein NFE2L1 mediates *de novo* generation to restore proteasome capability [62]. In addition to proteasome genes, a study has demonstrated that NFE2L1 allows the expression of the chaperone p97/VCP as an adaptive recovery response to proteasome inhibition [104]. Baseline expression and induction during ER stress of Herpud1, an element of the ERAD pathway, was discovered to be NFE2L1-dependent in both mouse and human cells [105]. A recent comprehensive analysis of the NFE2L1-MafG heterodimer-dependent genes has revealed their involvement in ER-related protein processing, chaperone functions, ubiquitin-mediated degradation, and RNA metabolism. This indicates that NFE2L1 regulates the cellular response to proteotoxic stress at multiple dimensions [106]. Interestingly, NFE2L1 optimizes proteasome levels as part of regular physiology and development, not just in response to acute exposure to external stresses. NFE2L1 deficiency in mouse brain or liver led to the reduced expression of PSM genes and POMP, impaired proteasome function and accumulated ubiquitinated and oxidative damaged protein [19,107,108]. Similar reductions in basal proteasome expression and activity are evidenced by SKN-1A/CnC-C inactivation in C. elegans and Drosophila [67,109,110]. Significantly, the regulation of SKN-1A/NFE2L1 by mTORC1 and OGT as described earlier can be considered as a preprogrammed adaptive response for cells to coordinate protein degradation capacity with active metabolism and prevent proteotoxic stress [57].

Previous suggestions implied that NFE2L2 could regulate proteasome gene expression to counteract oxidative stress in mouse liver [111,112]. However, studies conducted on human and mouse cells have demonstrated that the inactivation of NFE2L2 does not affect baseline or proteotoxic stress-induced proteasome expression [19,103]. The NFE2L2 activator SFN is known to induce the expression of proteasome genes, which was only partially attenuated in NFE2L1 KO livers [19]. This raises the possibility that the transcriptional regulation of proteasome capacity may depend on a particular form of cellular stress. Thus, while NFE2L1 promotes expression as an adaptive response to proteotoxic stress, NFE2L2 may mediate proteasome upregulation under oxidative stress. This arrangement aligns with their expression patterns, with NFE2L1 being strongly induced under proteotoxic stress, while NFE2L2 exhibits its highest levels under oxidative stress [50].

3.3. NFE2L1 in ER stress

ER is a crucial intracellular regulator of protein homeostasis monitoring the correct folding of proteins, a process precisely mediated by the ER chaperones [113]. Disruption of ER homeostasis leads to accumulation of uncontrollable misfolded protein known as ER stress, then adaptive unfolded protein response (UPR) can be triggered to facilitate protein folding and simultaneously attenuates aggregation of unfolded/misfolded protein, restoring normal ER function or leads to cell death if the disruption cannot be recovered [114]. UPR begins with the combination of ER chaperone BiP (also known as GRP78) with unfolded proteins, thus releasing BiP from three ER transmembrane protein sensors (i.e., PERK, IRE1α and ATF6), which are activated to transduce signals to the nucleus [114]. The corresponding representative signalling pathways are illustrated in Fig. 3. Notably, NFE2L2 has been well-established as a downstream effector of UPR, as Nrf2–Keap1 dissociation is induced directly by multiple UPR effectors including PERK, ATF4 and JNK [115]. However, the involvement of NFE2L1 in UPR requires further elucidated.

Recently, Toboz et al. identified ATF4, a critical UPR effector, as a direct promoter of NFE2L1 expression using ChIP-sequencing [116]. Since the activation of all three ER transmembrane protein sensors (i.e., PERK, IRE1α and ATF6) directly or indirectly contributes to ATF4 induction, it is conceivable that NFE2L1 may be further induced through multiple UPR pathways. Moreover, Katsuoka et al. suggested a potential interrelationship between NFE2L1 and x-box-binding protein 1 (XBP1) [106], which serves as a critical target of IRE1α [117]. Utilizing a unique tethered dimer assessment system, the NFE2L1-MafG heterodimer presents a significant overlap of binding sites with XBP1, especially in the regulatory regions of proteostasis-related stress response genes, including p97/Vcp, Tbce, and Ube4a [106]. Besides, JNK, a downstream target of IRE1α, has been proposed to phosphorylate and activate NFE2L1 [118]. It is noteworthy that the JNK signalling pathway is known to promote apoptosis [119]. Consistently, Ren et al. found that NFE2L1α deficiency leads to a reduction in cell-cycle arrest at the G2-M arrest and S-phase, along with suppressed apoptosis, indicating a potential pro-apoptotic role of NFE2L1α [120]. However, several research has clarified that NFE2L1 can also exert anti-apoptotic effects [20,21,24,121-123]. Further research is needed to determine how NFE2L1 regulates apoptosis in UPR.

NFE2L1 can be affected by the PI3K/Akt signalling and RAS/MAPK signalling under ER stress. Both PI3K/Akt signalling and RAS/MAPK signalling antagonize tuberous sclerosis complex 1/2 (TSC1/2) to promote nutrient-sensing mTORC1 signalling [124]. Subsequently, mTORC1 prompts NFE2L1 activation to enhance proteasome synthesis and ERAD [57]. Moreover, STAT3, another transcription factor promoting NFE2L1 expression, could be activated by both mTORC1 and ROS, thereby contributing to NFE2L1 induction under ER stress [14,125]. In addition, the nutrient-sensing pathway named AMPK signalling may antagonize NFE2L1 since AMPK can impede mTORC1 signalling by maintaining TSC1/2 activity [126]. In turn, NFE2L1 itself can inhibit AMPK phosphorylation through direct binding [93]. In summary, NFE2L1 activation can be achieved by signalling pathways governed by the three ER stress sensors (PERK, IRE1α and ATF6), as well as PI3K/Akt signalling and MAPK signalling pathways. Then NFE2L1 participates in the regulatory mechanism of UPR to enhance ERAD, the folding capacity of ER and mitigate ER stress, and regulate autophagy and apoptosis.

