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Health position paper and redox perspectives – Bench to bedside transition for pharmacological regulation of NRF2 in noncommunicable diseases

Antonio Cuadrado [a,b,c,d,*], Eduardo Cazalla [a,b,c,d], Anders Bach [e], Boushra Bathish [f], Sharadha Dayalan Naidu [f], Gina M. DeNicola [g], Albena T. Dinkova-Kostova [f], Raquel Fernández-Ginés [a,b,c,d], Anna Grochot-Przeczek [h], John D. Hayes [f], Thomas W. Kensler [i], Rafael León [j], Karen T. Liby [k], Manuela G. López [l,m,n], Gina Manda [o], Akshatha Kalavathi Shivakumar [p], Henriikka Hakomäki [p], Jessica A. Moerland [k], Hozumi Motohashi [q,r], Ana I. Rojo [a,b,c,d], Gerasimos P. Sykiotis [s], Keiko Taguchi [t,v], Ángela M. Valverde [u], Masayuki Yamamoto [v], Anna-Liisa Levonen [p,**]

[a] Department of Biochemistry, Medical College, Autonomous University of Madrid (UAM), Madrid, Spain
[b] Instituto de Investigaciones Biomédicas Sols-Morreale (CSIC-UAM), Madrid, Spain
[c] Instituto de Investigación Sanitaria La Paz (IdiPaz), Madrid, Spain
[d] Centro de Investigación Biomédica en Red de Enfermedades Neurodegenerativas (CIBERNED), Madrid, Spain
[e] Department of Drug Design and Pharmacology, Faculty of Health and Medical Sciences, University of Copenhagen, Universitetsparken 2, 2100, Copenhagen, Denmark
[f] Jacqui Wood Cancer Centre, Division of Cancer Research, Ninewells Hospital and Medical School, University of Dundee, Dundee, DD1 9SY, Scotland, UK
[g] Department of Metabolism and Physiology, H. Lee. Moffitt Cancer Center, Tampa, FL, 33612, USA
[h] Department of Medical Biotechnology, Faculty of Biochemistry, Biophysics and Biotechnology, Jagiellonian University, Krakow, Poland
[i] Translational Research Program, Fred Hutchinson Cancer Center, Seattle, WA, 98109, USA
[j] Instituto de Química Médica, Consejo Superior de Investigaciones Científicas (IQM-CSIC), 28007, Madrid, Spain
[k] Indiana University School of Medicine, Department of Medicine, W. Walnut Street, Indianapolis, IN, 46202, USA
[l] Department of Pharmacology, School of Medicine, Universidad Autónoma Madrid, Madrid, Spain
[m] Instituto de Investigación Sanitario (IIS-IP), Hospital Universitario de La Princesa, Madrid, Spain
[n] Instituto Teófilo Hernando, Madrid, Spain
[o] Radiobiology Laboratory, Victor Babes National Institute of Pathology, Bucharest, Romania
[p] A.I. Virtanen Institute for Molecular Sciences, University of Eastern Finland, Kuopio, Finland
[q] Department of Medical Biochemistry, Graduate School of Medicine Tohoku University, Sendai, Japan
[r] Service of Endocrinology, Diabetology and Metabolism, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland
[s] IDAC, Tohoku University, Sendai, Japan
[t] Laboratory of Food Chemistry, Department of Applied Biological Chemistry, Graduate School of Agricultural and Life Sciences, The University of Tokyo, Japan
[u] Instituto de Investigaciones Biomédicas "Sols-Morreale" UAM-CSIC, Instituto de Investigación Sanitaria La Paz (IdiPaz), Centro de Investigación Biomédica en Red de Diabetes y Enfermedades Metabólicas Asociadas (CIBERDEM), ISCIII, Madrid, Spain
[v] Department of Biochemistry and Molecular Biology, Tohoku Medical Megabank Organization, Tohoku University, Sendai, Japan

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ABSTRACT

Nuclear factor erythroid 2-related factor 2 (NRF2) is a redox-activated transcription factor regulating cellular defense against oxidative stress, thereby playing a pivotal role in maintaining cellular homeostasis. Its dysregulation is implicated in the progression of a wide array of human diseases, making NRF2 a compelling target for therapeutic interventions. However, challenges persist in drug discovery and safe targeting of NRF2, as unresolved questions remain especially regarding its context-specific role in diseases and off-target effects. This comprehensive review discusses the dualistic role of NRF2 in disease pathophysiology, covering its protective and/or destructive roles in autoimmune, respiratory, cardiovascular, and metabolic diseases, as well as diseases of the digestive system and cancer. Additionally, we also review the development of drugs that either activate or

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* Corresponding author. Department of Biochemistry, Medical College, Autonomous University of Madrid (UAM), Madrid, Spain.
** Corresponding author. A.I. Virtanen Institute for Molecular Sciences, University of Eastern Finland, Kuopio Campus, Neulaniementie 2, P.O. Box 1627, 70211, Kuopio, Finland.
E-mail addresses: antonio.cuadrado@uam.es (A. Cuadrado), anna-liisa.levonen@uef.fi (A.-L. Levonen).

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inhibit NRF2, discuss main barriers in translating NRF2-based therapies from bench to bedside, and consider the ways to monitor NRF2 activation *in vivo*.

Abbreviations

6-MSITC	6-(methylsulfinyl) hexyl isothiocyanate
AD	Alzheimer's disease
AEM1	ARE expression modulator 1
AGE	advanced glycation end product
AIH	autoimmune hepatitis
AKR	aldo-keto reductase
ALDH3A1	aldehyde dehydrogenase 3-A1
ALS	amyotrophic lateral sclerosis
AMPK	AMP-activated protein kinase
AP-1	Activating Protein-1
APE1	apurinic/apyrimidinic endonuclease 1
ApoE	apolipoprotein E
ARDS	acute respiratory distress syndrome
ARE/EpRE	antioxidant/electrophile responsive element
BACH1	BTB domain and CNC homolog 1
BDL	bile duct ligation
BHA	butylated hydroxyanisole
bZIP	basic leucine zipper
CBP	CREB binding protein
CDDO	cyanoenone triterpenoid 2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid
CDDO-EA	CDDO-ethylamide
CDDO-Im	CDDO-imidazolide
CDDO-Me	CDDO-methyl, bardoxolone methyl
CDDO-TFEA	CDDO-trifluoroethylamide
CEBP	CCAAT enhancer binding protein
CNC	cap'n'collar
CNS	central nervous system
CO	carbon monoxide
COPD	chronic obstructive pulmonary disorder
CORM-A1	CO-releasing molecule A1
CREB	cAMP-response element binding protein
CRL	Cullin-RING E3 ligase
CsMBE	CNC-sMAF binding element
CVD	cardiovascular disease
DAMP	damage-associated molecular pattern
DDC	3,5-diethoxycarbonyl-1,4-dihydrocollidine
DMF	dimethyl fumarate
DMPK	drug metabolism and pharmacokinetic
DRF	diroximel fumarate
EAM	experimental autoimmune myocarditis
EGFR	epidermal growth factor receptor
EMT	epithelial-mesenchymal transition
eNOS	endothelial nitric oxide synthase
ER	endoplasmic reticulum
FAS	fatty acid synthase
FP	fluorescence polarization
FRAP	fluorescence recovery after photobleaching
G6PDH	glucose-6-phosphate dehydrogenase
GI	gastrointestinal
GLC	glutamyl cysteine ligase
GPX	glutathione peroxidase
GSH	glutathione
GSK-3	glycogen synthase kinase-3
GST	glutathione *S*-transferase
HAECs	human aortic endothelial cells
HDAC3	histone deacetylase 3
HFD	high fat diet
HO-1	heme oxygenase-1
HRD1	HMG-CoA reductase degradation protein 1
HTS	high-throughput screening
IBD	inflammatory bowel disease
IKK	IκB kinase
IL	interleukin
IPF	idiopathic pulmonary fubrosis
ITPR3	inositol 1,4,5-trisphosphate receptor
IκB	IkappaB
KEAP1	Kelch like ECH associated protein 1
KO	knock-out
KPC	Kras and P53 mutant
LDL	low-density lipoprotein
LDR	LDL receptor
LPS	lipopolysaccharide
MAFF	MAF bZIP Transcription Factor F
MAFG	MAF bZIP transcription factor G
MAFK	MAF bZIP Transcription Factor K
MARCO	macrophage receptor with collagenous structure
MARE	Maf Recognition Element
MASH	metabolic dysfunction-associated steatohepatitis
MDA	malonyl dialdehyde
ME	malic enzyme
MMF	monomethyl fumarate
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MS4A	membrane-spanning 4-domains subfamily A
MTHFD2	methylenetetrahydrofolate dehydrogenase/cyclohydrolase
NADPH	nicotinamide adenine dinucleotide phosphate
NAE1	NEDD8-activating enzyme E1
NASH	non-alcoholic steatohepatitis
NCATS	National Center for Advancing Translational Science
Neh	NRF2-ECH homology
NF-E2-p45	nuclear factor-erythroid 2
NFκB	nuclear factor kappa-B
NMR	nuclear magnetic resonance
NO	nitric oxide
NOX	NADPH oxidase
NQO1	NAD(P)H:quinone oxidoreductase 1
NRF2	nuclear factor erythroid 2-related factor 2
NSCLC	non-small cell lung cancer
oxLDL	oxidized low-density lipoprotein
PAMP	pathogen-associated molecular pattern
PBMCs	peripheral blood mononuclear cells
PD	Parkinson's disease
PGC-1α	peroxisome proliferator activated receptor coactivator-1α
PPAT	phosphoribosyl pyrophosphate amidotransferase
PPP	pentose phosphate pathway
PROTAC	proteolysis-targeting chimaera
RAGE	AGE receptor
ROS	reactive oxygen species
RRMS	relapsing-remitting multiple sclerosis
RXRα	retinoid X receptor alpha
SAR	structure-activity relationship
SelS	selenoprotein S
SERCA2A	sarcoplasmic reticulum-adenosine triphosphatase 2A
SLE	lupus erythematosus
sMAF	small musculoaponeurotic fibrosarcoma
SNP	single nucleotide polymorphism
SPR	surface plasmon resonance

STING	stimulator of interferon genes
T2D	type 2 diabetes
THIQ	tetrahydroisoquinoline
TLR	toll-like receptors
T_{max}	time to peak drug concentration in plasma
TME	tumor microenvironment
TNFα	tumor necrosis factor alpha
TR-FRET	cell-free time-resolved fluorescence resonance energy transfer
UDCA	ursodeoxycholic acid
ULK	Unc-51 like autophagy activating kinase
US FDA	United States Food and Drug Administration
VCAM1	vascular cell adhesion molecule 1
WAT	white adipose tissue
β-TrCP	β-transducin repeat-containing protein

1. Historical perspective

The study of enzyme induction by cancer chemopreventive agents conducted during the 1970s and 1980s has profoundly shaped the NRF2 field. Prior to the discovery of NRF2, the laboratories of Paul Talalay and Lee Wattenberg reported that feeding rodents with diets that contained a phenolic and electrophilic antioxidant, butylated hydroxyanisole (BHA), increased the activity of the drug-metabolizing enzymes epoxide hydrolase, NAD(P)H:quinone oxidoreductase 1 (NQO1) and glutathione *S*-transferase (GST) as well as the levels of acid-soluble sulfhydryl (*i.e.*, total glutathione, GSH) in liver and forestomach [1,2]. These studies facilitated the identification of the Antioxidant Response Element (ARE), the common regulatory element within these genes and the subsequent discovery of NRF2 (nuclear factor erythroid 2-related factor 2; encoded by *Nfe2l2*) binding to ARE thereby controlling the metabolism and elimination of xenobiotics from the body [3–5] (Fig. 1A).

NRF2 was identified as a member of the NF-E2-p45 like basic leucine zipper transcriptional activators that are referred to as the Cap'n'Collar (CNC) family [5,6]. As CNC family proteins possess a basic leucine zipper (bZIP) domain but cannot bind to DNA as monomers or homodimers, small musculoaponeurotic fibrosarcoma (sMAF) proteins are essential for this interaction (Fig. 1 A, B). CNC factors bind to DNA as a heterodimer with MAFs proteins (MAFF, MAFG and MAFK). Of note, while sMAF proteins contain a bZIP domain, they lack a transactivation domain, thus sMAFs need to heterodimerize with CNC factors to regulate gene expression [7–9]. The transcription factor homolog 1 with BTB and CNC domain (BACH1), which also carries a bZIP structure, can compete with NRF2 hence repressing the expression of NRF2 target genes [8,10] (Fig. 1B).

At the time of its discovery, NRF2 was believed to be essential for growth and differentiation of erythroid lineage cells by analogy with NF-E2-p45 (nuclear factor-erythroid 2). However, its physiological function

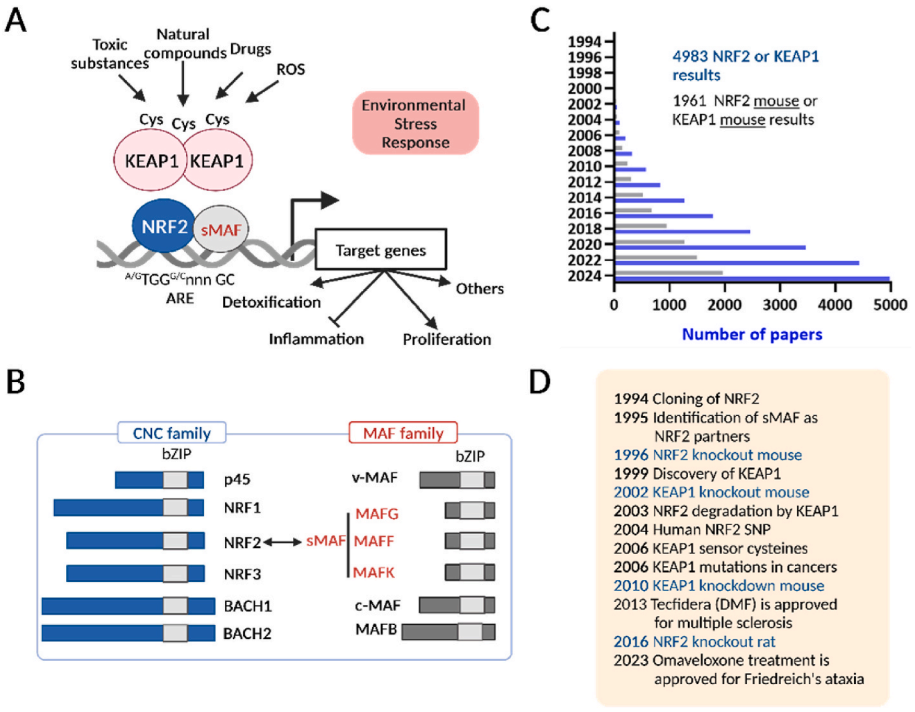


Fig. 1. The KEAP1-NRF2 system in environmental stress response. A. Cysteine residues in KEAP1 serve as sensors for external and/or internal chemicals, a mechanism commonly referred to as the "Cysteine Code". NRF2 is a transcription factor belonging to the CNC family. NRF2 forms a heterodimer with sMAF and binds to the CsMBE (CNC-sMAF Binding Element), also known as the ARE/EpRE (Antioxidant/Electrophile Responsive Element). This NRF2-sMAF heterodimer governs the expression of an array of target genes related to detoxification, proliferation, and inhibition of inflammation among other processes. B. Structure comparison of NRF2-related proteins from the CNC family with the bZIP marked in a grey box on the left column. On the right column the simplified protein structure of the MAF family is represented, sMAF proteins that interact with NRF2 are highlighted in red. C. Since the cloning of NRF2, over the past 30 years, there has been a steady rise in the number of papers related to NRF2 or KEAP1 (depicted in orange) and those associated with NRF2 mouse or KEAP1 mouse (shown in grey). The paper search was conducted in Pubmed (https://pubmed.ncbi.nlm.nih.gov) as of Feb 4, 2025. D. Chronologic table illustrating the progression of the KEAP1-NRF2 studies including its discovery, the heterodimerization with sMAF proteins, the development of KO animals (highlighted in blue), key aspects of its regulation and the approval of NRF2 activators by the FDA for disease treatments. *Abbreviations: ROS, reactive oxygen species; CNC, cap'n'collar; ARE, antioxidant response element; Cys, cysteine; NRF2, nuclear factor erythroid 2-related factor 2; sMAF, small musculoaponeurotic fibrosarcoma; KEAP1, Kelch like ECH associated protein 1; SNP, single nucleotide polymorphism; BACH, BTB domain and CNC homolog; DMF, Dimethyl fumarate.*

was not obvious because unlike p45, which is only expressed in erythroid, megakaryocytic and mast cells [11], NRF2 is expressed in many cell types and tissues [5]. As the consensus binding site for NF-E2-p45 (5′-TGACNNNGC-3′) found in the promoter regions of genes for rat *Nqo1* and a rat class Alpha GST Ya subunit [3], it was postulated that NRF2 might regulate ARE-containing genes. This hypothesis was demonstrated in a seminal study, using dietary administration of BHA to wildtype and NRF2-null mice. It was found that BHA increased the expression of *Nqo1* and Alpha-, Mu- and Pi-class *Gst* protein subunits in the liver and intestine of wildtype mice, but not in the liver or intestine of NRF2-null mutant mice [4], demonstrating that NRF2 is required for the induction by BHA of genes encoding certain drug-metabolizing enzymes. Subsequently, the screening for AREs in the genome has led to the identification of hundreds of putative NRF2-responsive genes [12]. Research on NRF2 has been steadily growing, leading to a progressive understanding of this transcription factor (Fig. 1C). This journey began with its cloning [5] and continued with the characterization of its main repressor, KEAP1 [13]. Key milestones include the establishment of NRF2 [14] and KEAP1 knockout mouse [15] and rat models [16]. More recently, the FDA has approved several NRF2 activators, such as dimethyl fumarate (DMF, Tecfidera®, Biogen) for multiple sclerosis and omaveloxolone (Skyclarys™) for Friedreich's ataxia (Fig. 1D). It is now understood that NRF2 is a pleiotropic transcription factor that participates in the control of multiple cytoprotective genes involved in numerous cellular functions including redox homeostasis, metabolism, cell proliferation, differentiation, autophagy, immune response, and inflammation [12,17].

2. Structural organization and regulation of NRF2 by E3 ubiquitin ligases

NRF2 contains 605 and 597 amino acids in humans and mice, respectively. Sequence comparison among vertebrates has identified seven homology regions, termed Neh (NRF2-ECH homology), with specific functions that are described in Fig. 2A.

To exert the chemoprotective function, NRF2 activity is induced under stress conditions. The main mechanism of NRF2 regulation is *via* the control of protein stability by the E3 ligase adapter KEAP1 (Kelch like ECH associated protein 1, Fig. 2B). KEAP1 contains 25 and 27 cysteine residues in mice and humans, respectively. Specific redox active cysteine residues within KEAP1 react with various electrophiles or undergo oxidative modifications. In unstressed conditions, NRF2 is constitutively degraded through ubiquitination by KEAP1 (Fig. 2C). When exposed to electrophiles or reactive oxygen species (ROS), these stressors modify critical cysteines of KEAP1, leading to stabilization and nuclear accumulation of NRF2 [17]. Importantly, current data indicate that stabilization is not due to release of NRF2 but instead the KEAP1/NRF2 complex is blocked, and it is the newly synthetized NRF2 which cannot be bound to KEAP1, accumulates and goes to the nucleus [18]. Subsequently, NRF2 activates the expression of antioxidant and detoxification enzyme genes. Hence, NRF2 induction is essentially a depression from the constitutive KEAP1-mediated repression, mechanism similar to the hypoxia response system [19].