3.4. NFE2L1 in mitochondrial unfolded protein response (UPR^{mt})

Mitochondrial defect encompasses a broad spectrum of dysfunction, including the accumulation of misfolded proteins within the mitochondrial matrix and impaired OXPHOS capacity [127]. The mitochondrial unfolded protein response (UPR^{mt}) is a transcriptional

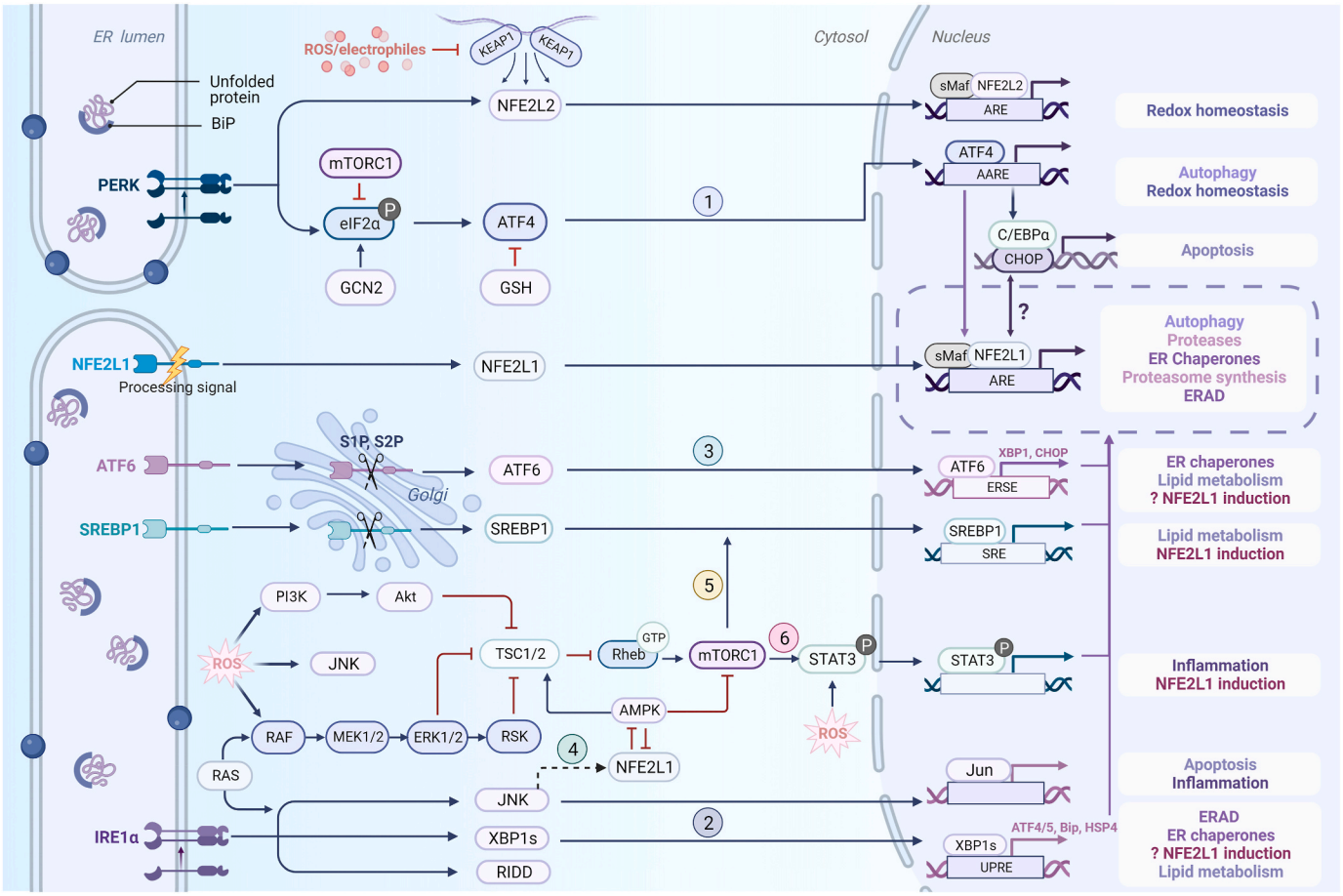

Fig. 3. NFE2L1 is postulated to be cooperated with UPR^{ER}.
UPR activation is achieved by three ER stress sensors (i.e., PERK, IRE1α, and ATF6) with the corresponding representative signalling pathways as illustrated above. (1) NFE2L1 can be activated via PERK/eIF2α/ATF4 axis. In addition, NFE2L2 can also be activated by dimerized PERK to maintain redox homeostasis. (2) IRE1α can be dimerized under ER stress to enable XBP1s to transactivate ATF4/5, BiP and HSP4, thus it is proposed that XBP1s can indirectly activate NFE2L1 to further promote the ER expansion, ERAD and lipid metabolism. (3) Activated ATF6 may lead to NFE2L1 induction indirectly via ATF6/XBP1/ATF4 pathway. (4) JNK is speculated to phosphorylate and activate NFE2L1. PI3K/Akt signalling and RAS/MAPK signalling also participate in NFE2L1 activation via (5) mTORC1/SREBP1/NFE2L1 pathway or (6) mTORC1/STAT3/NFE2L1 pathway. NFE2L1/2 = nuclear factor erythroid 2 (NF-E2)-related factor 1/2, ERAD = ER-associated degradation, PERK = UPR mediator pancreatic ER kinase (PKR)-like ER kinase, GCN2 = general control nonderepressible 2, eIF2α = eukaryotic translation initiation factor 2 subunit alpha, ATF4/5/6 = activating transcription factor 4/5/6, CHOP = C/EBP-Homologous Protein, C/EBPα = CCAAT enhancer binding protein alpha, KEAP1 = Kelch like ECH associated protein 1, S1P/S2P = Golgi-resident site-1/2 protease, SREBP1 = sterol regulatory element-binding protein 1, PI3K = phosphatidylinositol 3-kinase, TSC1/2 = tuberous sclerosis complex 1/2, mTORC1 = mechanistic target of rapamycin complex 1, STAT3 = signal transducer and activator of transcription 3, RSK = Ribosomal S6 kinase, AMPK = AMP-activated protein kinase, IRE1α = inositol-requiring enzyme 1alpha, JNK = c-jun N-terminal kinase, XBP1s = spliced x-box-binding protein 1, RIDD = IRE1alpha-dependent decay, ERSE = endoplasmic reticulum stress response elements, SRE = serum response elements, UPRE = unfolded protein response elements, BiP = Binding immunoglobulin protein.

response that is typically activated under such circumstances to establish mitochondrial-to-nuclear communication, facilitating the restoration of cellular network. The UPR^{mt} coordinates various pathways, including the ubiquitin-proteosome system, the antioxidant system, mitochondrial biogenesis, and mitophagy, to aid in the recovery process [128-130].

The canonical UPR^{mt} pathway is orchestrated by the phosphorylation of eIF2α by GCN2 [131] or PERK in response to increased ROS, depleted amino acids and ER stress [131,132]. This phosphorylated form of eIF2α induces the integrated stress response (ISR), which involves selective translation of mRNAs with open reading frames in the 5′ untranslated regions. Notably, these mRNAs encode important transcription factors such as ATF4, ATF5, and CHOP, while overall protein synthesis is hindered [133]. Toboz et al. revealed that *NFE2L1* is a GCN2-dependent target of ATF4, indicating that NFE2L1 might act as a positive downstream effector in UPR^{mt} [116]. Furthermore, Hu et al. argued that the basal expression of UPR^{mt}-associated genes, including ATF4, ATF5, CHOP, and their targets GRP75 (also known as HSPA9) and FGF21 were reduced to varying degrees in *NFE2L1*$^{-/-}$ cells [92]. This finding demonstrated that NFE2L1 could act as a significant activator in UPR^{mt}. However, whether these genes are direct targets of NFE2L1 remains unclear. In summary, NFE2L1 may form a positive feedback loop in the activation of the canonical UPR^{mt} pathway.

4. NFE2LI-mediated diseases and therapeutic intervention

Accumulating evidence has unravelled that NFE2L1 exerts influence over adipocyte hypertrophy, inflammation, and insulin resistance through the regulation of redox balance [75], proteostasis [50], and mitochondrial homeostasis [116]. Thus, NFE2L1 dysfunction can instigate the spontaneous onset and advancement of various conditions including cancers [12-15], neurodegenerative diseases [20], inflammatory and autoimmune diseases [16-19], and vascular diseases [22] (Table 2). The upstream regulators and downstream targets of NFE2L1 are also summarized in Table 2.

Table 2
The overview of molecular mechanism in NFE2L1-modulated diseases.

Diseases	Expression	Genotype of mice/cells	Upstream regulators of NFE2L1	Downstream effectors of NFE2L1	Refs
Cancers					
Liver cancer	↑/↓	HEK293 cells, NFE2L1$\alpha^{-/-}$ subcutaneous carcinoma xenograft in nude mice	–	CDK2, CDK6, Cyclin D1, p53, p21, α-Catenin, β-Catenin, SNAI1, SNAI2, MMP9, and MMP17	[120]
		HepG2 cells with Cd exposure	DDI2	Mt-1, Mt-2	[155]
		HepG2, MHCC97H, MHCC97L, and HEK-293T cell lines	–	p53, CDH1, TCF4, MMP9, Wnt5A, Wnt11A, FZD10, LEF1, SMAD4, and PTEN	[15]
		Hepatoma cell lines (SNU354, SNU423) with mitochondrial defects	ROS, STAT3, and NDUFA9	STX12	[14]
		HepG2 cell line	41BBL	41BBL	[12]
Breast cancer	↓	MDA-MB-231 cells	MRTF-A	MRTF-A, miR-219	[136]
		DDI2-deficient MDA-MB-231 cells	DDI2	PSMB4, PSMB7, PSMC4, PSMD12, and caspase 3	[145]
Lung cancer	↑	LUAD cell lines (PC-9, Calu3, A549, and HCC827)	miR-4701-5p, SLCO4A1-AS1	β-catenin	[156]
		Human bronchial epithelial cells (BEAS-2B) treated with arsenite	–	Snail1, E-cadherin	[13]
Neuroblastoma	↑	Neuroblastoma cells M17 (CRL-2267) and SH-SY5Y (CRL-2266)	–	p62	[143]
Multiple myeloma	↑	AMO-BZB cells treated with LNA gapmeR ASO and the MM xenograft model	MALAT1, KEAP1	MALAT1	[152]
Neurodegenerative disorders and developmental dysfunctions					
Parkinson's disease	↑	SH-SY5Y neuronal cells	–	PSMB6/β1, PSMA3/α7, PSMA2/α2, PSMC4/Rpt3 and caspase 3/7	[21]
		LUHMES dopaminergic neurons exposed to MPP+ and rotenone	GSH, ATF4	–	[121]
		Fischer 344 PD rats	6-OHDA	–	[157]
Alzheimer's disease	↑	Icariin-induced PC12 cells	–	Hrd1/synoviolin	[20]
		C. elegans AD model	NGLY1, DDI-1/DDI2	–	[67]
Spinal and bulbar muscular atrophy (SBMA)	↓	AR113Q knockin mice	DDI2	–	[158]
Inflammatory and autoimmune diseases					
Nonalcoholic steatohepatitis (NASH)	↓	NFE2L1-L Liver-specific KO mice	–	GSTM3, GSTM6, GSTP2, GSTA1, Mt-1, and Mt-2	[84]
		NFE2L1-L Liver-specific KO mice	ATF4, CHOP	Grp78, Grp94, Gadd34, and Pdi	[19]
Atherosclerosis	↑	LPS-induced RAW264.7 cells	-	TRIM59	[118]
Multiple sclerosis (MS)	↓	C57Bl/6 mice with EAE induction	PBX1	c-20S-specific subunit β5	[159]
Insulinomas	–	NFE2L1-KD MIN6 cells, and diabetic Akita mice administrated with streptozotocin (STZ)	–	Epcam, Esrp1, Snail1, Snail2, and Zeb1	[97]
Type-2 diabetes (T2D)	↓	NFE2L1-KD MIN6 cells	–	MMA	[160]
		MIN6 β-cells, Nrf1(b)-KO mice	–	GLUT2, HK1, LDH1, GAPDH, HK4 and AMPKα	[161]
Vascular Diseases					
Myocardial ischemia reperfusion injury (MIRI)	↑	human iPSC-derived cardiomyocytes, crossing NFE2L1$^{fl/fl}$ mice with αMHC-Cre transgenic mice	–	PSMA1, PSMD1, SOD1, and HMOX1	[22]
Renal ischemia-reperfusion injury (IRI)	↓	TCMK-1 cells (no. CCL-139) transfected with antagomir miR-92a-3p, I/R induced mice	miR-92a-3p	Caspase-1, NLRP3, IL-1β, IL-18, and HMOX1	[162]

a. "↑" or "↓" indicate the expression correlation between NFE2L1 and distinct diseases is positive or negative, respectively.
b. "-" in "*Expression*" means the expression level of NFE2L1 is similar in wild-type cell line.
c. "-" in other parts means no relevant information to our knowledge.