The main alternative pathway to KEAP1 regulation is the GSK-3/β-TrCP axis. Glycogen synthase kinase (GSK-3) is a serine/threonine protein kinase that phosphorylates NRF2 at specific serine residues, creating a recognition motif for β-Transducin repeat-Containing Protein (β-TrCP) (Fig. 2A), an adaptor protein of the SCF E3 ubiquitin ligase complex. β-TrCP then facilitates NRF2 ubiquitination, leading to its proteasomal degradation. This pathway serves as an alternative NRF2 regulatory mechanism, independent of oxidative stress signals. Inhibition of GSK-3β, often through the PI3K/AKT pathway, stabilizes NRF2, enhancing its transcriptional activity and cytoprotective functions (Fig. 2C) [20–22].

KEAP1 and β-TrCP might have different roles in the regulation of cytoplasmic *vs*. nuclear NRF2 stability. Thus, KEAP1 is located mainly in the cytoplasm [23], anchored to the actin cytoskeleton [13], while β-TrCP might regulate NRF2 in the nucleus. This is supported by the nuclear location of its ubiquitylation machinery components (SKP1, CUL1 and CDC34) [22,24,25].

HMG-CoA reductase degradation protein 1 (HRD1), an E3 ubiquitin ligase sometimes called synoviolin, is a multipass endoplasmic reticulum (ER) membrane protein that has been identified as a downstream effector of the IRE1 branch of the unfolded protein response. In cirrhotic livers, activation of the XBP1-HRD1 arm of ER stress transcriptionally up-regulated HRD1, resulting in enhanced NRF2 ubiquitylation and degradation and attenuation of the NRF2 signaling pathway. Direct interaction between the C-terminal domain of HRD1 and the Neh4–5 domains of NRF2 has been demonstrated, with the Cys291 within the RING domain of HRD1 indispensable for its ubiquitin ligase activity [26].

3. The role of NRF2 in human disease states

3.1. NRF2 in the resolution of inflammation

Peripheral or central low-grade inflammation is a key driver in numerous chronic diseases such as diabetes, hypertension, metabolic syndrome, cancer, and neurodegenerative diseases. NRF2 regulates the innate immune response by interfering directly or indirectly with its major innate immune components such as toll-like receptors (TLRs), nuclear factor kappa-B (NFκB) and the inflammasome.

TLRs signaling enhances the expression of the autophagy cargo receptor p62, also known as sequestosome1/SQTM1. P62 can bind to KEAP1 favoring its degradation *via* autophagy and, thereby, NRF2 can translocate to the nucleus to promote the expression of genes involved in antioxidant responses and cellular protection mechanisms [27–29]. Furthermore, the promoter region of the *SQSTM1* gene contains AREs, which favor a positive feedback loop between p62 and NRF2 [30]. Therefore, p62 can be considered a link between the immune response and the antioxidant system *via* the TLR/p62/autophagy/NRF2 axis.

The *NFE2L2* gene, which encodes the transcription factor NRF2, contains binding sites in its promoter region for NF-κB, a key regulator of inflammatory responses. Activation of NF-κB can enhance *NFE2L2* transcription, leading to increased NRF2 expression. Elevated NRF2 levels subsequently promote the expression of antioxidant and cytoprotective genes, which can mitigate oxidative stress and inflammation. This interaction establishes a positive feedback loop: NF-κB activation induces NRF2 expression, and the resulting NRF2 activity can suppress excessive NF-κB-mediated inflammatory responses, thereby maintaining cellular homeostasis [31].

Given that NFκB signaling is redox sensitive [32], NRF2 can also regulate NFκB through the induction of the antioxidant response [33]. Similar to NRF2, IκB kinase-β (IKKβ) possesses an ETGE motif that enables its binding to KEAP for ubiquitination and proteasomal degradation. Therefore, under basal redox conditions, active KEAP1 can suppress NFκB signaling by inducing IKKβ proteasomal degradation and therefore increasing the protein levels of IκB [34]. The results from NRF2-deficient mice treated with LPS or tumor necrosis factor α (TNFα) evidenced that the activity of IKKβ as well as inflammatory markers were increased compared to wildtype mice, supporting the notion that NRF2 can regulate the innate immune response by suppressing NFκB activation *in vivo* [35]. Taken together, the NRF2 and NFκB signaling pathways cooperate to maintain physiological homeostasis by regulating the cellular response to stress and inflammation.

Inflammasomes are multiprotein complexes that function as a pathogen recognition receptor that recognize microbial PAMPs, DAMPs, and ROS [36]. Activation of the NLRP3 inflammasome mediates the cleavage of caspase-1 and the secretion of the pro-inflammatory cytokine interleukin-1β (IL-1β) that ultimately induces pyroptosis, a lytic from of cell death, to protect the hosts from a wide range of pathological signals [37]. There is a crosstalk between the NRF2 and inflammasome

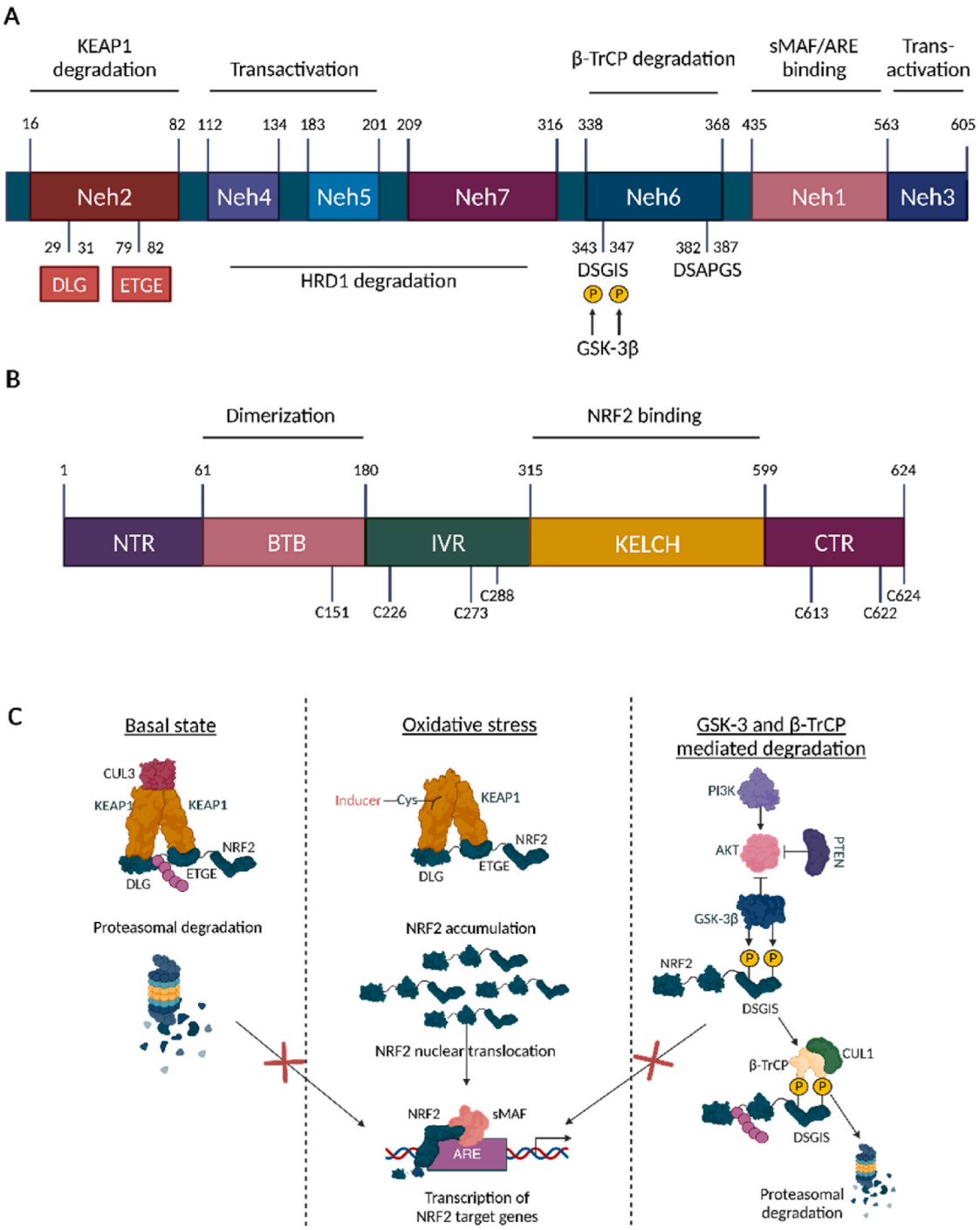


Fig. 2. A. Protein structure of the transcription factor NRF2. NRF2 contains seven conserved Neh domains. Neh1 serves as a heterodimerization domain with MAFs proteins and DNA binding. Neh2 and Neh6 direct NRF2 to proteasome-mediated degradation *via* KEAP1 and β-TrCP, respectively. Neh3, Neh4 and Neh5 are the transactivation domains, and Neh4 and Neh5 direct NRF2 to HRD1-mediated proteasomal degradation in the context of endoplasmic reticulum stress. Phosphorylation by GSK3-beta is needed in the DSGIS domain in Neh6 for β-TrCP degradation. The positions of each domain correspond to the human NRF2 protein. **B. Structure of KEAP1.** KEAP1 structure consists of five distinctive domains, NTR, BTB, IVR, Kelch, and CTR. The domains contain cysteine residues that react with various electrophiles, serving as sensors of redox changes. **C. KEAP1-NRF2 mechanism of action in basal state, under oxidative stress, and the GSK-3 and β-TrCP mediated degradation.** Under basal conditions, NRF2 is degraded through ubiquitination mediated by KEAP1. During oxidative or electrophilic stress, the sensor cysteines in KEAP1 undergo modifications by electrophiles and reactive oxygen species that result in KEAP1 conformational change, preventing ubiquitination of NRF2. As a result, NRF2 accumulates and translocates to the nucleus, leading to the transcription of NRF2 target genes. An alternative pathway to regulate NRF2 is the GSK-3/β-TrCP axis. GSK-3 inhibits NRF2 through phosphorylation of serine residues within the Neh6 domain, leading to the recognition by the β-TrCP-CUL1 ubiquitin ligase and subsequent proteasomal degradation. *Abbreviations: Neh, NRF2-ECH homology; ARE, antioxidant response element; Cys, cysteine; NRF2, nuclear factor erythroid 2-related factor 2; sMAF, small musculoaponeurotic fibrosarcoma; KEAP1, Kelch like ECH associated protein 1; HRD1 HMG-CoA reductase degradation protein 1;CUL, cullin; GSK-3, glycogen synthase kinase 3; β-TrCP, β-transducin repeat-containing protein; HRD1, Hydroxymethyl glutaryl-coenzyme A reductase degradation protein.*

pathways. NRF2 suppresses the transcription of NLRP3 inflammasome-associated genes, including those coding for NLRP3, proIL-1β, and proIL-1α [38,39]. p62 and PGAM5 are regulators of the NRF2/KEAP1 as well as the NLRP3 inflammasome pathways. p62 activates NRF2 [40] and antagonizes NLRP3 inflammasome activation [41,42], whereas PGAM5 is required for inflammasome activation and negatively influences NRF2 activity [43]. Finally, NRF2 inducers inhibit inflammasomes and, consequently, inflammation [44].

NRF2 can also directly regulate cytokine release and immune cell recruitment. Kobayashi et al. [39] were the first to show that NRF2 can regulate the inflammatory response independently of the antioxidant response. In LPS treated macrophages, NRF2 interfered with the transcriptional activation of the proinflammatory cytokines *IL6* and *IL1b* by binding next to their promotor region, hence preventing RNA polymerase II recruitment [39]. Additionally, NRF2 activation stabilizes the IL8 mRNA [45] and increases IL-17D expression, cytokines implicated in the antitumor immune response [46]. Moreover, NRF2 activates the expression of macrophage-specific genes, such as macrophage receptor with collagenous structure, a receptor required for bacterial phagocytosis, or CD36, a scavenger receptor for oxidized low-density [47].

NRF2 can also regulate inflammation *via* Heme Oxygenase-1 (HO-1), an inducible enzyme that regulates oxidative stress and inflammation through its enzymatic activity and the bioactive molecules it generates (biliverdin, free iron and carbon monoxide) after heme degradation (Fig. 3). NRF2 is the primary transcriptional regulator of HO-1. It directly binds to the AREs in the *HMOX1* promoter, significantly enhancing its transcription and ensuring a robust cellular defense against oxidative stress and inflammation. However, HO-1 expression can also be regulated by other transcription factors such as AP-1 (Activator Protein-1), HIFs (Hypoxia Inducible Factors) or NFκB [48]. Furthermore, HO-1 can also be regulated by the transcriptional repressor Bach1. Under basal conditions, Bach1 binds to Maf recognition elements (MAREs) in the *HMOX1* promoter, inhibiting its transcription. Upon exposure to inducers like heme or oxidative stress, Bach1 is displaced or degraded, relieving its repressive effect and allowing transcriptional activation of *HMOX1* [49]. Therefore, regulation of inflammation by NRF2 is controlled by multiple mechanisms to ensure its effective resolution.

3.2. NRF2 in autoimmunity

Several excellent and comprehensive reviews have addressed the role of NRF2 in specific autoimmune diseases including systemic lupus erythematosus (SLE) [50], rheumatoid arthritis [51], vitiligo [52], as well as multiple sclerosis [53], and psoriasis [54], and therefore these pathologies will not be extensively discussed here. Herein, we will focus on less frequently discussed autoimmune disease, where NRF2 may play a role.

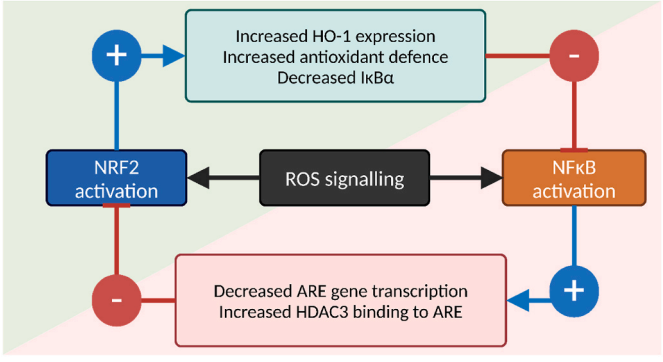


Fig. 3. Negative feedback regulation of the NRF2 and NFκB pathways. NRF2 activates NFκB by neutralizing ROS production, and by activating HO-1 and antioxidant enzymes. NRF2 also prevents the degradation of IκBα which translates to inhibition of NFκB. On the contrary, NFκB mediated transcription reduces NRF2 activation by decreasing ARE gene transcription. Furthermore, increased recruitment of HDAC3 to the ARE region induced by NFκB prevents NRF2 activation. *Abbreviations: NRF2, nuclear factor erythroid 2-related factor 2; NFκB, nuclear factor kappa-B; CBP, CREB binding protein; ARE, antioxidant response element; HDAC3, histone deacetylase 3; HO-1, heme oxygenase-1.*

3.2.1. Autoimmune nephritis

The first publication on NRF2 and autoimmunity dates back to 2001 [55], demonstrating that NRF2 knock-out (KO) female mice develop autoimmune nephritis that resembles the kidney disease observed in some patients with SLE. Specifically, the autoimmune nephritis phenotype was first detected in mice at around 40 weeks of age, while severe histological lesions were present in older mice (>60 weeks) and were accompanied by increased levels of lipid peroxidation and shortened lifespan [55]. However, the impact of NRF2 on autoimmune nephritis may vary depending on the context. For example, in a genetic model of nephritis, caused by a mutation in the FAS-encoding gene, that renders cells defective in TNFα-mediated apoptosis, the genetic ablation of NRF2 had a protective role, presumably *via* restoring apoptosis [56]. Therefore, whether NRF2 can be considered a target for autoimmune nephritis, and whether NRF2 inhibition or activation should be pursued, might be dependent on the specific genetic and immune context.

While the first studies on the topic focused on the kidney, it was subsequently shown that female NRF2 KO mice develop multi-organ autoimmunity, as is typical in SLE, with immune deposits detected in kidney, liver, heart, and brain [57]. This study noted that while the kidney is the major organ of autoimmune damage in the absence of NRF2, other tissues may also be affected. In another study, multiorgan autoimmune inflammation was documented in NRF2 KO mice with enhanced proliferative response of $CD4^+$ T cells, altered ratios of $CD4^+/CD8^+$ cells, and decreased basal and inducible expression of certain phase II detoxification enzymes and antioxidant genes in lymphoid cells *in vivo* [58]. In addition to nephritis, NRF2 KO mice developed inflammatory lesions in multiple tissues, including lymphocytic sialitis; dermatitis, hyperkeratosis, and/or epidermal clefts on the skin of the tail; myocarditis; vasculitis; and pancreatitis, these pathophenotypes being prevalent in female mice [61].

3.2.2. Autoimmune thyroiditis

Autoimmune thyroiditis is among the most common autoimmune diseases. Both environmental (e.g., iodine intake) and genetic factors play a role. Regarding the latter, several single nucleotide polymorphisms (SNPs) known to increase the risk of hypothyroidism reside in thyroid-specific genes or in genes related to autoimmunity, inflammation, and/or cellular defense to stress. As shown in a case-control candidate-gene association study, one such hypothyroidism-risk associated SNP is a functional polymorphism in the promoter of *SELENOS* gene that encodes selenoprotein S (SelS) with protective roles against inflammation and ER stress [59]. In the same cohort, when the functional SNPs in the *NFE2L2* promoter were also considered in relation to the risk of hypothyroidism, only subjects with one or more minor alleles in both *SELENOS* and *NFE2L2* showed an increased risk [60]. At the molecular level, there was evidence for bidirectional positive feedback between the NRF2 and SelS pathways, with reduced expression of SelS in thyroid follicular cells in NRF2 KO mice, and reduced activity of NRF2 signaling when SelS expression was experimentally decreased in cultured thyrocytes [60].

3.2.3. Autoimmune myocarditis

The role of NRF2 in experimental autoimmune myocarditis (EAM) was examined in a study involving female mice injected subcutaneously with cardiac myosin together with complete Freund's adjuvant [61] The mice developed extensive infiltration areas that correlated with apoptosis and oxidative stress and with higher levels of inflammatory and cardiac damage markers, cardiac dysfunction, hypertrophy, and

emerging fibrosis. Concurrent treatment with the lipoxin A4 analogue BML-111 showed a protective effect, and *in vivo* and *in vitro* studies suggested that the beneficial effects of BML-111 were likely mediated by the activation of NRF2. However, NRF2 KO mice were not used in this study [61]. In a follow-up study, the same group showed that the cardioprotective role of BML-111 was mainly mediated by the prevention of increased oxidative stress and NRF2 downregulation in EAM. *In vitro* studies with cardiomyocytes from wildtype and NRF2 KO mice showed that BML-111 activates NRF2 signaling and prevents sarcoplasmic reticulum-adenosine triphosphatase 2A (SERCA2A) downregulation and Ca^{2+} mishandling, thereby attenuating EAM-induced tissue damage and cardiac dysfunction [62]. However, the study did not establish the EAM model in NRF2 KO mice, and the human samples were from patients with acute (likely viral) myocarditis as opposed to autoimmune myocarditis. The pathogenetic mechanisms of viral myocarditis are complex and can involve both immune-related non-autoimmune and true autoimmune phenomena. More recently, studies in rat [63] and mouse [64] models of EAM showed protective effects of a natural extract (*Boswellia serrata* gum resin) and ursolic acid, respectively, and implicated NRF2 activation as a potential mechanism underlying the beneficial effects. However, like the previous studies, neither of these studies utilized NRF2 KO mice. In summary, to further support the validation of NRF2 as a target for autoimmune myocarditis, it would be relevant to establish the EAM model in NRF2 KO animals, and to examine the activation status of NRF2 in cardiac biopsies from patients with well-established subacute/chronic autoimmune myocarditis.