4.1. NFE2L1 in cancers and potential anticancer drugs

Cancers stand as the foremost cause of mortality worldwide, claiming over 10 million lives annually [134]. Accumulating research has substantiated the pivotal role of NFE2L1 in various malignancies, particularly liver cancer, breast cancer, lung cancer, and multiple myeloma (MM) [120,135,136]. Mechanistically, the stress-responsive NFE2L1 exerts control over crucial aspects of cancer biology, encompassing proliferation, epithelial-mesenchymal transition (EMT), invasion, metastasis, cell cycle progression, cell stemness, and immune infiltration. Consequently, NFE2L1 either hinders or promotes the development and progression of malignancies [12-15]. Despite progresses in curative surgery and perioperative chemotherapy, patients afflicted with advanced metastases continue to face unfavourable prognoses. Therefore, targeting NFE2L1 holds great promise as an avenue to facilitate cancer therapy via approaches such as targeted therapy, chemotherapy, and radiotherapy.

4.1.1. NFE2L1 in carcinogensis

Carcinogenesis can be perceived as the ultimate result of prolonged ER stress, persistent UPR signalling, and severe oxidative stress. Consequently, NFE2L1, through its role in maintaining ER homeostasis, induces ER transformation and proliferation of *NFE2L1*$^{-/-}$ cells from conditional KO mice with spontaneous cancer [137]. Notably, NFE2L1 holds particular significance in hepatocellular carcinoma (HCC) due to its involvement in regulating cellular redox, genomic integrity, and lipid metabolism within liver [85]. Reports have indicated downregulation or depletion of NFE2L1 in metastatic liver cancer [120]. In hepatoma, NFE2L1 serves as a dominant tumour suppressor by inhibiting the Wnt/β-catenin pathway or PI3K-PDKI-Akt pathway, thereby impeding the EMT process, invasion and metastasis of HCC cells. Additionally, silencing NFE2L1 shorten the G1 phase of cell cycles, promoting cell proliferation [15]. NFE2L1 also curbs HCC aggressiveness by maintaining the interaction between redox homeostasis and tumour immune evasion. Recently, Qiu et al. unveiled that NFE2L1 activates 41BBL as an

immune checkpoint, enhancing the infiltration of $CD8^+$ T cells into the tumor and triggering cancer cells necrosis [12]. NFE2L1α, the longest isoform of ER-resident NFE2L1, has also been reported to impede HCC progression via modulating cell cycle dynamics and apoptosis [120]. In comparison, TCF11 serves as a more effective tumour suppressor in the malignant transformation [138]. Apart from its tumour-suppressive role, NFE2L1 can be upregulated by OXPHOS dysfunction and promote the EMT process in HCC by modulating oxidative stress and mitochondrial functions via ROS/STAT3/NFE2L1/STX12 pathway [14]. Thus, the co-expression of STX12 and NFE2L1 may function as diagnostic and therapeutic biomarkers for HCC. In brief, NFE2L1 mainly serves as a tumour suppressor in liver cancer, and its deficiency disrupts the cell cycle and immune response of cancer cells, thus promoting HCC progression.

In addition to liver cancer, NFE2L1 has been demonstrated to be downregulated in triple-negative breast cancer (TNBC), colorectal cancer and lung cancer, while being upregulating in prostate cancer [136,139-142]. Regarding TNBC, overexpressed NFE2L1α impedes the proliferation and metastasis of cancer cells via inhibiting myocardin-related transcription factor A (MRTF-A) by miR-219 [136]. NFE2L1 also serves as a tumour suppressor in colorectal cancer, contributing to the complementary stabilization of proteasome activity in colorectal cancer cells with NFE2L3 via the NFE2L3/CPEB3/NFE2L1 axis [139]. Recent research has unveiled the involvement of NFE2L1 in lung tumourigenesis, with the NFE2L1 expression level in non-small cell lung cancer (NSCLC) cells being linked to increased overall survival of NSCLC patients [142]. Moreover, NFE2L1 was identified to be differentially expressed in prostate cancer (PC) [140]. Its isoform p65-NFE2L1, induced by dihydrotestosterone, facilitate androgen receptor (AR) transactivation to promote PC progression [141]. The efficacy of the androgen deprivation therapy (ADT) in PC can be attenuated by ROS-induced sustained AR signalling, thus negatively targeting p65-NFE2L1 has the potential to extend the duration of response towards ADT. Since NFE2L1 is also a key oncogenic transcription factor, it may serve as a prognostic indicator in other malignancies, including neuroblastoma [143], multiple myeloma (MM) [9,135], and diffuse large B-cell lymphoma (DLBCL) [144].

In summary, NFE2L1 plays a dual role in cancer, acting as both a suppressor and promoter, while its various splicing isoforms (NFE2L1α, TCF11, and p65-NFE2L1) have been identified to have distinct functions in cancer. However, there remains a dearth of research on NFE2L1 in other cancers, especially gastric cancer. Therefore, it is imperative to conduct further investigation to elucidate the role of NFE2L1 in these aspects.