3.2.4. Autoimmune hepatitis

Autoimmune hepatitis (AIH) represents a substantial unmet medical need. In an experimental model of liver injury, administration of the natural antioxidant dihydroquercetin had a significant protective effect against concanavalin A-induced fulminant hepatitis, likely through antioxidant and anti-inflammatory mechanisms, including the induction of the NRF2 response [65]. In alternative models of AIH, similar protective effects with a potential involvement of NRF2 have been reported for carbon monoxide (CO)-releasing molecule A1 (CORM-A1) [66]; the traditional Chinese herbal formula Jiang-Xian HuGan [67]; the natural quinonoid triterpene pristimerin [68]; the soybean isoflavone daidzein [69]; the flavonoid vitexin [70]; the anti-inflammatory metabolite (and known NRF2 activator) 4-Octyl itaconate [71]; the triterpenoid Cucurbitacin E glucoside [72]; escin, the active constituent of a natural mixture of triterpene saponin glycoside [73]; the antioxidant and anti-inflammatory natural products alpha-mangostin [74] and Garcinone E [75]; koumine, the most abundant alkaloid in a traditional Chinese medicine plant extract [76]; recombinant fibroblast growth factor 4 [77]; the non-steroidal anti-inflammatory drug (cyclooxygenase-2 inhibitor) celecoxib [78]; and the non-selective opiate receptor antagonist naloxone [79]. However, while activation of NRF2 signaling was documented with variable levels of evidence in these studies, none of them used NRF2 KO mice in an AIH model to directly examine the *in vivo* relevance of NRF2 as a protective factor in this setting.

3.2.5. Primary biliary cholangitis

In primary biliary cholangitis, the bile ducts in the liver are chronically inflamed and progressively destroyed, leading to primary biliary cirrhosis. Evidence for a possible protective role of NRF2 in this context came from a study analyzing human liver biopsies before and after treatment with ursodeoxycholic acid (UDCA) with known antioxidant properties. Indeed, the post-treatment biopsies showed decreased levels of oxidative DNA damage in hepatocytes or bile duct cells and upregulation of nuclear phosphorylated NRF2 in bile duct cells, as well as upregulation of the expression of antioxidant genes in the liver, suggesting NRF2 as a potential therapeutic target in this setting [80]. However, in a mouse model of biliary and liver damage induced by ligation of the bile duct, prior treatment with oltipraz, an antiparasitic drug that has been shown to activate NRF2, exacerbated the severity of liver injury [81]. In a rat model of bile duct ligation (BDL), treatment with flavonoid rutin showed protective effects that correlated with an attenuation of the BDL-induced reduction of the NRF2 antioxidant response [82]. Moreover, in a rat model of BDL, combined treatment with triterpene astragaloside IV and the phenolic phytochemical ferulic acid synergistically alleviated hepatic fibrosis; astragaloside IV was shown to activate NRF2 in the liver [83]. However, in a mouse model of biliary and liver damage induced by BDL, prior treatment with oltipraz, an antiparasitic drug that has been shown to activate NRF2, exacerbated the severity of liver injury [78].

Cholestatic injury can also be induced experimentally by chemical means. In a study that used a diet containing 3,5-diethoxycarbonyl-1,4-dihydrocollidine (DDC) to cause cholangitis and biliary fibrosis, mice with liver-specific genetic hyperactivation of NRF2 were protected from almost all DDC-induced injury [84]; this study also confirmed prior results showing that deletion of NRF2 results in a cholestatic phenotype but does not augment liver injury following BDL [85]. In contrast, NRF2 KO mice are more sensitive than wildtype mice to liver damage induced by the treatment with lithocholic acid, which is the most toxic bile acid [86].

The relationship between NRF2 and biliary cell health is apparently complex, as illustrated by the demonstration that NRF2 is a direct negative regulator of the transcription of the gene encoding the inositol 1,4,5-trisphosphate receptor (ITPR3), which is the most abundant intracellular calcium release channel in cholangiocytes [87]. The study found increased expression of NRF2 and lower levels of ITPR3 in the bile ducts from rats with cholestasis and patients with cholangiopathic disorders compared to control rats or patients with other liver disorders, respectively [87]. The finding of aberrant NRF2/KEAP1 regulation in such patients was also confirmed in a separate study showing decreased NRF2 expression in these patients with primary biliary cholangitis, which was even more reduced in patients with cirrhosis [88]. Consistently, patients with end-stage primary sclerosing cholangitis and concomitant inflammatory bowel disease (IBD) showed dysregulation of antioxidant responses [89].

3.3. NRF2 in chronic respiratory diseases

As the center for external respiration, the lungs are constantly exposed to xenobiotic insults including pollutants, allergens, and infectious agents. These agents create a highly oxidative microenvironment that can damage cells and contribute to tissue injury and the development of chronic pulmonary diseases [90]. As a result, cytoprotective pathways including NRF2 are elevated in pulmonary tissues compared to other organs [91]. Disruption of these cytoprotective mechanisms in the lung and respiratory tract resulted in the accumulation of ROS, leading to cellular injury and increased susceptibility to the development of pulmonary disorders. NRF2 is critical for maintaining redox balance in the lungs, and dysfunctional NRF2 activation has been linked to several respiratory disorders including chronic obstructive pulmonary disorder (COPD), pulmonary fibrosis, lung cancer, sleep apnea, asthma, acute respiratory distress syndrome (ARDS) and others [92,93] (Fig. 4).

3.3.1. Asthma

Asthma is a chronic lung condition characterized by inflammation of the airways and excess mucus production which results in narrowed airways and difficulty breathing (Fig. 4). Increased oxidative stress from exposure to cigarette smoke, allergens, viruses, and environmental pollutants can trigger asthma development and progression through the amplification of chronic inflammatory processes, bronchial hyperresponsiveness, and subsequent tissue damage [94]. As the first line of defense against increased ROS and oxidative stress, NRF2 is a protective factor in the pathogenesis of asthma [95].

NRF2-deficient mice are prone to severe allergen-driven airway

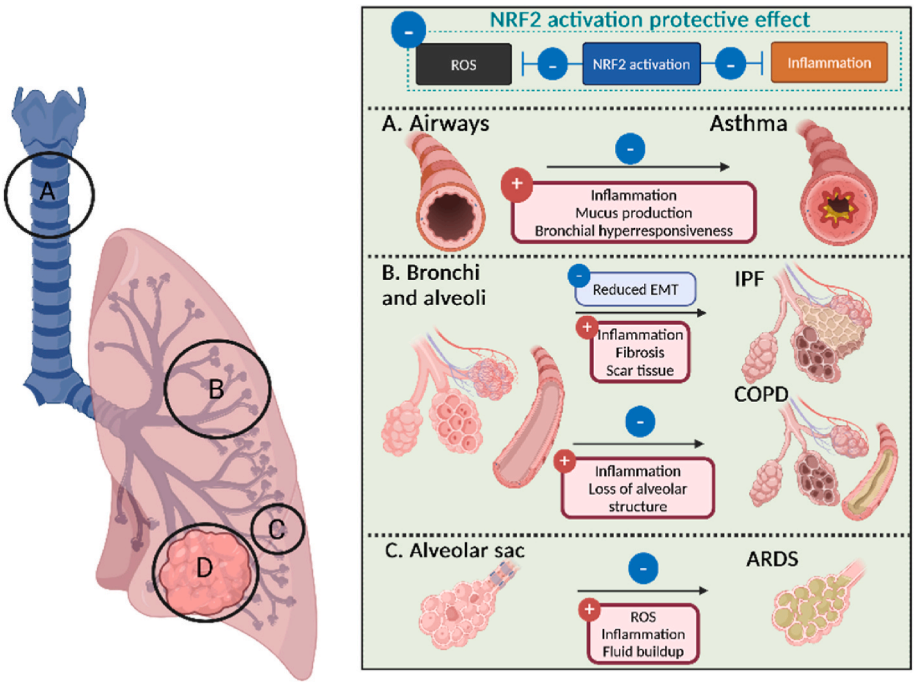


Fig. 4. Dysfunctional NRF2 activation implicated in pulmonary disorders. A) Asthma. Chronic inflammation, excess mucus production, and bronchial hyperresponsiveness in asthma are alleviated by NRF2-mediated anti-inflammatory activity. **B) IPF and COPD.** Idiopathic pulmonary fibrosis (IPF) results from excess deposition of fibrous matrix, resulting in scar tissue formation. NRF2 activation blocks disease progression by reducing matrix deposition and EMT through antioxidant and anti-inflammatory pathways. Chronic obstructive pulmonary disease (COPD) develops because of chronic inflammation and loss of alveolar structure. NRF2 activation alleviates inflammation by detoxifying ROS and blocking COPD disease progression. **C) ARDS.** ROS accumulation, inflammation, and bilateral fluid buildup lead to acute respiratory distress syndrome (ARDS). NRF2 activation prevents or ameliorates ARDS by detoxifying harmful ROS and reducing inflammation. *Abbreviations: NRF2, nuclear factor erythroid 2-related factor 2; EMT, epithelial-to-mesenchymal transition; ROS, reactive oxygen species; IPF, idiopathic pulmonary fibrosis; COPD, chronic obstructive pulmonary disease; ARDS, acute respiratory distress syndrome.*

inflammation, bronchial hyperresponsiveness, and enhanced asthmatic response severity compared to wildtype littermates [96]. This increased susceptibility to asthma in NRF2 KO mice is delineated by increased oxidative stress, excess mucus production, and exacerbated airway constriction. Conversely, both cell-specific genetic activation of NRF2 in lung epithelial cells and pharmacological NRF2 activation with 2-trifluoromethyl-2′-methoxychalone during allergen challenge reversed the asthmatic response in mice [97] (Fig. 4A). Similarly, sulforaphane improved the bronchoprotective response against deep inspiration of methacholine in patients suffering from moderate asthma [98]. In a murine model of Th2-dominant asthma, NRF2 was inhibited in the lungs of asthmatic mice. While asthma is well-managed clinically with inhaled corticosteroids, these treatments only alleviate symptoms. A more comprehensive understanding of the roles of NRF2 and oxidative stress in the pathology of asthma may provide an avenue for the development of novel therapeutics centered on achieving long-term asthma remission [99].

3.3.2. *Idiopathic pulmonary fibrosis*

Idiopathic pulmonary fibrosis (IPF) is a heterogenous group of lung disorders characterized by excessive accumulation of fibrous matrix in the lungs, which results in the destruction of alveolar structure, the formation of scar tissue, loss of compliance, and compromised gas exchange [100] (Fig. 4). As IPF progresses, symptoms worsen from cough and fatigue to respiratory failure and eventually death [100]. While the etiology of the disease is unknown, risk factors include family history and lifestyle habits such as cigarette smoking [101]. Triggers such as environmental pollutants, autoimmune disorders, chronic infections, and cigarette smoking result in sustained inflammation and accumulation of ROS, causing injury to alveolar cells, excess deposition of extracellular matrix, and the development of IPF [102]. Because ROS has been implicated in the pathogenesis of IPF, NRF2 activation may protect against the onset of IPF. Indeed, IPF fibroblasts express lower levels of NRF2 compared to normal fibroblasts [103]. Additionally, NRF2 KO exacerbated fibrosis in multiple preclinical mouse models of IPF [104,105] and, conversely, NRF2 activators prevented or delayed the onset of IPF [106,107] (Fig. 4B).

One of the emerging hallmarks of IPF progression is the epithelial-mesenchymal transition (EMT), a process by which epithelial cells lose their epithelial characteristics and gain mesenchymal phenotypes [108]. Although a direct causal link between EMT and IPF remains elusive, the two processes correlate in preclinical models of lung fibrosis [109]. These observations have led to the targeting of EMT to clinically manage IPF [110]. Importantly, NRF2 activation in murine models of IPF suppressed the progression of EMT by reducing the expression of the EMT-relevant proteins NUMB, SNAIL, SLUG, TWIST and EMT-related protein, and this protective effect was lost in NRF2 KO mice [111–113].

Two drugs are currently approved for the treatment of IPF: the tyrosine kinase inhibitor nintedanib and the pyridine pirfenidone [114]. While not curative, pirfenidone slows the progression of IPF by inhibiting the exaggerated fibrotic response through anti-inflammatory, antioxidant, and anti-fibrotic effects [115]. Pirfenidone directly inhibits the protease furin [116] which disrupts TGF-β synthesis, indirectly activating NRF2 [117]. A recent study by Chang et al. demonstrated that treatment with nanoparticles co-loaded with NRF2 pDNA and pirfenidone alleviated oxidative stress in type II alveolar cells and attenuated myofibroblast overactivation, reversing IPF disease progression [118]. Importantly, the co-loaded nanoparticles were significantly more effective than nanoparticles loaded with either agent alone. These studies suggest that targeting NRF2 may be a potential strategy for both the prevention and treatment of IPF.

3.3.3. *COPD*

Chronic pulmonary oxidative stress results in chronic inflammation

of the airways and destruction of the alveolar structure, which can severely limit airflow and progress to COPD [119] (Fig. 4B). The main causes of COPD are environmental toxicants, particularly cigarette smoking, leading to low grade inflammation and increased production of ROS [119]. NRF2 KO mice were highly susceptible to developing emphysema, a major phenotype observed early in the development of COPD, after exposure to cigarette smoke compared to NRF2 wildtype mice [120,121]. Conversely, emphysema was attenuated in wildtype mice exposed to cigarette smoke and treated with the potent NRF2 activator CDDO-Im (cyanoenone triterpenoid 2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid-Imidazolide) [121]. In humans with a history of smoking, the NRF2 target proteins HO-1, NQO1 and GPX2 were decreased in the lung tissues and alveolar macrophages of patients with emphysema compared to patients without emphysema, while KEAP1 expression was increased [122]. NRF2 expression was further reduced in lung tissues and myeloid cells of smokers who developed COPD [123]. Taken together, these studies suggest that loss of NRF2 activity is an important early event in the development of COPD.

Disease progression in COPD is defined by an intermittent, acute deterioration, and the symptoms require additional therapeutic intervention [124]. These exacerbations are associated with poor clinical outcomes, decreased quality of life, and mortality. These events are mainly triggered by respiratory infections which increase pulmonary inflammation and accumulation of ROS, thereby further damaging the afflicted tissues [124]. Increased production of pro-inflammatory factors and decreased NRF2 activity in both lung tissue and immune cells are associated with a higher frequency of exacerbations in COPD patients [125,126]. The knockdown of NRF2 increased the entry and replication of the influenza virus in human nasal epithelial cells, which was attenuated by NRF2 activation with sulforaphane and epigallocatechin gallate [127]. Conversely, NRF2 KO mice infected with influenza and exposed to cigarette smoke had a higher frequency of inflammatory events compared to NRF2 wildtype mice [128]. These studies linking NRF2 to COPD development and progression have led to the consideration of pharmacological NRF2 activators for therapeutic intervention in COPD [47,129].

3.3.4. Acute respiratory distress syndrome

Acute respiratory distress syndrome (ARDS) is a serious complication of existing conditions, diseases, or injuries which affect the lungs bilaterally and is often fatal [130]. Fluid buildup in the alveolar sacs and breakdown of surfactant compromise lung function, resulting in hypoxemia and death if emergency treatment is not administered [131] (Fig. 4). ROS accumulation in damaged tissues plays a major role in the development of ARDS, contributing to a feed-forward mechanism by which damaged tissue triggers inflammation and immune cell infiltration, which further damages tissues and eventually spirals into respiratory failure [132]. Without proper redox balance, cells are more susceptible to this escalating damage. NRF2 KO mice are more susceptible to ARDS compared to wildtype mice [133–135]. In humans, polymorphisms in NRF2 affecting its function are correlated with increased susceptibility to ARDS [136]. Activation of NRF2 in Covid-19 patients suffering from ARDS had clinical benefit, reducing the severity of the cytokine storm and lessening lung injury [137–139]. Patients suffering from traumatic lung injury-induced ARDS have shown a reduced NRF2 activity, and the activation of NRF2 in these patients ameliorated ARDS by improving arterial blood oxygenation and reducing inflammatory cytokines [140] (Fig. 4C). These promising results suggest that NRF2 activation may be a suitable strategy for therapeutic intervention in ARDS. However, the rapid and unpredictable nature of ARDS and the varied etiology complicate the translation of experimental findings into the clinic [141].

NRF2 plays a central role in the development and progression of many pulmonary disorders. Overall, the effects of NRF2 activation in the healthy lungs protect against pathological development. NRF2 activation can prevent or slow the progression of COPD, IPF, asthma, and ARDS. However, discrepancies between studies and the difficulty in translating experimental results to clinically relevant settings remain a challenge. With NRF2 activators in clinical use and under development, it is critical to understand the relationship between NRF2 and pulmonary disorders and further studies are needed to elucidate these specific mechanisms.

3.4. NRF2 in the digestive system and metabolic diseases

The major non-neoplastic diseases that in humans affect the digestive system and ancillary organs include oesophagitis, gastric and duodenal ulceration, IBD, gall stone disease, pancreatitis and hepatitis. A unique feature of the gastrointestinal (GI) tract is that it harbours a broad spectrum of commensal micro-organisms, some of which contribute to good health by producing short-chain fatty acids that enhance epithelial barrier function and prevent inflammation whilst others are potentially harmful because their production of short-chain fatty acids is minimal and/or they produce toxins [142–144].

3.4.1. Barrett's oesophagus

In the human, along with obesity and smoking, chronic gastro-esophageal reflux represents the principal cause of oesophagitis and a major risk factor for Barrett's oesophagus and oesophageal adenocarcinoma [145]. Bile acids within the reflux material stimulate oesophagitis by causing oxidative stress [146]. Importantly, NRF2 KO mice are more sensitive to oesophagitis than their wildtype counterparts [147], but it is not known whether pharmacological activation of NRF2 in humans protects against gastroesophageal reflux disease. In human oesophageal Barrett's cell lines (CPB and BAR-10T), ectopic overexpression of NRF2 protects against oxidative DNA damage and double-strand DNA breaks caused by exposure to a cocktail of bile salts in an acidic pH 4.0 medium [148]. Interestingly, short-term treatment (20 min) of human oesophageal cells with the bile salt cocktail in a manner that mimics gastroesophageal reflux results in activation of NRF2 [148], presumably as an adaptation to stress. NRF2 is overexpressed in human oesophageal adenocarcinoma cells compared with non-neoplastic oesophageal cells, as is apurinic/apyrimidinic endonuclease 1 (APE1, also called REF1), and it has been reported that APE1/REF1 is responsible for the overexpression of NRF2 through a mechanism that involves inhibitory phosphorylation of GSK-3 through APE1/REF1 overexpression [149].

3.4.2. Crohn's disease and ulcerative colitis

Chron's disease and ulcerative colitis are the most prevalent forms of inflammatory bowel disease encountered globally. They are distinct disorders, with the former presenting anywhere throughout the GI tract as chronic relapsing transmural inflammatory lesions interspersed by normal mucosa that are progressive and destructive, and the latter presenting only in the colon as a continuous lesion that is superficial but can lead to erosions, ulcers, and bleeding [150,151]. The causes of Crohn's disease and ulcerative colitis are poorly understood, though both are multifactorial and involve genetic susceptibility to environmental agents that trigger an inappropriate immune response. Dysbiosis represents a key feature of both diseases, with a decrease in gut microbiota diminishing the epithelial cell barrier [152], which provokes heightened immunoreactivity of the gut and chronic oxidative stress [153]. It is plausible that the activation of NRF2 attenuates IBD in two ways. Firstly, by inducing the expression of antioxidant genes that combat oxidative stress and/or ferroptosis, and secondly by regulating the expression of Claudin 4, which improves tight junctions in the GI tract, increases gut barrier integrity, and diminishes the likelihood of inflammation [147,154]. Consistent with this view, NRF2 KO mice are more sensitive to colitis [155] and radiation-induced proctitis [156] than wildtype mice. No studies have been reported in which specific NRF2 activators have been employed in patients with IBD. However, it has been reported that the treatment of ulcerative colitis patients with

indigo naturalis, which is used in patients refractory to TNF therapy, activated both the aryl hydrocarbon receptor and NRF2, increasing expression of antioxidant genes and inhibiting ferroptosis [157]. The extent to which activation of NRF2 contributes to the efficacy of indigo naturalis in treating ulcerative colitis is not known.

3.4.3. Non-alcoholic steatohepatitis

Non-alcoholic steatohepatitis (NASH) is a disorder of the liver in which steatosis (i.e., fat content of the liver >5 %) is accompanied by inflammation in individuals who do not consume excess alcohol, with neither steatosis nor hepatitis preceding the other [158]. Recently, NASH has been renamed metabolic dysfunction-associated steatohepatitis (MASH) to more accurately represent the condition [159]. NASH is associated with obesity and the metabolic syndrome, and as it is very prevalent globally, it is of great concern as it can progress to cirrhosis and cancer [160]. Whilst the causes of NASH involve genetic predisposition coupled with overnutrition and dysbiosis, multiple molecular mechanisms are involved, including insulin resistance, lipotoxicity, mitochondrial dysfunction, oxidative stress, inflammation, ER stress, apoptosis, and fibrosis [161,162] (Fig. 5). Many drugs are under development for NASH [163]. In mice, there is ample evidence that in experimental NASH, activation of NRF2 can ameliorate liver steatosis, inflammation, and fibrosis [164]. However, it is surprising that drugs that target the NRF2-KEAP1 axis have not been explored to treat NASH. Interestingly, whilst not involving NASH, there is increasing epidemiological evidence that consumption of 2–4 cups of coffee per day slows progression of liver fibrosis and diminishes the incidence of hepatocellular carcinoma [165,166]. Coffee contains numerous chemicals that may protect against liver disease including diterpenes, chlorogenic acid, and N-methylpyridinium which activate NRF2 [167,168]. Further work is required to establish the extent that NRF2 activation can attenuate liver disease in humans.

3.4.4. Diabetes and glucose metabolism

In many pathophysiological conditions, disruption of metabolic homeostasis leads to an imbalance of fundamental cellular processes including metabolism, bioenergetics, and oxidative stress. Among metabolic diseases, diabetes mellitus is dominant in the NRF2 diseasome. In particular, in type 2 diabetes (T2D), oxidative stress has been linked with disruption of the insulin signaling cascade and subsequent development of insulin resistance in relevant peripheral tissues controlling glucose metabolism [169]. Also, in a pre-diabetic condition characterized by excessive insulin secretion, ROS can damage mitochondria, which will eventually interrupt the cellular machinery coupling glucose metabolism to insulin secretion leading to β-cell dysfunction [170]. Under this pathological setting, ROS may also induce metabolic rewiring in β-cells by increasing Warburg-like lactate production *via* HIF-1α resulting in disruption of glucose sensing and insulin secretion [171]. Extensive research is thus being conducted to identify means to reduce ROS to successfully tackle T2D.

Mouse studies have demonstrated that NRF2 plays a complex role in tissue-specific actions of insulin in liver, skeletal muscle, and adipose tissue. NRF2 KO mice were partially protected from high fat diet (HFD)-induced obesity and developed a less insulin-resistant phenotype than wildtype controls [172]. Importantly, NRF2 KO mice had elevated plasma FGF21 protein and mRNA expression in liver and white adipose tissue (WAT) [172] (Fig. 5). A more recent study revealed that NRF2 KO mice had increased Sirtuin 1 levels, supporting the beneficial metabolic adaptation of NRF2 KO mice to an obesogenic trigger by enhancing lipolysis and increasing energetic metabolism [173]. Unlike global NRF2 deficiency, the loss of NRF2 in myeloid cells did not protect against HFD-induced insulin resistance, suggesting a dominant role for NRF2 in the non-myeloid compartment in the development of obesity-induced WAT inflammation and insulin resistance [174]. Surprisingly, despite the better insulin sensitivity in HFD-fed global NRF2

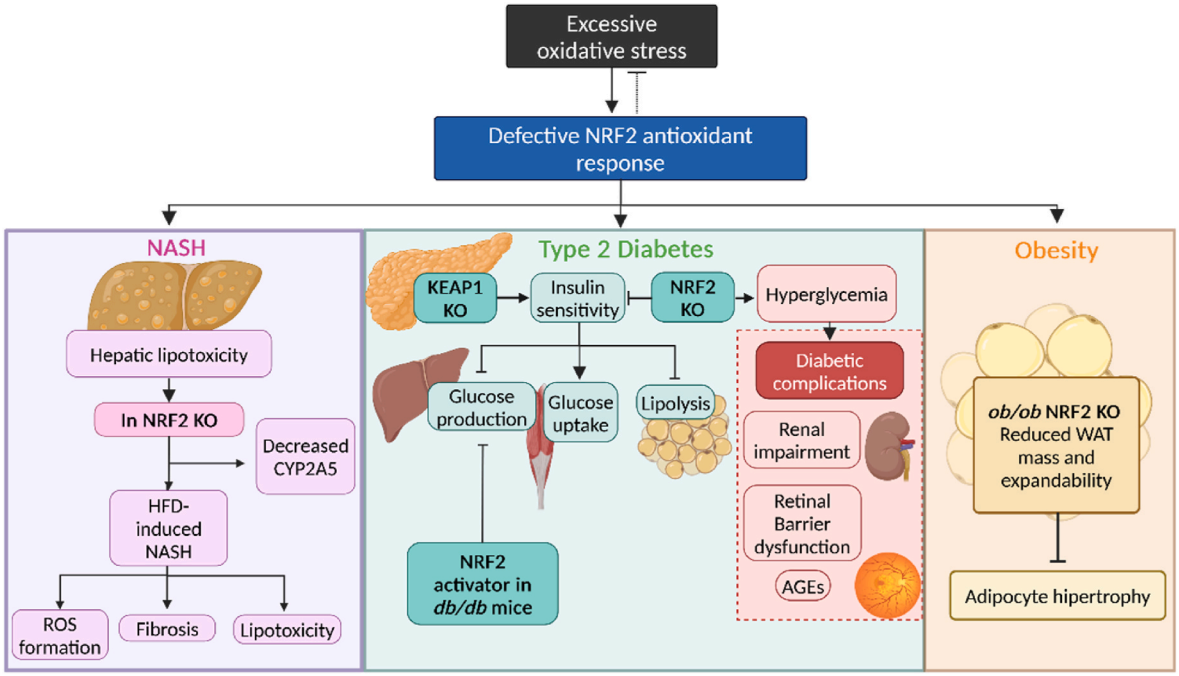


Fig. 5. Defective NRF2-mediated antioxidant response in metabolic diseases. Schematic picture of the impact of excessive oxidative stress and defective NRF2-mediated antioxidant responses in key tissues (liver, adipose tissue, skeletal muscle, pancreas) involved in metabolic diseases (type 2 diabetes, obesity, NASH). In NASH, the hepatic lipotoxicity in the NRF2 KO mice caused a decrease in CYP2A5 and results in NASH upon HFD. This NASH is characterized by ROS formation, fibrosis and lipotoxicity. In type 2 diabetes, a defective NRF2 response results in a reduced insulin sensitivity, affecting the glucose uptake, lipolysis and increasing glucose production. This hallmark of insulin desensitization leads in the NRF2 KO mice to hyperglycemia and diabetic complications. Regarding obesity a key characteristic is the adipocyte hypertrophy, which upon the combination of ob/ob mice with NRF2 deficiency is alleviated due to a reduced WAT mass and expendability. *Abbreviations: NASH, non-alcoholic steatohepatitis; NRF2, nuclear factor erythroid 2-related factor 2; KO, knockout; HFD, high fat diet; ROS, reactive oxygen species; AGE, advanced glycation end product; WAT, white adipose tissue.*

KO mice due to enhanced insulin signaling in liver and skeletal muscle, they developed NASH due to excessive hepatic lipotoxicity upon oxidative stress [175] (Fig. 5). The role of NRF2 in the metabolic syndrome has also been examined in leptin-deficient (*ob/ob*) mice [176]. In this model, both global and adipocyte-specific NRF2 deficiency reduced WAT mass, but aggravated insulin resistance, hyperglycemia, and hypertriglyceridemia (Fig. 5). The absence of NRF2 in WAT resulted in lower expression of genes related to antioxidant response, inflammation, adipogenesis, lipogenesis, glucose uptake, and lipid transport. These findings support a novel role for NRF2 in controlling WAT expansion which is crucial to maintaining insulin sensitivity and glucose and lipid homeostasis.

Another key aspect related to the metabolic effects of NRF2 is its effect on glucose metabolism. Genetic activation of NRF2 by hypomorphic knockdown of *Keap1* (Keap1$^{flox/-}$) or oral administration of an NRF2 activator suppresses the onset of diabetes in diabetic *db/db* mice by downregulating glucose 6-phosphatase through the repression of cAMP-CREB signaling in hepatocytes and other gluconeogenic genes such as peroxisome proliferator activated receptor coactivator-1α (PGC-1α) [177]. Moreover, genetic activation of NRF2 increased the phosphorylation of AMP-activated protein kinase (AMPK) in the liver and enhanced insulin signaling in skeletal muscle, resulting in a substantial improvement of glucose tolerance [178] (Fig. 5).

Genetic factors affecting NRF2 signaling have been poorly studied in humans and only limited data linking the *NFE2L2* gene with diabetes are available. In a Chinese population, the *NRF2* rs6721961 polymorphism has been associated with pathologic ROS formation and the risk of newly diagnosed T2D and may also contribute to impaired insulin secretory capacity and development of insulin resistance [179]. The same SNP was associated with diabetes in Mexican mestizo men [180]. Moreover, in Mexican mestizo subjects, the polymorphisms rs1800566 of NQO1, rs7211 of TXNIP, rs2071749 of HMOX1, and the rs6721961 and rs2364723 of NFE2L2 were genotyped in 627 diabetic subjects and 1020 controls. The results showed that the rs7211 polymorphism is a protective factor against obesity in non-diabetic subjects and women. Moreover, the rs2071749 was positively associated with obesity and the rs6721961 was negatively associated with diabetes in men whereas no association was found for rs1800566 and rs2364723 polymorphisms [180].

Chronic hyperglycemia contributes to the pathogenesis of diabetic complications due to non-enzymatic glycation of proteins that favor spontaneous glucose auto-oxidation and the formation of advanced glycation end products (AGEs) which, in turn, interact with their receptors (RAGEs) causing severe damage in tissues. Several studies have addressed the role of NRF2 in diabetic complications using cellular and animal models. In mesangial cells, activation or overexpression of NRF2 inhibited the promoter activity of *TGFB1* in a dose-dependent manner, whereas NRF2 knockdown had an opposite effect [181]. Very recently, the protective effect of NRF2 has been shown in the kidneys of diabetic *Akita* mice in which NRF2 deficiency worsened renal function manifested by mesangiolysis and dilatation of distal tubules, supporting the use of NRF2 inducers for treating diabetic kidney disease [182]. With respect to diabetic retinopathy, hyperglycemic NRF2 KO mice showed increased ROS levels in the retina together with a reduction in retinal GSH and exhibited early onset of blood-retina barrier dysfunction and exacerbated neuronal dysfunction [183]. Regarding human studies, in a case-control study performed with Chinese Han volunteers, a significant difference was found in genotypic and allelic frequencies of four SNPs of the *NFE2L2* gene was found between T2D patients with and without complications, including peripheral neuropathy, nephropathy, retinopathy, foot ulcers, and microangiopathy [184]. Moreover, the −617C/A polymorphism within the *NFE2L2* promoter was significantly associated with diabetic nephropathy in Chinese Han patients with T2D [185]. Overall, the protective role of NRF2 against both diabetic nephropathy and retinopathy supports the contention that NRF2 activators could be used to treat these modalities.

In conclusion, overwhelming evidence exists from NRF2 KO and KEAP1 knockdown mice, as well as mouse disease models, that NRF2 profoundly influences chronic inflammatory disease in the digestive system and metabolic diseases. Interestingly, in the human, promoter polymorphisms in the *NFE2L2* gene are associated with increased risk of chronic gastritis [186], ulcerative colitis [187], and alcohol-associated liver cirrhosis [188]. The challenge now is to employ specific NRF2 activators to translate these findings into the human.

3.5. NRF2 in cardiovascular diseases

The rationale for NRF2 being a promising candidate drug target in the treatment of cardiovascular diseases (CVDs) is strong. ROS overproduction and impaired antioxidant defense underlie endothelial dysfunction, loss of nitric oxide (NO) bioavailability, and the development of CVDs, among them atherosclerosis, hypertension, ischemia-reperfusion injury, and cardiac failure [189,190] (Fig. 6). Second, NRF2 activity is compromised in the elderly [191] when the prevalence of CVDs is the highest [192]. The expected therapeutic potential of NRF2 is further strengthened by numerous papers reporting the critical protective role of NRF2 target genes in the pathogenesis of CVDs, for example glutathione peroxidase (GPX) [193], HO-1 [194], and NQO1 [195]. Moreover, the hope for modulation of NRF2 activity in the treatment of CVDs has been fueled by the idea of targeting the intrinsic antioxidant system in the face of the failure of antioxidant therapy [196]. It was however tempered by the conflicting reports showing an ambiguous role for NRF2 in CVD pathology, which raised confusion and uncertainty among researchers.

The most striking data that demonstrates the detrimental role of NRF2 in the pathogenesis of CVDs comes from studies on atherosclerosis (Fig. 6A). Atherosclerosis is a condition characterized by infiltration of the arterial wall by immune cells, which accumulate oxidized low-density lipoproteins (oxLDL), leading to the formation of fatty plaques that narrow the arteries. It is a process dependent on NADPH oxidase (NOX)-derived ROS and endothelial cell dysfunction [197], supported by the finding demonstrating inhibition of atherosclerotic lesion formation in *Apoe*$^{-/-}$/*p47phox*$^{-/-}$ mice [198]. In contrast, the *Apoe*$^{-/-}$ GPx-1 [193] and HO-1 KO animals [194] showed an accelerated plaque formation, which suggested the protective role of NRF2 in atherogenesis. Unexpectedly, three independent studies reported that *Apoe*$^{-/-}$*Nrf2*$^{-/-}$ mice were protected from the development of lesions, compared to wildtype or *Nrf2*$^{+/-}$ on the ApoE-null background [199–201]. The postulated mechanisms for the pro-atherogenic effects of NRF2 included lower plasma cholesterol levels in ApoE/NRF2 double KO mice, which showed an increase in liver cholesterol content, elevated lipogenic gene expression in the liver, and lower macrophage infiltration in the plaque [201]. Other studies indicated attenuation of IL-1-dependent inflammation and decreased expression of the oxLDL scavenger receptor CD36 in mice lacking NRF2 signaling [199,200]. Delayed atherogenesis in the global absence of NRF2 activity was also found in *Ldlr*$^{-/-}$ mice [202]. In contrast, *Ldlr*$^{-/-}$ mice transplanted with *Nrf2*$^{-/-}$ bone marrow had aggravated atherosclerosis compared to mice receiving wildtype bone marrow [203,204], which was associated with the pro-inflammatory phenotype of NRF2-deficient macrophages [204]. These data support the concept that the pro-atherogenic role of NRF2 may be related to the systemic effects of NRF2 on lipid metabolism, whereas the expression of NRF2 in monocytes/macrophages could be protective against atherosclerosis.

Regarding cardiac ischemia (Fig. 6B) resulting from the narrowing of the arteries feeding myocardium, experimental data show that increased ROS production and oxidative stress are strongly associated not only with ischemia-reperfusion injury [205] but also with acute ischemia [206]. Therefore, an increase in oxidative damage and impaired blood flow restoration could potentially be expected in NRF2 deficient mice. Paradoxically, neovascularisation and blood flow recovery are faster and more effective in mice devoid of NRF2 signaling, which was

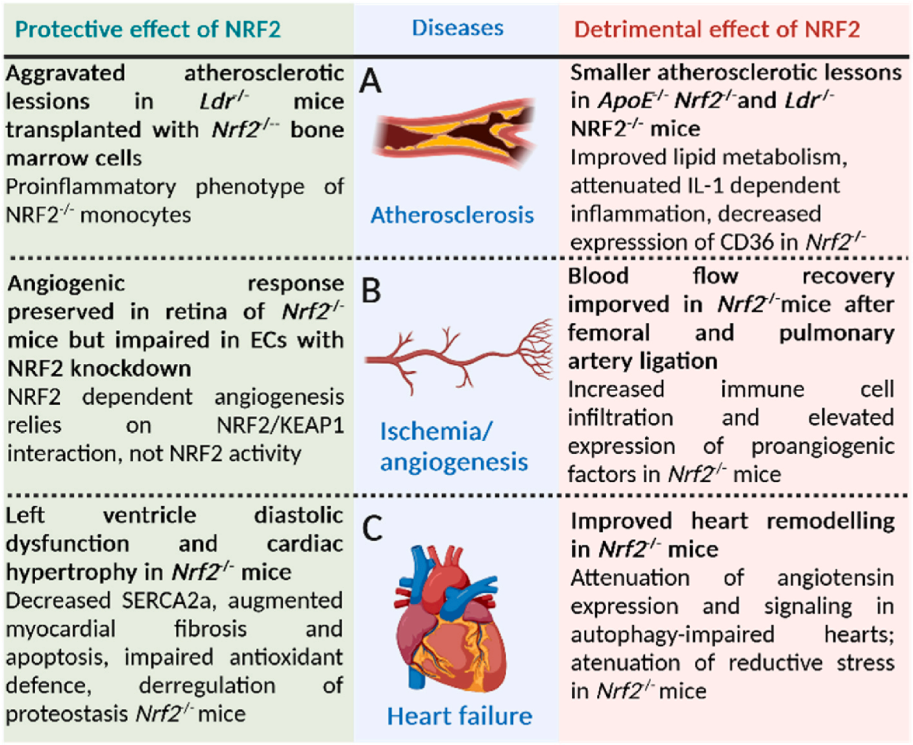


Fig. 6. NRF2 exhibits diverse effects across cardiovascular diseases. NRF2 can present both positive and negative effects in different heart diseases (atherosclerosis, heart failure, ischemia, and aneurysm). In atherosclerosis, NRF2 deficiency aggravates lesions but reduces atherosclerosis size, improving lipid metabolism and decreasing inflammation. For ischemia, NRF2 plays a dual role, promoting angiogenesis and immune cell infiltration. In heart failure, NRF2 KO leads to dysfunction and hypertrophy, but paradoxically improves heart remodeling while attenuating angiotensin expression. *Abbreviations: NRF2, nuclear factor erythroid 2-related factor 2; LDR, low-density lipoprotein receptor; ApoE, apolipoprotein E; IL-1, interleukin 1; EC, endothelial cell; KEAP1, Kelch like ECH associated protein 1; SERCA2a, sarcoplasmic reticulum-adenosine triphosphatase 2A; VCAM1, vascular cell adhesion molecule 1; eNOS, endothelial nitric oxide synthase.*

reported for two experimental models of tissue ischemia: femoral artery ligation and pulmonary artery ligation [206–208]. This effect was related to increased immune cell infiltration in the ischemic tissue and elevated expression of proangiogenic factors [207,208], which shows that the modulation of the cytoprotective response by NRF2 can be overshadowed by its influence on inflammation. In particular, the angiogenic response of endothelial cells in the retinal assay, which is independent of the inflammatory component, is similar between NRF2 KO and wildtype mice [191]. Furthermore, NRF2-dependent angiogenesis not related to inflammation is governed by the NRF2-KEAP1 interaction rather than the transcriptional activity of NRF2 [191,209,210]. It was shown that siRNA-mediated knockdown of NRF2 in human aortic endothelial cells (HAECs) blocks GDF-15- and SDF-1-induced angiogenesis. However, none of these factors trigger NRF2 binding to ARE or ARE-dependent target gene transactivation. Moreover, the angiogenic response to GDF-15 and SDF-1 is preserved in HAECs overexpressing dominant-negative NRF2. Therefore, NRF2-dependent non-inflammatory angiogenesis does not rely on NRF2 transcriptional activity. Instead, the mechanism is based on the sequestration of KEAP1 by NRF2, which, in the absence of NRF2, inhibits podosome assembly and endothelial cell migration. Accordingly, in the retinal angiogenesis assay—a model independent of inflammation—comparable blood vessel formation is observed between WT and NRF2 KO mice. This further supports the NRF2-KEAP1 interaction-dependent mechanism of angiogenesis, as the Neh2 domain binding KEAP1 is present in NRF2 KO mice [191]. Similar transcription-independent effect of NRF2 was described in the context of retrograde trafficking of mitochondria. In this case, the mechanism also relies on the undisturbed interaction between KEAP1 and NRF2; otherwise, KEAP1, when not sequestered by NRF2, leads to the degradation of MIRO2, a mitochondrial GTPase that links mitochondria to microtubules [211].