4.1.2. Anti-tumour effects of NFE2L1

Numerous novel studies have been performed on the regulatory molecules and pathways associated with NFE2L1 as a biomarker and therapeutic target in various tumors (Table 1) [123,125,145-148]. The antioxidant stress response cascades mediated by NFE2L1 hold great promise as effective targets for tumour therapy, and the concurrent inhibition of proteasomes and NFE2L1 has been proven to enhance the therapeutic efficacy against malignancies. Therefore, NFE2L1 inhibitors can be employed either alone or in combination with other medications for targeted therapy, chemotherapy, and radiotherapy. Moreover, NFE2L1 also functions in ameliorating the side effects (e.g., nephrotoxicity) of chemotherapeutic agents, as NFE2L1 signalling can attenuate the cytotoxic activity of anti-tumour drugs by maintaining cellular homeostasis [149]. For instance, silibinin can alleviate cisplatin-induced apoptosis in acute kidney injury (AKI) by NFE2L1-modulated antioxidative effects via the ROS/MAPK signalling pathway [24].

4.1.2.1. The alone anticancer function of NFE2L1. Distinct molecules (i.e., Metformin, RU42633, MG132, and α-T3E) have been identified as NFE2L1 inhibitors to be employed independently to elicit anti-tumour effects in malignancies via inducing oxidative stress or proteotoxic stress within cancer cells. Metformin, a primary medication of T2D, was corroborated to inhibit NFE2L1 to induce ROS accumulation in an AMPK-independent manner, thereby hampering liver cancer progression [147]. Metformin has been found to exhibit inhibitory effects on the abundances of $NFE2L1^{\Delta N1}$, which lacks the first N-terminal 50 amino acids of NFE2L1, rather than NFE2L2. This suggests that the inhibitory impact of MET on NFE2L1 may be contingent upon the specific domain of NFE2L1, namely its N-terminal domain (NTD) [147]. This may offer a theoretical foundation for targeting NFE2L1 in the treatment of hepatoma through intervention in oxidative stress. Moreover, the estrogen-associated metapristone (RU42633) can downregulate NFE2L1 via miR-492 to inhibit the progression of endometrial cancer [146]. The in-depth relationship between NFE2L1 and apoptosis in endometrial cancer cells treated with RU42633 treatment remains elusive. Apart from apoptosis and oxidative stress, NFE2L1 inhibitors can also exert anticancer effects by targeting the role of NFE2L1 in proteasome maintenance. For instance, MG132 downregulates Proteasome 20S Subunit Beta 2 (PSMB2) to hinder NFE2L1 activation and impede the gastric cells proliferation by suppressing proteasome activity [123]. In terms of malignant mesothelioma, α-T3E exerts cytotoxic effects on chemoresistant H2452 cells by inactivating NFE2L1, inducing ER stress, and disrupting proteasome homeostasis [125]. Another recent study substantiated that NFE2L1 can induce p62, a Ub receptor for autophagy, to diminish aggregated ubiquitinated proteins and prolong cell survival

Table 1
The antitumor drugs target the transcriptional and post-translational processing of NFE2L1.

Drugs	Targets	Mechanism	Tumor cell line	Year	Refs
LU-102	20S β2 sites	Combine with CFZ and inhibit 20S β2 and β5 sites to decrease the formation of active NFE2L1	Human breast cancer cells (SUM149)	2017	[150]
WRR139	NGLY1	Block NGLY1-driven de-N-glycosylation of NFE2L1	MM cells (U266, H929), ALL cells (Jurkat)	2017	[151]
LNA gapmeR ASO	MALAT1	Potentiate BTZ cytotoxicity by the downregulation of NFE2L1 via KEAP1	MM cells (NCI-H929, RPMI-8226)	2018	[152]
CB-5083	p97	Combine with BTZ and inhibit p97-modulated retrotranslocation of NFE2L1	MM cells (RPMI8226)	2017	[153]
NMS-873	p97	Combine with CFZ and impede the p97-mediated retrotranslocation of NFE2L1	TNBC cells (MDA-MB-231)	2020	[145]
doxycycline	DDI2	Combine with CFZ and inhibit DDI2 to limit NFE2L1 transcriptional activity	TNBC cells (MDA-MB-231)	2020	[145]
NFV	DDI2	Enhance BTZ toxicity by inhibiting DDI2 to block the nuclear translocation and proteolysis of NFE2L1	Human colorectal cancer cells (HCT116)	2020	[154]
	DDI2	Potentiate BTZ or CFZ cytotoxicity via impeding DDI2-NFE2L1 pathway partially	MM cells (ARH77, U266, L363)	2022	[148]
Metformin	NTD	Inhibit NFE2L1 transcription, trigger NFE2L1 degradation and induce the accumulation of ROS	Human hepatoma cells (HepG2)	2021	[147]
RU42633	miR-492	Metapristone downregulate NFE2L1 and Klf5 through miR-492	Endometrial cancer cells (RL95-2, Ishikawa)	2021	[146]
MG132	PSMB2	Inhibit PSMB2 to decrease proteasome activity via suppressed NFE2L1 activation	Gastric cancer cells (NCl-N87, AGS)	2022	[123]
α-T3E	PSMB5-7	Inhibit PSMB5-7 and determine proteasome homeostasis via the inactivation of NFE2L1	Malignant mesothelioma cells (H28, H2452)	2022	[125]

under proteasome inhibition in neuroblastoma cells, implying the potential of NFE2L1 inhibitors as therapeutic targets for neuroblastoma [143].

4.1.2.2. NFE2L1 potentiates the efficacy of other anticancer strategies. Inhibiting NFE2L1 can potentiate the cytotoxicity of anti-tumour drugs and provide a more potent therapeutic effect. For instance, targeting NFE2L1 can augment the anti-tumour activity of VER-155008, particularly in cancer cells with suppressed HSP70 and proteasome activity [163]. In addition, there is increasing evidence supporting the effectiveness of combining NFE2L1 inhibitors with PIs in cancer treatment. UPS is commonly hyperactivated in neoplasia cells to proliferate and survive. Therefore, PIs such as bortezomib (BTZ), carfilzomib (CFZ), and ixazomib have been approved by the FDA for use in cancer therapy [164]. However, the efficacy of PIs remains limited in solid tumors [122], and patients with multiple myeloma (MM) often develop resistance to proteasome inhibition methods [165]. NFE2L1 offers a promising avenue to enhance the anticancer efficacy of PIs and improve clinical outcomes. Normally, NFE2L1 undergoes continuous degradation by the 26S proteasome. However, in the presence of PIs, NFE2L1 can be activated to compensate for the proteotoxic stress induced by 26S proteasome inhibition in tumour cells, leading to drug resistance, also known as the "bounce-back" response. This phenomenon plays a critical role in the acquisition of drug resistance by tumors treated with PIs [166]. Thus, by blocking the NFE2L1-mediated proteasome "bounce--back" response and inhibiting the retrotranslocation, de-N-glycosylation, and nuclear translocation of NFE2L1, we can enhance the anti-cancer potential of PIs. The feasibility of co-therapy with PIs and NFE2L1 inhibitors is supported by accumulating evidence (see Table 1).