Ambiguous data on the role of NRF2 in cardiovascular pathomechanisms are also reported for heart failure studies (Fig. 6C). NRF2 KO mice subjected to cigarette smoke-induced cardiac dysfunction [121] and pressure overload–induced cardiac hypertrophy [212] showed a worse phenotype than wild type animals. The protective effect of NRF2 on cardiac hypertrophy was also confirmed in mice that overexpress NRF2 in cardiomyocytes [213]. Activation of antioxidant defense, regulation of metabolism, prevention of cell death and autophagy modulation are postulated to mediate the NRF2-dependent cardioprotection [121,212,213]. On the other hand, one of the follow up studies reported that NRF2 could also have detrimental effects in the heart at the later stages of the pressure overload-induced cardiac hypertrophy. Maladaptive heart remodeling was associated with autophagy impairment, which was proposed to be a discriminating factor for the protective or deleterious role of NRF2 in cardiac failure [214]. Another postulated mechanism for the detrimental effects of NRF2 in cardiac disease is the reductive stress favored by NRF2 activity shown in a CryAB overexpression cardiomyopathy model [215]. Notably, the phase III clinical trial for the treatment of chronic kidney disease with bardoxolone methyl, a potent electrophilic activator of NRF2, was ceased due to the increased ratio of the heart failure and death in patients compared to the placebo group [216]. Although the putative mechanisms of bardoxolone toxicity were ascribed to the effects on hypertensive endothelin signaling [217], the underlying mechanisms still require more extensive investigation.

In aggregate, the effects of NRF2 in the cardiovascular system appear to be ambiguous. The disappointing outcome of the bardoxolone trial, together with the complexity of the role of NRF2 in the cardiovascular system and the KEAP1-mediated NRF2-independent actions of NRF2 activators and KEAP1 interacting proteins [218,219], motivates further research on the complexities of the KEAP1-NRF2 pathway in the context

of cardiovascular diseases.

3.6. NRF2 in neurodegenerative diseases

No disease-modifying therapy is currently available for any neurodegenerative disease, and neuronal loss cannot be halted by symptomatic treatments. Recently, NRF2 has emerged as a promising therapeutic target in the central nervous system (CNS) since its activation could prevent the alteration of common molecular pathomechanisms of several neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD) or amyotrophic lateral sclerosis (ALS) among others (Fig. 7). In fact, as it will be discussed later, an NRF2 activator, omaveloxolone, has recently received approval from the United States Food and Drug Administration (US FDA) to be used for the therapy of Friedreich's ataxia.

The *NFE2L2* gene is ubiquitously expressed through the CNS and can be detected in neurons and glial cells in *post-mortem* human and animal tissues. However, its expression levels are differentially modulated depending on diverse factors such as cellular linage, neuronal maturation state, or disease stage. For instance, brain cells involved in

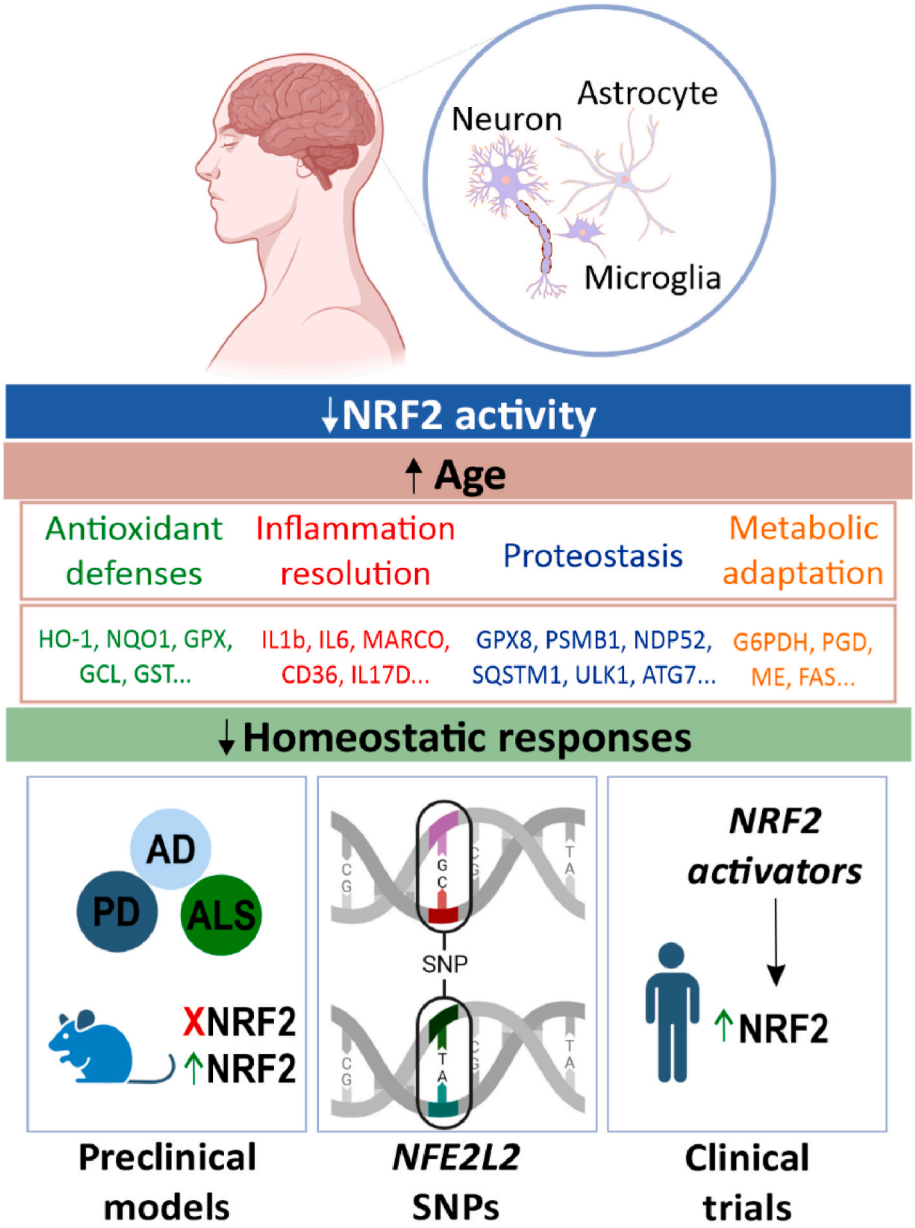


Fig. 7. NRF2 as a promising therapeutic target to reinforce the endogenous protective program in the central nervous system. Aging is the primary risk factor for developing neurodegenerative diseases in the CNS leading to homeostatic deviations including loss of activity of NRF2. This reduction negatively impacts on the expression levels of crucial genes associated with antioxidant defenses, inflammation resolution, proteostasis, and metabolic adaptation. Preclinical and genetic studies for main degenerative diseases, such as PD, AD and ALS, pave the way for investigating the therapeutic role of NRF2 in clinical trials enrolling patients suffering from neurodegenerative diseases. Some SNPS have been associated with a decreased risk or delayed onset of these neurodegenerative diseases, in certain populations, while others have been associated with earlier onset. These observations suggest the potential therapeutic effect that NRF2 could provide for neurodegenerative diseases *Abbreviations: NRF2, nuclear factor erythroid 2-related factor 2; HO-1, heme oxygenase-1; NQO1, NAD(P)H:quinone oxidoreductase 1; GPX, glutathione peroxidase; GCL, glutamyl cysteine ligase; GST, glutathione-S-transferase; IL1b, interleukin 1β; IL6, interleukin 6; MARCO, macrophage receptor with collagenous structure; IL17D; interleukin 17D; PSMB7, proteasome subunit b type-7; NDP52, Calcium-binding and coiled-coil domain-containing protein 2; SQSTM1, sequestosome 1/p62; ULK1, unc-51 like autophagy activating kinase 1; ATG7, Autophagy Related 7; G6PDH, glucose-6-phosphate dehydrogenase; PGD, phosphogluconate dehydrogenase; ME, malic enzyme; FAS, fatty acid synthase. AD, Alzheimer's disease; PD, Parkinson's disease; ALS, amyotrophic lateral sclerosis.*

homeostatic adaptation such as microglia and astrocytes exhibit a higher level of *NFE2L2* expression compared to neurons [220]. NRF2 expression is repressed in mature primary neurons but not in astrocytes obtained from the mouse embryonal cortex [221]. Regarding *postmortem* brain samples, the characterization of NRF2 expression and downstream target genes is controversial. For instance, dopaminergic neurons from PD patients exhibited higher levels of nuclear NRF2 compared to those from healthy subjects [222], however, the cytoprotective proteins associated with NRF2 expression, NQO1 and p62, were partly sequestered in Lewy bodies, suggesting an impaired neuroprotective capacity of NRF2 [223]. Other studies have reported increased expression of NRF2 targets, such as HO-1, NQO1, or p62, in AD brains [224–227]. Furthermore, neurons under proteotoxic attack also expressed p62 and nuclear NRF2 in AD patients [228]. NRF2 mRNA and protein levels are decreased in the motor cortex and spinal cord of ALS patients compared to normal brain [229]. The relationship between p62 and KEAP1 was investigated in the brains of patients with AD, PD, and ALS. Biochemical analyses showed that p62 and KEAP1 interacted with each other in AD brains and were present in the same fractions. Histopathological examination showed that KEAP1 is accumulated in Lewy bodies in PD, neurofibrillary tangles in AD, and skein-like inclusions in ALS [230]. One possible explanation for these discrepancies is that NRF2 levels might change during aging, disease progression and brain regions.

Aging is the primary risk factor for developing neurodegenerative diseases [231]. Homeostatic deviations that result from ageing include loss of activity of NRF2, inferring that a gradual decline in its expression or function could be a significant contributor to the onset and progression of neurodegeneration (Fig. 7). Compelling evidence for NRF2 repression in aging came from a study of Hutchinson-Gilford progeria syndrome, a rare fatal premature aging disorder caused by the overexpression of a mutant version of Lamin A, called progerin, which sequesters NRF2, hence avoiding its activation [232]. Accordingly, a transcriptomic analysis demonstrated that NRF2 KO mice reproduce 7 and 10 of the most dysregulated pathways in human ageing and AD brains, respectively [233]. Analysis of NRF2 basal expression in ageing models produced mixed results, suggesting that age-dependent changes in NRF2 levels vary between brain regions, and the loss of NRF2 activity is particularly relevant in regions that exhibit high NRF2 activity in young animals [233,234]. Chronic airborne pollution exposure induced GCLC, GCLM, HO-1, NQO1 mRNA and protein similarly in the cerebellum, liver, and lung of young mice. However, middle-aged mice showed impaired NRF2 signaling [235]. In brain injury models, aging not only worsened brain damage but also increased oxidative stress and reduced antioxidant capacity when compared to younger animals, as demonstrated by a reduction in the expression of NRF2 dependent genes [236]. NRF2 and HO-1 expression was induced in the subventricular zone of young but not of aged mice in response to a parkinsonian toxin [237]. These studies suggest that the capacity of NRF2 to respond to insults is altered with age.

Some SNP haplotypes of *NFE2L2* were associated with decreased risk or delayed onset of PD, AD, or ALS (Fig. 7). A case-control study demonstrated that three SNPs in the *NFE2L2* promoter (rs6721961, rs6706649, and rs35652124) represent a protective haplotype [238] that reduced the onset of the disease or even the risk of PD in Swedish and Polish cohorts [239]. However, this protective association was not replicated in neither Taiwanese or Chinese populations [240,241], suggesting genomic differences in ethnicities and environmental factors in different geographical regions. Several SNPs were identified as susceptibility factors in cells from PD-patients mucosa upon exposure to smoke extract or pesticide [242]. Extensive screening of *NFE2L2* gene by direct sequencing to detect polymorphisms revealed two exonic SNPs in *NFE2L2* (c.351 T > A and c.423 G > T), resulting in conversion of D117 to E and Q141 to H, respectively. These SNPS located near the pyrimidine-rich region of the 3′splicing acceptor are significantly associate with PD in a Chinese cohort. The presence of these exonic polymorphisms does not alter *NFE2L2* mRNA levels. However, when NRF2 variants carrying these exonic SNPs were overexpressed, the mRNA levels of GSTP1, GSTM1 and HO-1 were reduced. Further evidence is required to elucidate the underlying molecular mechanisms [241]. Regarding AD, one haplotype allele was associated with 2-year earlier age onset of AD, suggesting that common variants of the *NFE2L2* gene may affect disease progression, potentially altering clinically recognized disease onset [243]. Interestingly, one SNP at the MS4A (membrane-spanning 4-domains subfamily A) locus, one of the most significant loci associated with AD risk, creates an aberrant antioxidant response element capable of binding NRF1 and NRF2 [244]. ALS onset was analyzed in two studies regarding three functional promoter SNPs in *NFE2L2* that were previously linked to high gene expression. Interestingly, this *NFE2L2* haplotype was associated with 4.0 years later disease onset in a subgroup of ALS patients [245]; however, no association was found between biochemical markers of redox balance and *NFE2L2* polymorphisms in another study [246]. The application of a system medicine approach to NRF2 demonstrated that alteration of its expression and activity is a common mechanism in a subnetwork of diseases (the NRF2 diseasome). Remarkably, AD, PD, Huntington's disease, and ALS constitute a cluster consistent with alterations in the protein interaction network of NRF2 [247]. Altogether, it is possible that a slight activation of NRF2, such as that found for some functional haplotypes of the *NFE2L2* gene, should be enough to evoke a protective mechanism in the brain.

Given the wide cytoprotective functions of the NRF2 transcriptional program, 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. Overwhelming evidence from different preclinical studies supports the role of NRF2 in the pathogenesis of neurodegeneration. In general, deletion of NRF2 usually worsens disease phenotype, whereas overexpression or pharmacological activation of NRF2 is protective in animal models of neurodegeneration. The beneficial effects of NRF2 have also been reported on the pathological status of AD. Hippocampal neurons of *APP/PS1* mice were protected upon NRF2 overexpression delivered by viral vectors [248]. Similarly, NRF2 deficiency aggravates the phenotypes of AD model mice, such as APP/TAU [233,249,250] and APP/PS1 [251] mice. On the contrary, KEAP1 knockdown in *AppNL-G-F/NL-G-F* knock-in mice represses inflammatory cytokine gene expression, enhances GSH synthesis, and reverses memory impairment [252]. In a mouse model of MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)-induced PD, NRF2 deficiency exacerbates astrogliosis and microgliosis with elevated expression of inflammation markers [253]. The toxicity of astrocytes expressing ALS-linked mutant SOD1 to co-cultured motoneurons was reversed by NRF2 overexpression. NRF2 overexpression in astrocytes significantly delayed onset and extended survival in two ALS mouse models [254,255]. Pharmacological approaches have been performed to test whether NRF2 is a relevant target to ameliorate the neurodegenerative process. Carnosic acid, synthetic triterpenoids, dimethyl fumarate (DMF), and 6-(methylsulfinyl) hexyl isothiocyanate (6-MSITC) have been shown to improve cognitive function [252,256,257]. Treatment with 6-MSITC protects neuronal functions after unilateral intrastriatal injection of 6-hydroxydopamine [258]. Daily oral gavage of DMF protected nigral dopaminergic neurons and decreased astrocytosis and microgliosis from stereotaxic delivery of recombinant adeno-associated viral vector expressing human α-synuclein [259] and TAU [223]. CDDO-EA (cyanoenone triterpenoid 2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid-Ethylamide) and CDDO-TFEA (cyanoenone triterpenoid 2-cyano-3, 12-dioxooleana-1,9-dien-28-oic acid-Trifluoroethylamide) when administered at the pre-symptomatic stage, significantly attenuated weight loss, enhanced motor performance, and extended the survival of the $SOD1^{G93A}$ mice. When administered at the symptomatic stage, NRF2 activation was neuroprotective and slowed disease progression [260]. Notably, mice treated with S[+]-apomorphine showed induction of NRF2 controlled genes in the brain and significant attenuation of motor dysfunction in $SOD1^{G93A}$ mice [261]. Altogether, these results highlight the potential of pharmacological NRF2 activation as a promising strategy to combat

neurodegeneration.

3.7. NRF2 in cancer

NRF2 plays a dual role in the development and progression of cancer (Fig. 8). The protective function of NRF2 was first highlighted in cancer chemoprevention as NRF2 is a master regulator of the Phase II detoxification enzyme genes [262]. The Phase I detoxification enzymes convert xenobiotics to carcinogenic electrophiles, which are detoxified by the Phase II detoxification enzymes by conjugation with hydrophilic moieties, including GSH [263]. While NRF2-deficient mice exhibit increased susceptibility to chemical carcinogens [264], cancer genome research revealed loss-of-function mutations of *KEAP1* and gain-of-functions of *NFE2L2* in several human cancers, including lung, head and neck and oesophageal cancers, resulting in hyperactivation of NRF2 and poor prognosis of cancer patients [265]. Based on results from cellular and animal experiments, cancers with NRF2 hyperactivation are expected to be highly dependent on NRF2 activity for their malignant phenotypes: therapeutic resistance, aggressive tumor growth, enhanced cancer stemness, metastasis and immunoevasion [266], leading to the idea that NRF2 is an effective therapeutic target and has fostered the development of NRF2 inhibitors. Such NRF2 addiction status needs to be carefully evaluated in human cancers, which will be addressed by future clinical trials of NRF2 inhibitors currently in development. From a different point of view, NRF2 hyperactivation was found to confer metabolic vulnerabilities on cancer cells as tradeoffs, which provides potential therapeutic targets other than NRF2 itself [267,268].

Intriguingly, simple persistent stabilization of NRF2 is not enough to establish NRF2 addiction status. *Keap1* disruption in mouse hematopoietic stem cells leads to exhaustion, which is rescued by concurrent disruption of *Nfe2l2* [269], and NRF2-overexpressing Drosophila cells and KEAP1-deficient murine cells become losers in cell competition [270,271]. How NRF2 changes its role from a guardian to an invader requires further study.

One of the clear differences of NRF2 status in normal cells and NRF2-hyperactivated cancer cells is the duration and magnitude of NRF2 activation. In normal cells, NRF2 is transiently activated in response to stress that inhibits KEAP1-mediated degradation of NRF2. In contrast, cancer cells can exhibit persistent stabilization of NRF2 at almost maximum levels, leading to continuous high expression of its target genes. For example, CEBPB is one of the NRF2 target genes and is induced following NRF2 activation, sharing only a short time period with NRF2 in normal cells whereas, in NRF2-activated cancer cells, CEBPB expression is continuously activated by NRF2, which leads to the NRF2-CEBPB cooperativity that does not happen in normal cells [272]. NRF2 and CEBPB cooperatively generate a unique enhancer at the *NOTCH3* locus, leading to promotion of the cancer stemness of non-small cell lung cancers (NSCLC) [273], and contribute to the generation of super-enhancer at *AKR1C1-AKR1C2* locus, further increasing drug resistance (Fig. 8) [272].

Central to the cytoprotective effects of NRF2 is the synthesis of the antioxidant GSH, which is composed of cysteine, glycine, and glutamate.

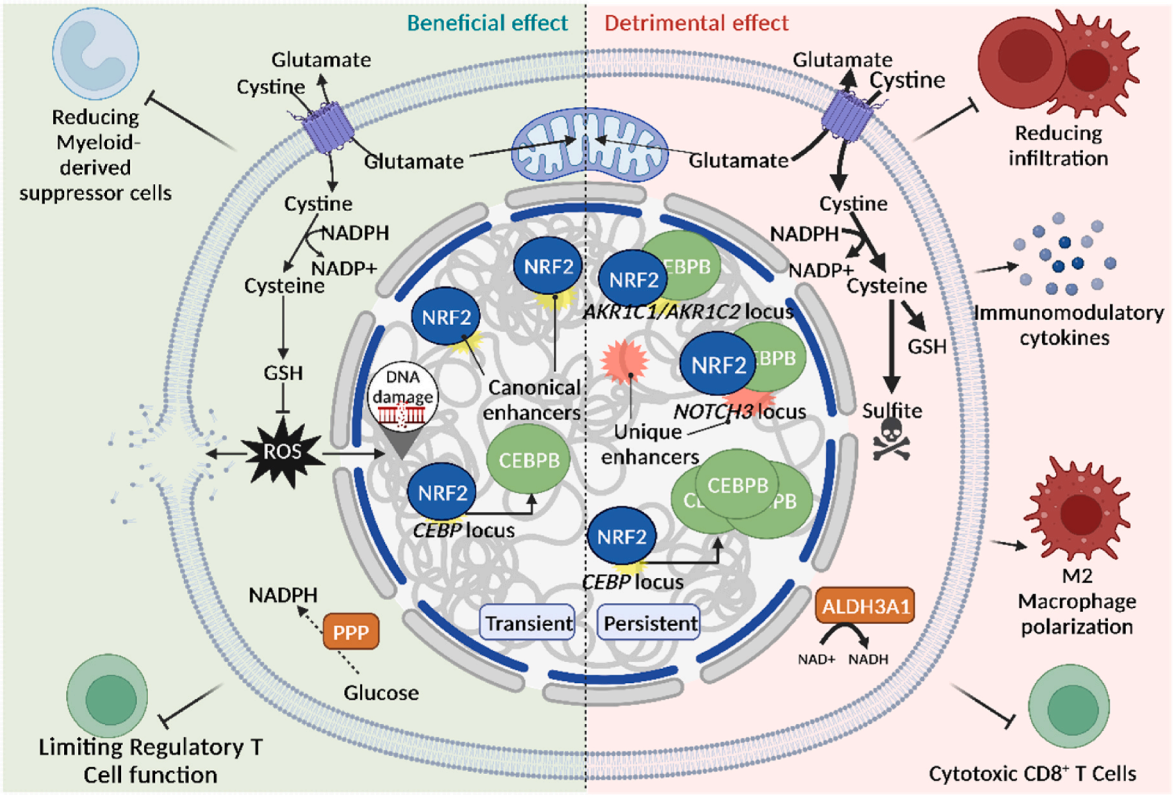


Fig. 8. Dichotomy of NRF2 in cancer. NRF2 plays an important role in cytoprotection from oxidative stress (beneficial effect, left half) and supports malignant phenotypes of cancer cells (detrimental effect, right half). NRF2 functions at three layers, transcription, metabolism, and tumor immunity, are illustrated. On the beneficial effect, NRF2 binds to its canonical enhancers upon oxidative stress, which can damage the DNA and is blocked by antioxidative enzymes regulated by NRF2, as well as NADPH mediated by NRF2 promotion of the PPP. In physiological conditions, NRF2 activation is transient and is eventually repressed by its degradation mechanism. On the other hand, NRF2 hyperactivation in cancer can result in worse prognosis and becoming dependent on NRF2 activity, inducing constant CEBPB expression. This leads to NRF2-CEBPB cooperativity that does not happen in normal cells, generating a unique enhancer at the NOTCH3 locus, leading to promotion of cancer stemness and contributes to the generation of super-enhancer at AKR1C1-AKR1C2 locus, further increasing drug resistance. Loss of KEAP1 regulation results in NRF2 promotion of immunomodulatory cytokines, inhibition of CD8 T cells, reduced immune system cells infiltration and induction of the M2 polarization of macrophages. *Abbreviations: NADPH, nicotinamide adenine dinucleotide phosphate; GSH, glutathione; ROS, reactive oxygen species; PPP, pentose phosphate pathway; CEBP, CCAAT enhancer binding protein; NRF2, nuclear factor erythroid 2-related factor 2; AKR, aldo-keto reductase; ALDH, aldehyde dehydrogenase.*

NRF2 promotes xCT transcription to aid cystine entry [274], the reduction of cystine to cysteine through the transcriptional regulation of the thioredoxin system [275,276], and cysteine utilization for GSH synthesis (Fig. 8) [277–279]. NRF2 also promotes glutamine uptake and its incorporation into GSH to promote radiation resistance [280,281], thereby conferring dependence on glutamine and the glutamine transporter ASCT2 [267]. Finally, NRF2 supports GSH synthesis by increasing the availability of glycine from serine. NRF2 promotes the transcription of serine synthesis pathway enzymes to support GSH, nucleotides, and NADPH production in KEAP1 mutant NSCLC cells [282]. Moreover, KRAS/KEAP1 mutant NSCLC cells depend on GLUT8 for serine biosynthesis, linking serine addiction and glucose transport [283]. While GSH synthesis protects against ROS and cellular oxidation, the GSH synthesis machinery also has an important non-canonical function to protect against glutamate toxicity during cysteine-starvation induced ferroptosis [284]. NRF2 also protects against ferroptosis and promotes radiation resistance by maintaining iron homeostasis and suppressing lipid peroxidation [285,286].

NRF2 directly regulates the transcription of the oxidative pentose phosphate pathway (PPP) enzymes G6PD and PGD, and the non-oxidative PPP enzymes TKT and TALDO1 [280], and indirectly regulates the PPP through miRNA expression [287]. KEAP1 mutant NSCLC tumors rely on the activity of the PPP for growth [280,288]. Interestingly, while G6PD was required for KEAP1 deficient lung tumor growth, *ex vivo* analyses suggested an antioxidant-independent mechanism [289]. In contrast, a ROS-sensitizing CRISPR screen in KEAP1 mutant NSCLC cells identified G6PD as the top hit, suggesting that it also plays critical antioxidant function when ROS levels are high [290]. Alongside its antioxidant role, the NRF2-driven PPP generates R5P for nucleotides and NADPH for ribonucleotide reduction. NRF2 directly regulates the transcription of phosphoribosyl pyrophosphate amidotransferase (PPAT) and bifunctional methylenetetrahydrofolate dehydrogenase/cyclohydrolase (MTHFD2), key enzymes in *de novo* nucleotide synthesis [280]. *In vivo* CRISPR screening identified NRF2-driven *Pgd* and *Ppat* as vital for breast tumor recurrence by supporting both redox balance and enhancing *de novo* nucleotide synthesis [291].

Given these influences on metabolism and their beneficial contribution to tumorigenesis, it is not surprising that constitutive NRF2 activation following KEAP1 loss promotes tumor initiation, particularly in genetically engineered mouse models of lung cancer [267,288,292], and confers chemo- and radiation resistance in patients [293]. However, constitutive NRF2 activation is not always favorable and, in some models, does not promote tumor formation [294], antagonizes tumor progression [295], or impairs metastasis [296]. Here, we will discuss the metabolic effects of NRF2 that may contribute to these phenotypes. NRF2 induces NADH-reductive stress through the NAD^+-consuming enzyme aldehyde dehydrogenase 3-A1 (ALDH3A1) [268]. NRF2 also promotes reduced NADPH/$NADP^+$ and GSH/GSSG ratios that may contribute to reductive stress. Indeed, metastasis upon NRF2 loss was associated with the activation of signaling cascades that are redox regulated [296]. Cysteine accumulation defends against oxidative stress but also makes NSCLC cells vulnerable due to CDO1-mediated taurine pathway toxicity and NADPH depletion [297]. *CDO1* epigenetic silencing in NSCLC, especially KEAP1 mutant adenocarcinomas, counteracts this. The high rate of cystine import in NRF2 active cells also confers other vulnerabilities. Because xCT is a cystine-glutamate antiporter, cystine import must be matched by an equimolar amount of glutamate export and NADPH to reduce cystine. Accordingly, NRF2-active cells are in a glutamate-deficient state, which limits the TCA cycle anaplerosis and confers sensitivity to glutaminase inhibition [267,298]. Moreover, this glutamate-deficient state limits non-essential amino acid synthesis and confers sensitivity to asparaginase treatment [299]. KEAP1 mutant cells are also sensitive to glucose withdrawal due to NADPH depletion and an inability to reduce cystine [300]. Thus, NRF2 activation confers metabolic vulnerabilities that may confer bottlenecks for tumor progression and can be exploited therapeutically.

It is widely acknowledged that cancer cell-intrinsic oncogenic signaling pathways can modulate the tumor microenvironment (TME), thereby impairing the antitumor immune response [301]. Given that immune therapies, especially immune checkpoint inhibitors, have become the standard treatment for many solid cancers, understanding the mechanisms by which tumors can evade immune destruction is important to facilitate immunotherapy efficacy. The notion that aberrant NRF2 signaling in cancer cells might impact tumor immunity stems from clinical studies whereby activating mutations of *KEAP1/NFE2L2* were found to be associated with impaired response to checkpoint inhibitors in NSCLC [302]. This finding has been corroborated by other studies [303], and KEAP1 mutations have also been shown to be associated with immune cold tumor phenotype with low lymphocyte infiltration [292,304,305]. An immune evasive phenotype is not limited to the KEAP1 mutant NSCLC, but also in many squamous cell cancers, such as oesophageal and head and neck cancers, high NRF2 activity is associated with immune cold characteristics [305].

How cancer cell-intrinsic activation of NRF2 affects tumor immunity is incompletely understood and likely to be through multiple different mechanisms. Recently, the loss of KEAP1 was shown to decrease cytotoxic $CD8^+$ T cells and increase protumorigenic M2 macrophages *via* stabilization of EMSY, which suppresses the type I interferon response [306]. Type I interferon response is also inhibited directly by NRF2 *via* inhibition of the stimulator of interferon genes (STING) [307]. Other plausible mechanisms contributing to the NRF2-mediated immune evasion are inhibition of the expression of proinflammatory cytokines [39], altered expression of immunomodulatory genes [305] and competition for essential nutrients between cancer cells and T cells within the TME [308].

In addition to cancer cells, the NRF2 activity status in immune cells within the tumor stroma also affects antitumoral immune responses. NRF2 has an acknowledged role in immunity, and for example, T cell activation is under redox control in which NRF2 plays an important part [309]. In cancer, the role of stromal NRF2 in tumor progression is ambiguous. It has been shown using mouse models that modest activation of NRF2 in tumor stroma suppresses the progression of NRF2 overexpressing malignant tumors [310], and that NRF2 deficiency exacerbates the formation of lung metastases following implantation of mouse Lewis lung carcinoma cells [311], indicating that stromal NRF2 is important for antitumor response. In contrast, NRF2-activating drugs have been reported to promote metastatic spread in xenograft mouse models [312], and chronic administration of antioxidants does the same *via* a mechanism involving BACH1/NRF2 interplay [313]. As these studies have been conducted using different experimental models, further clarification of the mechanisms and distinction between various cell types within stroma using spatial techniques is warranted. This is especially important for the safety of NRF2 modifying drugs, as both NRF2 activators for the treatment of degenerative diseases and inhibitors for cancer are in active development [220].

4. Pharmacological regulation of NRF2

4.1. Electrophilic NRF2 inducers

In 1988, Paul Talalay and his colleagues identified a common chemical signature among inducers of cytoprotective enzymes, such as NQO1 and GSTs [314]. Michael acceptors are characterized by olefinic (or acetylenic) bonds that are rendered electrophilic by conjugation with electron-withdrawing groups, and thus are highly susceptible to nucleophilic attack, such as those carried out by reactive cysteines in proteins. Following the discovery of KEAP1 by Masayuki Yamamoto and his colleagues [13] as the repressor of NRF2, multiple investigators have shown that several cysteines in KEAP1 serve as sensors for electrophilic NRF2 inducers, leading to the idea of the “cysteine code” [315–318].

To date, electrophiles represent the largest and best-characterized class of NRF2 inducers, comprising natural products and (semi)

synthetic molecules. Hundreds of chemical structures have been designed or identified by various screening programs and shown to induce NRF2 in mammalian cells and organisms, as well as in human studies. Most electrophilic NRF2 inducers are exogenous to mammalian cells and organisms. However, many are present in plants, such as sulforaphane from broccoli [319], curcumin from turmeric [320], and fumarate (and fumaric acid esters) from Shepherd's purse [321]. In addition, electrophilic metabolites are formed endogenously, such as the Krebs cycle metabolite fumarate, which accumulates in fumarate hydratase deficiency [322], itaconate and the cyclopentenone prostaglandin 15-deoxy-delta^{12,14}-prostaglandin J_2, which accumulate during inflammation [323,324], the glycolytic intermediate methyl glyoxal, which increases in diabetes [325], and nitro-fatty acids [326,327]. Another category is represented by the semi-synthetic NRF2 inducers, such as the cyanoenone triterpenoids that are derived from the natural products oleanolic, ursolic and betulinic acids [328,329]. Here, we highlight sulforaphane, DMF, bardoxolone methyl and omaveloxolone (Table 1), electrophilic NRF2 inducers that have been extensively studied, two of which have entered clinical practice.

4.1.1. Sulforaphane

Using a bioassay-guided fractionation of extracts of commonly consumed plants for inducers of the classical NRF2 target NQO1, Zhang and colleagues [319] isolated the isothiocyanate sulforaphane [1-isothiocyanato-(4*R*)-(methylsulfinyl)butane] (Table 1) from broccoli extracts as the principal NQO1 inducer. Although the intact plant contains an inactive precursor, the methionine-derived glucosinolate glucoraphanin, the plant also has myrosinase, a hydrolytic enzyme which normally is physically separated from its glucosinolate substrate but encounters it upon plant tissue damage, resulting in the formation of a variety of reactive products, such as sulforaphane [330,331]. The electrophilic isothiocyanate (-N═C═S) group of sulforaphane readily reacts with protein cysteines, forming kinetically labile, reversible dithiocarbamates. C151 in the BTB domain of KEAP1 serves as the main sulforaphane sensor, although modifications in C38, C368 and C489 have been also reported [315,318,332–335].

Since its discovery as an NQO1/NRF2 inducer, sulforaphane and/or broccoli preparations rich in sulforaphane or glucoraphanin (which is converted to sulforaphane by the microbiota in the gastrointestinal tract) have been shown to be effective protectors in numerous preclinical models of chronic disease, and in human studies in healthy subjects as well as high-risk populations (reviewed in Refs. [331,336,337]). Currently, there are 284 patents and 82 registered clinical trials with various sulforaphane-rich preparations or stabilized sulforaphane for various disease indications. The use of NRF2 KO mice in some of the animal studies has demonstrated dependence on NRF2 for the protective effects of sulforaphane [181,338,339]. As in mice, in humans, induction of NRF2-dependent transcription by sulforaphane inversely correlates with pro-inflammatory responses [340–343].

4.1.2. Dimethyl fumarate

Dimethyl fumarate (DMF) (Table 1) was one of the compounds that contributed to the discovery of the Michael acceptor signature of NRF2 inducers: it was found that DMF and dimethyl maleate are effective NQO1 inducers in cells and in mice, whereas the potency of the corresponding acids (fumarate and maleate) is much lower, in agreement with the higher reactivity of the esters as Michael acceptors [314,321]. In humans, DMF induces NQO1 in peripheral blood mononuclear cells (PBMCs) *ex vivo* and *in vivo* [344]. NRF2 induction by DMF is consequent to modification of C151 in KEAP1 [345,346]. The beneficial effects in placebo-controlled Phase III clinical trials in patients with relapsing-remitting multiple sclerosis (RRMS) led to the US FDA approval of DMF (Tecfidera®, Biogen) for RRMS treatment in 2013 [347,348]. To date, more than 560 000 patients have been treated with DMF [349]. Since October 2017, the TEALS Study (ACTRN12618000534280) has been assessing the efficacy of DMF on disease progression measured by the Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised in sporadic ALS patients. In this study, there was no significant improvement in the primary endpoint, although there was a mild improvement in the patient's neurophysiological index [350]. Given the impairment of NRF2 in neurodegenerative diseases, activation of its pathway through more potent inducers could effectively be protective. Therefore, a window for brain protection upon NRF2 stimulation may still be feasible.

Despite its efficacy, some patients have low GI tolerability; this has led to the development of diroximel fumarate (DRF, Vumerity®, Biogen) as a second-generation disease-modifying drug, which was approved for clinical use by the US FDA in 2019. Additionally, monomethyl fumarate (MMF, Bafiertam®, Banner Life Sciences), the active metabolite of DMF and DRF, was also approved in 2020 for relapsing forms of multiple sclerosis. A recent pharmacokinetics study of DMF in patients with secondary progressive multiple sclerosis showed that MMF readily penetrates the blood-brain barrier, reaching concentrations in the cerebrospinal fluid that were 11 % of the plasma concentrations, with a time to peak drug concentration (T_{max}) in plasma of 5 h, and T_{max} in cerebrospinal fluid of 7 h [351]. In 2017, DMF (Skilarence®) was approved in Germany for the systemic treatment of moderate to severe plaque psoriasis. DMF is also being studied in other disease contexts, including both neurological (e.g., ALS, glioblastoma multiforme) and non-neurological (e.g., rheumatoid arthritis, cutaneous T cell lymphoma) conditions [349]. Currently, there are 372 patents and 147 registered clinical trials with DMF or its derivatives.

4.1.3. CDDO, bardoxolone methyl (CDDO-Me) and omaveloxolone

The naturally occurring oleanane triterpenoids are pentacyclic compounds with 30 carbon atoms, which are derived from the cyclization of squalene, and are structurally diverse due to a wide array of functional groups. In a programme led by Michael B. Sporn and Gordon W. Gribble, a large series of semi-synthetic triterpenoid analogues of oleanolic acid were synthesized and shown to be potent inhibitors of pro-inflammatory processes in murine macrophages in a manner that was independent of the glucocorticoid receptor [352]. Microarray analysis of cells that had been exposed to CDDO (Table 1) revealed the induction of numerous NRF2 transcriptional targets, including HO-1, NQO1, GSTA4, GCLc, and GR [353,354]. Importantly, the potency of CDDO derivatives in inducing NQO1 and suppressing pro-inflammatory responses was dependent on the presence of Michael acceptor functions at critical positions in rings A and C, and the most potent compound in this series modifies cysteines in purified recombinant KEAP1 [355]. Moreover, the anti-inflammatory and NQO1 inducer potencies of a series of CDDO derivatives were linearly correlated over 6 orders of magnitude of concentration.