When cancer cells expose to PIs-induced ER stress, the carboxyl terminus of NFE2L1 can undergo reverse transport from the ER lumen to the cytoplasm via p97/VCP, and then de-N-glycosylated via NGLY1. In this regard, several NFE2L1 inhibitors (CB-5083, NMS-87, WRR139, etc.) can negatively regulate NFE2L1 by targeting its retrotranslocation and post-translational modifications. CB-5083, for example, can block the p97-driven retrotranslocation of NFE2L1, thereby reducing the proteasome "bounce-back" response mediated by NFE2L1 and sensitizing tumour cells to BTZ-induced damage in MM [153]. Another p97 inhibitor NMS-873 can also impede the extraction of NFE2L1 from the ER and enhance its combination with CFZ to work against NFE2L1-mediated resistance to proteasome inhibition [145]. Furthermore, the cytotoxicity against BTZ-resistant MM cells can be achieved through NFE2L1/DDI2 knockout (KO) in the absence of PIs. Drugs targeting DDI2, such as doxycycline and NFV [167], can inhibit DDI2 and subsequently reduce the proteasome "bounce-back" effect, thereby enhancing the sensitivity of MM cells to BTZ or CFZ by blocking the nuclear translocation and hydrolysis of NFE2L1 [148]. Similar effects have been observed in colorectal cancer cells [154]. Intriguingly, a β2-selective drug LU-102 not only inhibits the 20S β2 subunit of the 26S proteasome but also inactivates NFE2L1 by inducing its aggregation. By co-inhibiting the β5 activity, LU-102 completely blocks the proteasome "bounce-back" effect, leading to ER stress-induced apoptosis in breast cancer cells when used in combination with CFZ [150]. In addition to breast cancer, LU-102 has demonstrated synergistic cytotoxicity with ibrutinib in MM [168], BTZ and CFZ in MM [169], and ONX-0914 in acute lymphoblastic leukemia (ALL) [170] and in MM [135]. In general, NFE2L1 inhibitors can inhibit NFE2L1 activation by impeding its retrotranslocation, de-N-glycosylation and nuclear translocation. When combined with anti-tumour drugs, especially PIs, they exhibit significant anti-tumour effects in targeted therapy.

In addition, NFE2L1 also participate in metal-based chemotherapy. Several metal compounds can disrupt UPS and interfere with proteasome function [171], thus NFE2L1 can mediate detoxification of metal exposure by maintaining proteostasis to protect cells from patulin cytotoxicity [172], and cadmium toxicity [173]. Persistent toxic stress can induce several cancers, for instance, prolonged arsenic exposure is highly linked to lung cancer development. The overexpression of long-isoform of NFE2L1-L can accelerate EMT process by enhancing EMT inducer SNAIL1 and decreasing epithelial biomarker E-cadherin in arsenite-induced lung cancer [13]. Therefore, NFE2L1 may enhance cancer cells' chemoresistance to metal-based therapy to hamper the efficacy of chemotherapy. Interestingly, NFE2L1 can regulate metallothionein (MT) expression, which is positively associated with the chemoresistance of metal-based medications in cancers, such as cisplatin. This indicates the feasibility of DDI2-NFE2L1-MT axis inhibition in potentiating metal-based chemotherapy [155,173,174]. Although post-translational modification of NFE2L1 can improve the sensitivity of chemotherapeutic agents, the upstream mechanism of NFE2L1 activation by PIs is still unclear, so it is important to clarify the upstream mechanism of the proteasomal "bounce-back" effect to guide the application of PIs in solid tumors. Aside from targeted therapy and chemotherapy, NFE2L1 also participate in cancer radiotherapy. A recent study by Wang et al. showed that PIs can facilitate the mTORC1-NFE2L1 pathway, thereby increasing the sensitivity of hypopharyngeal cancer (HC) cells to radiotherapy. This effect is achieved by stabilizing DEP domain-containing mTOR-interacting protein (DEPTOR) [175]. STAT3, another upstream regulator of NFE2L1, was recently clarified to regulate cancer stemness and radioresistance [176]. Thus, it is hypothesized that the mTORC1-STAT3-NFE2L1 axis can be promisingly used in overcoming radioresistance in cancer radiotherapy.

4.2. NFE2L1 in neurodegenerative diseases

Neurodegenerative disorders encompass a diverse range of conditions, including Alzheimer's disease (AD), Parkinson's disease (PD) and Kennedy's disease. Developing medications that directly target neurodegeneration has proven to be exceedingly challenging [177]. Notably, the knockout of other genes within the CNC-bZIP family, except NFE2L1, failed to cause neuronal phenotypic disturbance and neurodegenerative diseases [9]. This suggests that NFE2L1 may hold unique potential as a drug target for maintaining the neuronal homeostasis. The UPS represents a major degradation machinery, and disruptions in UPS function are significantly linked to neurodegeneration. Consequently, NFE2L1 primarily exerts a neuroprotective role via modulating UPS impairment or proteotoxic stress instead of oxidative stress [108].

4.2.1. Alzheimer's disease (AD)

Neuronal stress response signals have a significant role in the pathophysiology of many age-dependent neurodegenerative disorders such as Alzheimer's disease (AD). AD stands as the most prevalent neurodegenerative disease and a leading cause of dementia [20]. Notably, NFE2L1 is demonstrated to be downregulated in AD, and this decreased activity of NFE2L1 is predicted to be mediated by Hdac5 and Hdac9A [178]. NFE2L1 is identified as a possible predominant gene expression regulators in the AD etiology, regulating primarily Vdac1 and Aplp2, which are associated with the pathogenesis of AD as well as Parkinson's disease (PD) [178]. Consistently, a brain-specific knockout of NFE2L1 was found to induce the neuronal apoptosis and the proteasome impairment [108]. Mutations that enhance the accumulation of amyloid beta are intimately correlated with adult-onset paralysis in AD [67]. A *C. elegans* AD model implicated that SKN-1A/NFE2L1 can be autonomously activated by proteasome dysfunction to mitigate the toxicity of amyloid beta and postpone the onset of AD via regulating UPR [67]. Moreover, the lifespan assays revealed that *skn1a* (*mg570*) can result in a 20% decrease in lifespan in comparison to the wild type, providing evidence that SKN-1A is essential for normal lifespan and promotes longevity by safeguarding proteasome abundance [67]. Consequently, augmenting NFE2L1 may be beneficial for combating human aging and age-dependent neurodegenerative disorders.