During the subsequent years, many more cyanoenone derivatives have been synthesized, including smaller structures, such as tricyclic and monocyclic derivatives [356,357]. The electron affinity of this group of compounds, expressed as the energy of their lowest unoccupied molecular orbital [E (LUMO)] correlates with their NQO1 inducer potency regardless of the molecule size [358]. In agreement, all of them target C151 in KEAP1 irrespective of size and shape [359,360]. Substitution of C151 with a serine in KEAP1 abrogates the NRF2 induction and cytoprotective activity of bardoxolone methyl (CDDO-Me) in cells and *in vivo* [361]. The co-crystal structure of the BTB domain of KEAP1 with CDDO shows that CDDO binds to a shallow groove containing C151 [362].

Extensive animal studies have demonstrated the protective effects of these compounds in numerous animal models of disease (reviewed in Ref. [329]). Two compounds progressed to clinical trials, namely CDDO-Me and omaveloxolone (Table 1) for a number of indications, including cancer, chronic kidney disease, pulmonary hypertension, pulmonary arterial hypertension, radiation dermatitis, ocular inflammation, and liver disease. There are currently 11 patents and 48 registered clinical trials with CDDO-Me or omaveloxolone. Based on data

Table 1
Electrophilic inhibitors of KEAP1 and their preclinical and clinical progression.

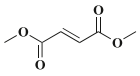
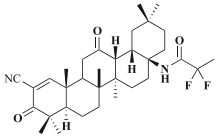
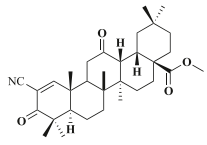
Compound	Type/Mechanism of action	Disease	Clinical trial	ClinicalTrials.gov identifier
Dimethyl Fumarate 	Fumaric acid ester Electrophilic modification of KEAP1-Cys-151	Primary Progressive Multiple Sclerosis	Approved	NCT02959658
		Rheumatoid arthritis	Phase II	NCT00810836
		Adult brain glioblastoma	Phase I	NCT02337426
		Cutaneous T cell lymphoma	Phase II	NCT02546440
		Obstructive sleep apnea	Phase II	NCT02438137
		Chronic lymphocytic leukemia Small lymphocytic lymphoma	Phase I	NCT02784834
		Glioblastoma	Phase I	NCT02337426
		Acute Ischemic Stroke	Phase I/II	NCT04890366
			Phase II	NCT04890353
		Intracranial Aneurysm Aneurysm, Brain Inflammation Vascular	Phase IV	NCT05959759
		Intracerebral Hemorrhage	Phase II	NCT04890379
		Systemic Sclerosis Pulmonary; Hypertension	Phase I	NCT02981082
		Lupus Erythematosus, Cutaneous	Phase II	NCT01352988
		Age-related Macular Degeneration (AMD)	Phase II	NCT04292080
		Covid19	Observational	NCT04834401
Omaveloxolone 	Synthetic triterpenoids Electrophilic modification of KEAP1-Cys-151	Friedreich's ataxia	Approved	NCT02255435
		Mitochondrial myopathy	Phase II	NCT02255422
		Inflammation and pain following ocular surgery	Phase II	NCT02065375
		Corneal endothelial cell loss Ocular pain Ocular inflammation Cataract surgery	Phase II	NCT02128113
		Melanoma	Phase I/II	NCT02259231
		Breast cancer	Phase II	NCT02142959
		Metastatic or Incurable Non-small Cell Lung Cancer Relapsed, Refractory Melanoma	Phase I	NCT02029729
		Hepatic Impairment	Phase I	NCT03902002
bardoxolone methyl (CDDO-Me) 	Synthetic triterpenoids Electrophilic modification of KEAP1-Cys-151	Renal Insufficiency, Chronic	Phase I	NCT01549769
		Diabetes Mellitus, Type 2	Phase II	NCT01053936
			Phase III	NCT01351675
			Phase I	NCT01551446
		End-Stage Renal Disease Type 2 Diabetes Mellitus	Phase II	NCT01576887
		chronic Kidney Disease Alport Syndrome Autosomal Dominant Polycystic Kidney	Phase III	NCT03749447
		Diabetic Kidney Disease	Phase III	NCT03550443
		Chronic Kidney Disease	Phase I	NCT01500798
		Type 2 Diabetes	Phase II	NCT02316821
		Autosomal Dominant Polycystic Kidney ADPKD	Phase III	NCT03918447
		Chronic Kidney Diseases	Phase II	NCT04702997
		Chronic Kidney Disease Type 2 Diabetes Diabetic Nephropathy	Phase II	NCT00811889
		Liver disease	Phase I/II	NCT00550849
		Hepatic impairment Healthy	Phase I	NCT01563562
		IgA nephropathy CKD associated with type 1 DM Focal segmental glomerulosclerosis Autosomal dominant polycystic kidney	Phase II	NCT03366337
		Advanced solid tumors lymphoid malignancies	Phase I	NCT00529438
			Phase I	NCT00508807
		Alport syndrome	Phase II/III	NCT03019185
		Pulmonary hypertension	Phase III	NCT03068130
		Connective Tissue Disease-Associated Pulmonary Arterial Hypertension	Phase III	NCT02657356
		Pulmonary Arterial Hypertension Pulmonary Hypertension Interstitial Lung Disease 9 more	Phase II	NCT02036970
		Covid19	Phase II	NCT04494646

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Table 1 (*continued*)

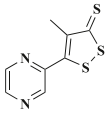
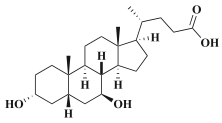
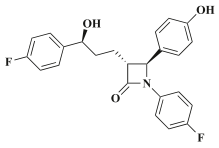
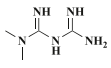
Compound	Type/Mechanism of action	Disease	Clinical trial	ClinicalTrials.gov identifier
Oltipraz	Organosulfur compound	Lung cancer	Phase I	NCT00006457
	Electrophilic modification of KEAP1-Cys-151	Non-Alcoholic Fatty Liver Disease	Phase III	NCT04142749
			Phase II	NCT01373554
			Phase III	NCT02068339
Ursodeoxycholic acid	secondary bile acid Electrophilic modification of KEAP1-Cys-151	Cholestasis	Phase II/III	NCT00846963
		Diarrhea	Phase IV	NCT02748616
		Cholelithiasis	Phase III	NCT02721862
		Primary biliary cirrhosis	Phase IV	NCT01510860
				NCT02937012
				NCT03665519
		Barrett oesophagus	Phase II	NCT01097304
		Low-grade dysplasia		
		Type 2 DM	Phase II	NCT02033876
			Phase II/III	NCT05902468
			Phase II/III	NCT05500937
			Phase IV	NCT04910178
		Obstructive Jaundice	Phase II	NCT01688375
		Primary Biliary Cholangitis	Phase IV	NCT04650243
			Observational	NCT03188146
		Polycystic Liver Disease	Phase II	NCT02021110
		Polycystic Kidney, Autosomal Dominant		
		End-Stage Kidney Disease	Phase IV	NCT02338635
		Parkinson Disease	Phase II	NCT03840005
			Phase I	NCT02967250
		COVID-19	Phase I/II	NCT05659654
			Observational	NCT05812612
		Acute Pancreatitis Due to Gallstones	Phase III	NCT04924868
		Short Bowel Syndrome	Phase IV	NCT01974336
		Non-alcoholic Fatty Liver Disease	–	NCT01548079
		Morbid Obesity	Phase II	NCT02244944
			Observational	NCT05256979
		Primary Sclerosing Cholangitis	Phase I	NCT01088607
		Cholecystolithiasis	Phase IV	NCT00161083
		Ulcerative Colitis	Phase II/III	NCT03724175
		Pouchitis		
		Rheumatoid Arthritis	Phase II	NCT05973370
		Liver Transplantation	Phase II	NCT01073202
		Ischemia-reperfusion Injury		
		Cholestasis		
		Colorectal Cancer	Phase II	NCT00062023
			Phase I	NCT00873275
		Gastric Cancer	Phase IV	NCT05410535
Ezetimibe	P62 phosphorylation	Non-alcoholic Steatohepatitis (NASH)	Phase IV	NCT01950884
		Endometrial Cancer	Phase I	NCT02767362
		Diabetes Mellitus, Type 2	Phase III	NCT04589351
		Diabetic Kidney Disease	Phase II	NCT00157482
			–	NCT00879710
			Phase IV	NCT05613400
			Phase IV	NCT04369664
			Phase III	NCT00551876
			–	NCT01424891
		Nonalcoholic Fatty Liver Disease (NAFLD)	Phase II	NCT02244944
			Phase IV	NCT03434613
		Acute Kidney Injury	Phase I	NCT02547402
		Stroke, Ischemic	Phase IV	NCT03993236
		Stable Angina	–	NCT00474123
		Prostate Cancer	Phase I	NCT02534376
		Kidney Disease, Chronic	Phase IV	NCT00125593
Metformin	Mixed, P62 phosphorylation	Breast cancer	–	NCT00984490
		Advanced protstate cancer	Phase II	NCT03137186
		Colon cancer	Phase II	NCT03359681
		Endometrial cancer stage I	Phase III	NCT04792749
		Huntington disease	Phase III	NCT04826692
		AD	Phase II/III	NCT04098666
		Ischemic reperfusion injury	Phase III	NCT05708053
		NAFLD	Phase III	NCT05521633

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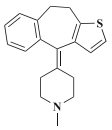
Table 1 (*continued*)

Compound	Type/Mechanism of action	Disease	Clinical trial	ClinicalTrials.gov identifier
Pizotifen 	Neh1 binding	Breast neoplasm Prostate cancer	Phase II Phase I	NCT02970682 NCT02055716 NCT01948362
Cetuximab (Monoclonal antibody)	p38 MAPK pathway activation	996 active clinical trials		

from clinical trials in Friedreich's ataxia patients [363–365], omaveloxolone (Skyclarys™) was approved for clinical use by the US FDA as the first and only drug for Friedreich's ataxia in February 2023 [366].

It is noteworthy that, although covalently modifying cysteine sensors in KEAP1, electrophilic NRF2 inducers do not disrupt the KEAP1-NRF2 protein-protein interactions. Using a quantitative Förster resonance energy transfer-based system combined with multiphoton fluorescence lifetime imaging microscopy of single live cells co-expressing KEAP1-mCherry and EGFP-NRF2 fusion proteins, it was shown that electrophilic NRF2 inducers, such as sulforaphane, disrupt the cycle of KEAP1-mediated NRF2 degradation by causing accumulation of the KEAP1-NRF2 complex, without release of NRF2 [367]. Consequently, free KEAP1 is not regenerated, and newly synthesized NRF2 is stabilized. Of note, the effect of sulforaphane on the KEAP1-NRF2 complex was not observed in cells co-expressing EGFP-NRF2 and C151S mutant KEAP1-mCherry, confirming that C151 is the primary target of sulforaphane.

The conclusion that electrophilic NRF2 inducers do not disrupt the KEAP1-NRF2 protein-protein interactions is further supported by biochemical experiments using titration nuclear magnetic resonance (NMR) spectroscopy with recombinant full-length KEAP1-6xHis protein and recombinant isotope-labelled Neh2 domain of NRF2 (6xHis-GST-$^{13}C^{15}N$ Neh2) [368]. In this setting, upon binding to KEAP1, the NMR signals corresponding to the intrinsically disordered Neh2 domain of NRF2 display line broadening. Conversely, upon release from KEAP1, the NMR signals corresponding to the Neh2 domain of NRF2 recovered. No recovery of the NMR signals was observed upon addition of electrophilic NRF2 inducers (sulforaphane, CDDO-Im and 15-deoxy-delta^{12,14}-prostaglandin J_2) to the protein complex, indicating that electrophiles do not dissociate the KEAP1-Neh2 interaction. This is in contrast with non-covalent KEAP1-NRF2 inhibitors (discussed in the next section), which have been shown to dissociate the protein complex both *in vitro* and in cells [368].

Recently, the crystal structure of the BTB and 3-box domains of human KEAP1 in complex with the CUL3 N-terminal domain was assessed, revealing a heterotetrameric assembly with a stoichiometry of 2:2 [369]. The same study showed that, although it lowers the affinity of the KEAP1-CUL3 interaction, CDDO does not disrupt the KEAP1-CUL3 protein complex. This result agrees with earlier studies in single live cells using a quantitative fluorescence recovery after photobleaching (FRAP)-based system with ectopically co-expressed KEAP1-EGFP and mCherry-CUL3 fusion proteins, where neither CDDO nor sulforaphane caused dissociation of the KEAP1-CUL3 protein complex [370].

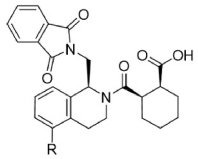
4.2. Non-covalent KEAP1-NRF2 inhibitors for NRF2 activation

Non-covalent KEAP1-NRF2 inhibitors target the KEAP Kelch domain and inhibit the KEAP1-NRF2 protein-protein interaction by displacing NRF2 either fully or partly. This prevents NRF2 ubiquitination and proteasomal degradation and hence induces NRF2 nuclear translocation and expression of NRF2-controlled genes [368]. Due to their non-covalent binding mechanism, such compounds generally have fewer off-target effects as compared to the electrophilic NRF2 activators, which react with cysteine residues of various proteins leading to side effects and uncertainties about the mode-of-action [218,220,371] Thus, the higher selectivity of non-covalent KEAP1-NRF2 inhibitors makes them attractive as chemical probes for investigating the biology of KEAP1 and NRF2 and as future drugs for diseases involving oxidative stress and inflammation. However, so far, no such compounds have entered clinical trials. A key challenge preventing this translocation is the binding pocket of the KEAP1 Kelch domain itself, which is relatively large and polar, with three centrally placed arginine residues important for binding to NRF2 [372]. As a result, most high-affinity KEAP1-NRF2 inhibitors contain one or more carboxylic acids and are relatively large to fit the pocket. Accordingly, many KEAP1-NRF2 inhibitors having high affinity to the KEAP1 Kelch domain also show issues with low membrane permeability, metabolic stability, oral bioavailability, or CNS permeability [372,373]. However, the KEAP1 drug discovery field has lately experienced a remarkable rise in promising compounds combining high affinity with drug-like physical properties and activity in various animal disease models, as detailed in recent reviews [371,374–376]. Here, we will provide an overview of this development and describe some of the most promising non-covalent KEAP1-NRF2 inhibitors. The structures and affinities of the highlighted compounds are shown in Table 2.

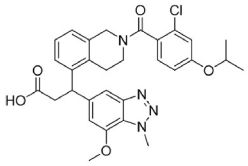
The first non-covalent KEAP1-NRF2 inhibitors - the tetrahydroisoquinoline (THIQ) compound **1** (also known as LH601A) and the 1,4-diaminonaphthalene compound **2** - were found by high-throughput screening (HTS) in 2013 [377,378] (see Table 2). The compounds showed modest affinities in the fluorescence polarization (FP) competition assay but gave rise to extensive drug discovery efforts from both academia and industry. Compound **1** was active in a reporter cell assay, induced NRF2 nuclear translocation, and upregulated NRF2 target genes and proteins at micromolar concentrations [377,379]. A structure-activity relationship (SAR) study led to some improvements in affinity, however, it was discovered that **1** is a P-glycoprotein substrate hence preventing studying its CNS effects [380]. Further optimization focusing on creating new interactions with deeper located residues of the KEAP1 Kelch domain resulted in the glycol-substituted THIQ analogue compound **3** with a 4-fold higher affinity than **1** in a cell-free time-resolved fluorescence resonance energy transfer (TR-FRET) assay that similar to the FP assay measures competition between KEAP1 Kelch and an NRF2-peptide [381]. Biogen, who discovered compound **2**, developed the benzotriazole-substituted THIQ analogue, compound **4**, by scaffold hopping and virtual screening [382]. It showed very high affinity by surface plasmon resonance (SPR), good potency in an NRF2 nuclear translocation assay (EC_{50} = 0.36 μM), oral activity in rats (F = 20 %), and the ability to increase mRNA levels of NRF2-controlled genes in kidney. However, its CNS permeability was low in correlation with a high efflux ratio *in vitro*. The methylated analogue, compound **5**, displayed a 10-folder higher affinity and better cell potency, but unfortunately also 10-fold higher efflux ratio [382]. Recently, a series of benzotriazole-substituted THIQ analogues, e.g. compound **6**, were published in a Chinese patent application to show high affinity and sub-micromolar cellular potency [383]. Also, C4X Discovery revealed >200 THIQ compounds, such as **7**, with nanomolar inhibitory activity by FP and cell assay potency [384,385]. Interestingly, this was followed

Table 2
Non-covalent KEAP1-NRF2 inhibitors.

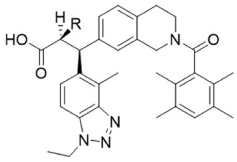
THIQs



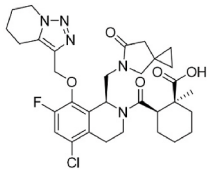
1 (R═H; IC_{50} = 2.3 μM, FP)
3 (R═$O(CH_2)_2OH$; IC_{50} = 183 nM (TR-FRET)



6
IC_{50} = 17 nM (FP)

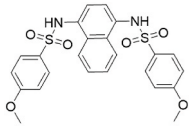


4 (R═H; K_d = 0.7 nM, SPR)
5 (R=CH_3; K_d = 0.07 nM, SPR)

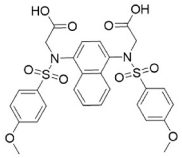


7
IC_{50} = 3.6 nM (FP)

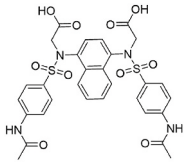
1,4-diaminonaphthalene-derived



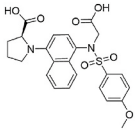
2
IC_{50} = 1.46 μM (FP)



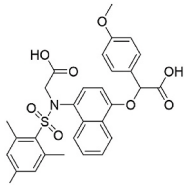
8
IC_{50} = 28.6 nM (FP)



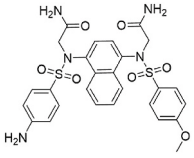
9
IC_{50} = 14.4 nM (FP)



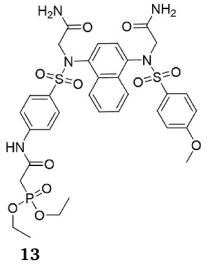
10
IC_{50} = 43 nM (FP)



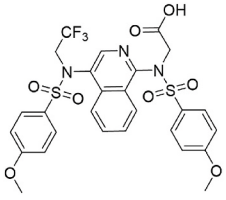
11
IC_{50} = 75 nM (FP)



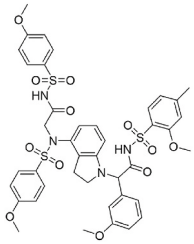
12
IC_{50} = 95 nM (FP)



13
IC_{50} = 940 nM (FP)

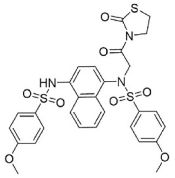


14
IC_{50} = 73 nM (FP)



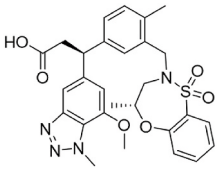
15
IC_{50} = 22 nM (FP)

Fragment-derived, macrocycles, α-fluoramide

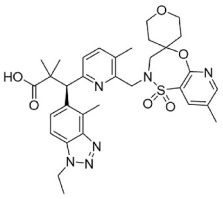


16
IC_{50} = 97 nM (FP)
(after prodrug release)

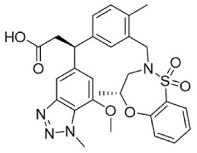
Table 2 (*continued*)



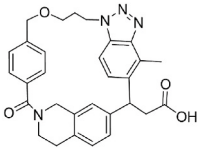
17
K_d = 1.3 nM (ITC)



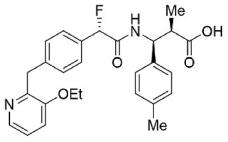
18
K_d < 1 nM (TSA)



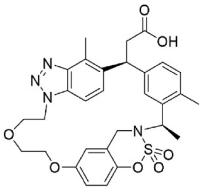
19
IC_{50} = 47 nM (TSA)



20
100 % inh.@100 nM (TR-FRET)



21
K_d = 4.15 (SPR)



22
K_d = 2.9 nM (SPR)

up with a series of equally active compounds, where the carboxylic acid was replaced by an amide [385].