The elevated level of mechanistic target of rapamycin (an mTOR

inhibitor) in AD has shown cognitive improvement in AD mouse models. This improvement is attributed, at least in part, to the promotion of autophagy [179]. Given that NFE2L1 also promotes autophagy, rapamycin and NFE2L1 may exert a synergistic protective effect in AD [115]. To put it succinctly, NFE2L1 is likely to play a neuroprotective role by enhancing proteasome function and autophagy while inhibiting aberrant apoptosis. It is worth exploring whether and how NFE2L1-mediated regulation of Vdac1 and aplp2 is involved in the pathogenesis of diseases. Recently, Li et al. clarified that Icariin, another promising agent for degenerative neuronal disorders, can trigger NFE2L1 to elevate Hrd1/Synoviolin expression to further suppress ER stress-induced apoptosis of neuroblastic cells [20]. They have uncovered five conserved NFE2L1-specific binding sites on the Synoviolin promoter in order to ascertain the potential implications of Icariin. It would be intriguing to examine the binding activity of NFE2L1 on the Synoviolin promoter in neurons derived from AD patients. Aside from rapamycin and Icariin, the administration of OA supplementation and the limitation of cholesterol intake in mice with AD were also validated to ameliorate the neuropathological phenotype of AD. [180]. Given the oleic acid promotes NFE2L1 while excess cholesterol inhibits NFE2L1 as described above, NFE2L1 may function as an underlying mechanism of dietary protection from AD [16,18].

4.2.2. Parkinson's disease (PD)

Preceded only by AD, PD stands as the second most prevalent neurodegenerative disorder, with its prevalence predicted to double over the next three decades [181]. PD's principal mechanisms encompass mitochondrial impairment, oxidative stress, and neuronal proteotoxic stress. In PD, the aggregation of ubiquitin (Ub) conjugates within neurons often disrupts proteasome activity to further induce the accumulation of α-synuclein and neuronal damage, thus resulting in PD development [121]. In this context, NFE2L1 is downregulated in PD and may alleviate the impaired protein turnover in PD to attenuate proteotoxicity and enhance neuronal resilience [21]. Sotzny et al. found that TCF11/NFE2L1 can be activated by rotenone, a mitochondrial complex I inhibitor, to induce proteasome biogenesis and prevent the apoptosis of dopaminergic neurons caused by the UPS disturbances in PD [21]. Hence, NFE2L1-mediated resistance to mitochondrial impairment in PD partially accounts for the "bounce-back" response [21]. NFE2L1 can also be upregulated by the extra supply of thiols, which can be derived from astrocytes to support neurons, to recover proteasome activity and degrade protein aggregates, thus alleviating PD [121]. Given that astrocytes are the primary providers of glutathione/glutathione precursors, by performing GSH supplementation, Gutbier et al. found that GSH can also upregulate NFE2L1 to enhance proteasomal activity, thereby affecting neuronal fate [121]. This indicates that the astrocytic neuroprotection or external thiols supply could provide a viable approach for PD treatment via NFE2L1 superinduction. In addition to proteotoxic stress, a high-fat diet can also contribute to PD development [182]. Ma et al. found that diet-induced obesity and 6-Hydroxydopamine (6-OHDA) can decrease nigrostriatal TCF11/NFE2L1 expression in PD mice model, denoting its possible role in the neuroprotection of PD [157].

4.2.3. Spinal and bulbar muscular atrophy (SBMA)

Spinal and bulbar muscular atrophy (SBMA), known as Kennedy's disease, is an adult-onset neurodegenerative and neuromuscular disorder resulting from the expansion of a CAG repeat in exon 1 of the androgen receptor (AR) gene [158]. In SBMA, both DDI2 and the cleaved 95 kDa NFE2L1 experience a reduction due to the inhibitory effect of the AR113Q protein, which hinders the processing and activation of NFE2L1 by DDI2 [158]. Consequently, this leads to the downregulation of UPS-related genes and the emergence of proteotoxic stress. Besides, NFE2L1 can increase the ubiquitination of polyglutamine (polyQ)-expanded AR to further trigger the proteasomal degradation of AR, and the activation of NFE2L1 by ASC-JM17, a curcumin analogue, can relieve SBMA symptoms by reversing UPS impairment [183]. Therefore, it is feasible to target NFE2L1 to attenuate the disease phenotypes of SBMA and other polyglutamine diseases.

4.2.4. Multiple sclerosis (MS)

The modulation of NFE2L1 in the dynamics of proteasome expression is also evident in autoimmune-mediated neurodegenerative diseases like multiple sclerosis (MS). MS is an inflammatory demyelinating disease that affects the central nervous system. The substantial decline of NFE2L1α and NFE2L1β in the spinal cord was clarified to reduce the c-20S-specific subunit β5 mRNA expression to affect proteasome composition in experimental autoimmune encephalomyelitis (EAE), the most widely utilized experimental model of MS [159]. Moreover, NFE2L1 can mediate innate immunity by reversing proteasome dysfunction. For instance, Schimidt et al. found that NFE2L1 can modulate the upregulation of proteasomes to prevent T cells from being impaired by proteostatic stress, denoting its possible role of NFE2L1 in immunoproteasome inhibition, a novel therapy for immune-mediated diseases [184].

4.3. NFE2L1 in inflammatory diseases

Recent studies have demonstrated unequivocally that NFE2L1 exerts anti-inflammatory function by regulating macrophage polarization [185], or downregulating the genes responsible for innate immune response and cytokine production [22]. In humans, the proteasome functions as a central modulator of inflammation [186]. As a core factor for proteasome activity maintenance, NFE2L1 plays an integral role in reversing the protein imbalance in inflammatory diseases such as non-alcoholic steatohepatitis (NASH) [16-19], and proteasome-associated autoinflammatory syndromes (PRAAS) [187] via UPR initiation.

4.3.1. Non-alcoholic steatohepatitis (NASH)

NASH is the inflammatory subtype of nonalcoholic fatty liver disease (NAFLD) resulting from the aberrant activation of hepatic immune cells and endothelial cells, and characterized by steatosis in response to the inflammatory mediators from hepatic adipocytes [188]. Recent studies have extensively elucidated the pathophysiology of NASH, suggesting that steatosis is the ultimate result of ER stress induced by the accumulation of lipid and ubiquitinated proteins [189]. In NASH, NFE2L1 was demonstrated to be downregulated and the inducible KO of NFE2L1 can cause ER stress by elevating the transcription of ER stress-associated genes to produce excessive ubiquitinated proteins, thus promoting NASH development [19]. As mentioned before, SKN-1A/NFE2L1 reduces fat accumulation in intestinal lipid droplets (LDs) via enhancing ERAD [16]. Mechanistically, 1) SKN-1A/NFE2L1 is activated in phosphatidylcholine (PC)-dependent manner, while the impairment of PC can induce steatosis, LDs storage and further NASH development; 2) NFE2L1 acts as an effective responder of elevated cholesterol levels, and its proteolytic domain regulates the LXR and suppress the activation of CD36 [18], which can recognize and uptake long-chain fatty acids (LCFAs) and oxidized low-density lipoproteins (ox-LDL) [17]. Therefore, it is postulated that NFE2L1 may be a potential drug target for NASH prevention and treatment by mediating ERAD to decrease lipid storage in response to ER stress.

4.3.2. Proteasome-associated autoinflammatory syndromes (PRAAS)

PRAAS is another inflammatory disease caused by inherited and/or *de novo* proteasome loss-of-function mutations. In PRAAS, these mutations can undermine proteasome proteolytic activity, induce polyubiquitinated protein aggregation and further initiate UPR [186]. Fever and lipodystrophy are common in PRAAS patients, and these symptoms are linked to adipocyte dysfunction and aberrant thermogenesis in adipose tissues [186]. NFE2L1 can partially recover proteasome function by promoting the expression of proteasome subunits in brown

adipocytes [187]. However, NFE2L1 failed to restore normalized adipogenesis and adipocyte dysfunction, albeit the evidence-based tight linkage between proteostasis and lipid metabolism [187]. In general, both NASH and PRAAS are concomitant with aberrant ER stress and can be ameliorated by NFE2L1-mediated ERAD. Therefore, NFE2L1 activation can serve as a novel therapeutic option for inflammatory diseases with proteotoxic stress. Unfortunately, the existing studies do not clarify the potential role of NFE2L1 in adipogenesis and lipodystrophy, thus necessitating further studies in these pertinent areas.

4.4. NFE2L1 in cardiovascular diseases (CVDs)

Cardiovascular Diseases (CVDs) such as atherosclerosis and myocardial ischemia-reperfusion injury (MIRI) are one of the leading causes of premature death globally [190]. Preventing cardiomyocytes from death and replenishing the lost myocardium are the central goals for heart repair, and NFE2L1 has been demonstrated to function in these two aspects (i.e., cardioprotection and regeneration) in newborns and adults [22]. The activated NFE2L1 can participate in neonatal heart regeneration by maintaining OXPHOS metabolism to promote the transcriptional response of cardiomyocytes [22,191,192]. In adults, NFE2L1 overexpression serves as a double-edged sword in vascular diseases, aggravating atherosclerosis [118] while forestalling or mitigating MIRI [22]. Atherosclerosis is a chronic inflammatory disorder of the arterial wall [193]. NFE2L1 can facilitate inflammation and atherosclerosis progression by negatively regulating the transcriptional processing of tripartite motif containing 59 (TRIM59) by JNK signalling in a LPS-treated mice model [118]. Conversely, NFE2L1 exerts cytoprotective function on cardiomyocytes in MIRI via the induction of a dual stress response including proteostatic stress and redox imbalance [22]. MIRI is an unavoidable risk event for acute myocardial infarction (MI) and no effective treatment is available for MIRI at present [160]. NFE2L1 can relieve MIRI-induced damage and protect cardiomyocytes against doxorubicin-induced cardiotoxicity via upregulating the genes correlated to the ERAD pathway, concomitant with the upregulated genes associated with antioxidant responses such as ROS scavenge and glutathione metabolism [22]. In general, the activation and enrichment of NFE2L1 are indispensable for neonatal heart regeneration and MIRI remission. Nevertheless, the possible role of NFE2L1 in other CVDs such as MI and heart failure has not been elucidated yet, and furthermore relevant research is still warranted.

5. Conclusion and perspectives

Accumulating evidence substantiates the indispensable role of NFE2L1 in maintaining cellular redox balance and protein homeostasis, both in normal cellular conditions and in response to cellular stresses. This paper presents a comprehensive overview of the currently established cellular mechanisms responsible for activating and regulating NFE2L1, which fine-tune NFE2L1 protein levels and transcriptional activity to modulate adaptive stress responses. This paper also illuminates the underlying molecular mechanisms that govern the specific stress-responsive effects of NFE2L1 on oxidative stress, including canonical antioxidant genes transcription and mitochondrial respiration, as well as its impact on proteotoxic stress, involving UPS maintenance and the induced expression of other defensive genes. Notably, the gain-of-function of NFE2L1 can be detected in HCC, lung cancer, neuroblastoma, MM, PD, AD, atherosclerosis and MIRI, while the loss-of-function of NFE2L1 is associated with in breast cancer, SBMA, MS and NASH. However, the emerging neuro-defensive role of NFE2L1 in neurodegenerative disorders remains inadequately elucidated. There is a notable dearth of research concerning the relationship between NFE2L1-mediated stress responses and crucial aspects such as mitochondrial function, lipolysis, and glucose metabolism. Further investigations are warranted to gain deeper insights into these unexplored dimensions and their connection to NFE2L1.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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