The 1,4-diaminonaphthalene scaffold has been subject to extensive SAR studies over the years [371,374–376]. First, two aliphatic carboxylic acid chains were attached to the sulphonamides of **2** to engage with the key arginine residues leading to compound **8** (CPUY192002) with nanomolar inhibitory activity in FP [386]. Jain et al. discovered that the two carboxylic acids could be replaced with amides with only a 2-fold impairment in affinity by FP [387]. Another optimization study focusing on improving solubility and drug-like properties of **8** provided the *p*-acetamido compound **9** (CPUY192018) with high inhibitory activity by FP and improved solubility [388]. In cells, **9** induced the expression of NRF2-controlled proteins at low micromolar concentrations and a reduction of pro-inflammatory cytokines was observed in cells as well as in mice treated with LPS [388,389]. Compound **9** has shown effects in various inflammatory disease models, such as ulcerative colitis [389], chronic kidney inflammation [390], retinal ischemia-reperfusion injury [391], and COPD [392] making it one of the most studied non-covalent KEAP1-NRF2 inhibitors.

Lately, several asymmetric 1,4-diaminonaphthalene analogues with high affinity to KEAP1, promising cellular potency, good pharmacokinetic properties, and activity in animal models have been developed. The proline derivative **10** was shown by cellular thermal shift assay to engage with KEAP1 in cells, activated several NRF2-controlled cytoprotective and anti-inflammatory genes *in vitro* and *in vivo*, and relieved acetaminophen-induced hepatotoxicity in mice [393]. Also, the 2-oxy-2-phenylacetic acid substituted naphthalene sulphonamide compound **11** reduced oxidative stress and inflammation markers in a macrophage cell line and in the serum of mice treated with LPS [394]. The first CNS active non-covalent KEAP1-NRF2 inhibitor, the aniline-derivative **12** (NXPZ-2), was reported by Sun et al. to induce NRF2 activity in an AD mouse model, improve learning and memory functions, and lead to reduction in p-Tau and $A\beta_{1\text{-}42}$ serum levels [395]. Follow-up studies exploiting the amino group as a chemical handle for further derivatization have led to more soluble compounds active in animal models of lung inflammation [396,397], and an oral active phosphodiester analogue (**13**) with activity in a transgenic AD mouse model [398].

To improve the metabolic stability, nitrogen-containing heterocycles have been explored as substitutes for the naphthalene core. The 1,4-isoquinoline scaffold provided high-affinity and metabolically more stable compounds [399], and the mono-acidic fluoroalkylated analogue **14** also showed good cellular activity and hepatoprotective effects in acetaminophen-treated mice [400,401]. Replacing the naphthalene with indoline and the diacetate moieties with acyl sulfonamides gave the non-charged compound **15**. Despite its size and complexity, this high-affinity compound showed antioxidant and cardioprotective effects in both cell and animal LPS-mediated heart injury models and good drug metabolism and pharmacokinetic (DMPK) properties [402]. Finally, in an alternative approach to enhance DMPK properties of the 1,4-diaminonaphthalene series, an ingenious prodrug strategy was applied by coupling a thiazolidinone moiety to the carboxylic acid, as in **16**, thereby masking its negative charge and improving the permeability properties [403]. The thiazolidinone prodrug moiety of **16** is cleaved by H_2O_2, hence it is supposed to release the active compound only at sites undergoing oxidative stress. The principle was demonstrated in macrophages and liver cells stimulated to produce H_2O_2 and in LPS-induced mice, while the compound showed high metabolic stability in gastric fluid, intestinal fluid, rat plasma, and microsomes [403].

Some potent and promising KEAP1-NRF2 inhibitors have been developed by fragment-based drug discovery. An X-ray crystallographic screening of 330 fragments identified phenylpropanoic acid as a hit, which was optimized by fragment-growing to occupy adjacent subpockets leading to the high-affinity compound **17** (KI-696) [404,405]. This compound potently induced NRF2 in a normal human bronchial epithelial cells and bronchial epithelial cells from COPD patients, while only minor activities were seen in a target panel of toxicity liabilities. Oral bioavailability was low in rats (F = 7 %), hence expression of NRF2-controlled genes in lungs, restoration of GSH levels, and reduction in ozone-mediated inflammation was demonstrated using slow intravenous infusion of compound **17**. Subsequently, different fragment-based drug discovery approaches have led to other high-affinity KEAP1-NRF2 inhibitors, but with a varied degree of cell potency illustrating the importance of careful optimizing physicochemical properties like topological polar surface area and $LogD_{7.4}$ to obtain good membrane permeability and cell activity [373,406–408]. Recently, several interesting analogues of compound **17** showing low nanomolar affinities and cellular potencies have been presented in patent applications by Janssen Pharmaceuticals (**18**) [409], Senju Pharmaceutical Co., Ltd [410], and Ube Industries, Ltd. [411]. Noticeably, Ube Industries with academic collaborators demonstrated remarkable effects of compound **19** (UBE-1099) in mice with Alport syndrome, such as reduced glomerulosclerosis, renal tissue inflammation, fibrosis, and prolonged life span [412].

Macrocycle compounds sometimes show enhanced affinity, selectivity, membrane permeability, and metabolic stability as a function of their increased rigidity. *In silico* screening of natural products followed by structure-based drug design led to high-affinity KEAP1-NRF2 macrocycle inhibitors, but it was not possible to also obtain good cellular activity [413,414]. In contrast, both Sanofi and Scohia Pharma have presented highly potent macrocycle analogues of Biogen's THIQ compound (**4**) [415,416], and Scohia's compound **20** markedly increased NQO1 mRNA levels in rat kidney and liver after a 3 mg/kg oral administration indicating its promise as a lead molecule for chronic kidney diseases and fatty liver diseases. Finally, Servier convincingly demonstrated that their compound **21** (S217879) has highly promising anti-NASH activities, including antioxidant effects and the ability to reduce steatosis, inflammation, and fibrosis in cells as well as in two mouse models of NASH [417]. Compound **21** showed good oral absorption, but a relatively low half-life (30–40 min). Still, NQO1 was upregulated in liver 24 h after dosing. Overall, the Servier study demonstrates that KEAP1 is a promising target for NASH; a conclusion supported by recent findings of **21** showing anti-steatotic effects, lowering of DNA damage, apoptosis and inflammation, and inhibition of fibrogenesis in liver tissue from patients with varying degree of NASH [418]. Other studies have also shown effect in NASH models using different types of KEAP1-targeting compounds [419–421].

Recently, SPR-based HTS campaign identified a novel series of potent and biologically active KEAP1-NRF2 inhibitors with a centrally placed α-fluoramide moiety important for interacting with the KEAP1 Kelch domain [422]. Optimization greatly improved DMPK properties and compound **22** showed high oral bioavailability (F = 42 %) and 5-fold increased kidney expression of HO-1 following a low oral dose (0.3–3 mg/kg) in rats [423].

In summary, despite KEAP1 being a challenging drug target, several non-covalent KEAP1-NRF2 inhibitors now exist that combine high affinity, cell activity, selectivity, acceptable DMPK properties, and *in vivo* activity. These demonstrate that it is possible to obtain high cell permeability and oral activity, even if including a carboxylic acid. Alternatively, neutral compounds, designed by bioisosteric replacement or prodrug strategies, have shown great promise. Overall, the field of non-covalent KEAP1-NRF2 inhibitors seems to be ready to take the next steps towards drug development.

4.3. Drug targets other than KEAP1 for NRF2 activation

4.3.1. GSK-3 and β-TrCP pathway

Given the significant involvement of aberrant GSK-3 activity in various pathologies, including AD, cancer, and CVDs [424], there is a promising opportunity for drugs targeting GSK-3 [425]. However, although several GSK-3 inhibitors have been used in clinical trials, their effect on NRF2 activation has been studied so far only in preclinical studies, summarized below.

Lithium, traditionally used in bipolar disorder treatment, is a classical GSK-3 inhibitor targeting both α and β isoforms, and it is traditionally used in bipolar disorder treatment [426,427]. It exerts its effects either by directly binding to Mg^{2+} or by causing inhibitory phosphorylation of the kinase. In a mouse model of kainate-induced excitotoxic neuron death, it was reported for the first time that the hippocampus of these mice exhibited a long-term activation of GSK-3 leading to reduced nuclear levels of NRF2 [428]. Lithium promoted NRF2 transcriptional activity and had a synergistic effect with sulforaphane. In other preclinical studies of streptozotocin-elicited diabetes [429], depression [399], AD [430], acute kidney injury [431], hepatitis C [432], and spinal cord injury [433], lithium exerted its protective effect at least in part though the activation of NRF2. Other GSK-3 inhibitors upregulate NRF2 in multiple preclinical settings, including tideglusib [434–436], enzastaurin [437] nordihydroguaiaretic acid and its derivative terameprocol [438,439], and SB216763 [440]. However, none of the ongoing clinical trials include the analysis of NRF2 activity. Novel GSK-3 inhibitors are currently at the *in vitro* validation stage of development, showing promising potential for further exploration [436].

The inhibitors of β-TrCP may also activate NRF2. Two small molecule inhibitors, erioflorin, isolated from *Eriophyllum lanatum* [441], and GS143, have been described [442,443], but their effect on NRF2 stability has not been analyzed. More recently a non-covalent NRF2/β-TrCP interaction inhibitor, termed PHAR, has been reported [25,444]. This small molecule was identified by *in silico* screening of over one million molecules from several chemical libraries presented toward the crystal structure of the WD40 propeller of β-TrCP [445]. PHAR inhibits β-TrCP-mediated ubiquitylation of NRF2 *in vitro* and disrupts the NRF2/β-TrCP interaction, increasing NRF2 levels in cell culture. The compound protected the liver against LPS-induced acute inflammation [445] and prevented the progression of NASH in a murine model [444]. Compared to KEAP1 targeting, pharmacological inhibition of the GSK-3/β-TrCP results in a much weaker induction of NRF2. This may have the advantage of maintaining NRF2 levels close to the physiological activity during prolonged treatment in chronic diseases.

4.3.2. Cullin 3 neddylation

Neddylation of Cullin 3 is important for proper functioning of the E3 ligase complex [446]. It is a posttranslational modification, in which ubiquitin-like protein NEDD8 is conjugated to target proteins destined for degradation [447]. Neddylation of Cullin 3 activates the Cullin-RING E3 ligase (CRL) and increases the ligase activity in CUL3-KEAP1 E3 complex, leading to increased ubiquitination of NRF2 [448]. Consequently, inhibition of the cullin neddylation pathway by inhibiting a NEDD8-activating enzyme E1 (NAE1) or DCN1 scaffold protein by small molecule inhibitors results in potent activation of NRF2 [449,450].

4.3.3. Pharmacological inhibition of HRD1

Loss of the NRF2-mediated cellular protection through HRD1-mediated ubiquitylation and subsequent proteasomal degradation of NRF2 may be crucial in determining liver disease outcome. The HRD1 inhibitor LS-102, was tested for its ability to alleviate liver cirrhosis in NRF2 deficient and wildtype mice. In wildtype mice, CCl4 increased XBP1s and HRD1 protein levels while decreasing NRF2 protein levels. Interestingly, LS-102 suppressed down-regulation of NRF2 induced by CCl4 treatment, restored alanine aminotransferase, malonyl dialdehyde (MDA) and 8-hydroxydeoxyguanosine levels as well as normal liver morphology, apoptotic cell death, and collagen deposition only in NRF2 wildtype mice [26].

4.4. Inhibitors of NRF2

Mutually exclusive gain-of-function mutations in NRF2 and loss-of-function mutations in KEAP1 as well as epigenetic and post-transcriptional modifications lead to constitutive activation of NRF2 signaling [17,451]. Such hyperactive signaling can provide a powerful selective advantage for tumors by rewiring metabolism to enhance proliferation, suppress oxidative and other stresses, alter cell death pathways and promote immune evasion [452,453]. The functional importance of NRF2 signaling as a "master regulator" of cell survival highlights the appeal of developing molecules to inhibit its actions in cancer.

Targeting transcription factors with pharmacological agents to inhibit their actions has been a tough nut to crack [454]. Most transcription factors, including NRF2, do not exhibit well-defined ligand--binding pockets (e.g., as do steroid receptors). They mainly act on protein-protein and protein-DNA interactions, which usually encompass large and flat interfaces that are difficult to target with small molecules. Small molecules typically work best as inhibitors when tightly occupying a pocket, often an enzymatic active site, on a protein. Such occupancy-driven pharmacology requires high drug levels, which often increases off-target binding and side effects. Other possible approaches to targeting NRF2 such as proteolysis-targeting chimaera (PROTAC), post-translational modification and NRF2-DNA interactions are in their earliest stages. Several clinical trials, however, have sought to exploit an alternative strategy - the metabolic vulnerabilities of KEAP1 or NRF2 mutant tumors [446,451].

To date, the screening platforms used for discovery of small molecule inhibitors of NRF2 have employed cellular systems for measuring alterations in transcriptional responses by qPCR of target genes and luciferase reporter assays. Such transcription activity-based phenotypic platforms tend to show high off-target rates and need confirmation of mechanisms of action for hit compounds.

The earliest NRF2 inhibitor described, brusatol, was identified by Zhang and colleagues in a natural product screen using MDA-MB-231-ARE-luc reporter cells [455] (Table 3). Brusatol is a triterpene lactone isolated from seeds of *Brucea javanica* (L.) Merr, a medicinal herb used in China for prevention of cancer and malaria [456]. Nanomolar concentrations evoked a dose-dependent reduction in NRF2 protein levels in multiple tumor cell lines without any effect on KEAP1 levels, thereby providing an initial inference of some level of specificity. Brusatol demonstrates activity *in vivo* in xenograft lung models [455] and an orthotopic colorectal mouse model [457] as well as attenuates the progression of tumor growth in genetic and chemical carcinogen models of lung cancer [458]. Mechanistic studies have subsequently revealed that the mode of action is not through direct inhibition of the NRF2 pathway, but as a general inhibitor of protein translation that broadly affects proteins with short half-life including NRF2 [459].

Using a chemical library screen based upon inhibition of NRF2 transcriptional activity in A549-ARE-luc cells Tsuchida et al. identified febrifugine and a synthetic halogenated derivative, halofuginone, as NRF2 inhibitors [460]. Febrifugine is a natural quinazolinone alkaloid found in the Chinese herb *Dichroa febrifuga*. Halofuginone has therapeutic activity against several cancer cell lines, although the clinical evaluation of the molecule in this context is quite limited. Halofuginone treatment of NRF2-addicted cancer cells, such as lung cancer-derived A549 cells or oesophagus cancer-derived KYSE70 cells, attenuates proliferation *in vitro*. In xenograft models, co-treatment with halofuginone enhances the anti-tumor effects of cisplatin against KYSE70 cells [460] and gemcitabine in KPC (Kras and P53 mutant) pancreatic cells [461]. Preclinical studies in mice have indicated dose-limiting toxicities of severe hematopoietic and immune cell suppression. To overcome this systemic toxicity, Panda et al. encapsulated halofuginone in polymeric micelles that released the drug in a slow and sustained manner. Suppressed growth of an NRF2 hyperactive lung adenocarcinoma was observed [462]. While halofuginone exerts multiple effects on cells, the inhibitory actions on NRF2 appear related to decreased NRF2 protein synthesis by inhibiting prolyl-tRNA synthetase; an inhibition that is rescued by the addition of proline [462]. NRF2 and other short half-life proteins are especially sensitive to such interventions. Thus,

Table 3
Features of representative NRF2 inhibitors.

Compound	Mechanism of action	Disease targets	Patents
Brusatol	General inhibitor of protein translation	Combination chemotherapy for cancer treatment	CN102106851A
Halofuginone	Decreased NRF2 synthesis through inhibition of t-prolyl-RNA synthetase	Cancer, neurological diseases, stroke, inflammation, autism, malaria, …	WO2018200608A1
IM3829: 4-(2-Cyclohexylethoxy)aniline	Inhibits ionizing radiation-induced nuclear translocation of NRF2	Increasing the radiosensitivity of lung cancer cells	KR20130079898A
Triptolide	Promotes interaction between NRF2 and CRM1 to enhance nuclear export	Suppresses growth of tumor xenografts in mice	–
ML385: N-[4-[2,3-Dihydro-1-(2-methylbenzoyl)-1H-indol-5-yl]-5-methyl-2-thiazolyl]-1,3-benzodioxole-5-acetamide	Interferes with sMAF-NRF2 complex formation; inhibition of mTOR signaling	Targeting NSCLC cells with KEAP1 mutations with combination chemotherapy; combination with cisplatin	CN111568923A
AEM1: ARE Expression Modulator 1	Unclear; broadly decreases NRF2-driven gene expression	Sensitizing cells with constitutively active NRF2 signaling to chemotherapeutic agents	–
Stigmasterol	Represses NRF2 protein levels, possibly by binding to NRF2 and decreasing transcriptional activity	Sensitization of cancer cells to cisplatin chemotherapy	–

halofuginone, like brusatol, is not a specific inhibitor of NRF2.

Liby, Odom and colleagues have recently described MSU38225 (2-[(3,5-dimethylphenyl)amino]-6-methyl-5-phenyl-3-pyridinecarbonitrile) as a NRF2 inhibitor with a distinctive, although not fully reconciled mode of action [463,464]. Also discovered with an ARE-luciferase cell line screen, MSU38255 decreases the expression of multiple downstream target genes. Protein levels of NRF2 decline, much less rapidly than seen with the global protein translation inhibitor brusatol, in a manner that can be blocked by the proteasome inhibitor MG132. The overall expression pattern of abundant cellular proteins was not changed. Intriguingly, NRF2 degradation by MSU38225 was independent of KEAP1 and β-TrCP, the two major drivers of NRF2 degradation. Isobologram analysis indicated additive activity with doxorubicin and topotecan, but synergy with carboplatin and 5-fluorourocil in NRF2-addicted A549 cells in culture. The combination of carboplatin and MSU38225 exhibited significantly enhanced efficacy in inhibiting tumor growth in A549 tumor xenografts compared to carboplatin alone. MSU38225 is a first-in-class inhibitor amenable to structure-activity studies to improve its poor solubility and probe its mode of action. The molecule is quite sensitive to small chemical changes around its core, producing some compounds that can be activators rather than inhibitors [464]. It appears to be a fertile scaffold for further optimization.

By contrast, several other classes of molecules identified by ARE-luciferase screens as inhibitors of NRF2 pathway signaling have a limited horizon for development at present. These include AEM1 (ARE Expression Modulator 1) [465], stigmasterol [466], multiple flavonoids including luteolin, trigonelline, and chrysin [467] as well as other natural products [468]. Limited information on mechanisms of action, limited potency and likely lack of specificity will impede the movement of these agents towards clinical utility.

Several inhibitory molecules alter the interaction of NRF2 with other proteins. Unlike brusatol, halofuginone and MSU38225, triptolide (a diterpenoid epoxide from *Tripteryglum wilfordii*) does not affect cellular levels of NRF2 whilst inhibiting the expression of NRF2 target genes [469]. Rather triptolide promotes the interaction between NRF2 and CRM1 to enhance the nuclear export of NRF2, potentially through a NES in the Neh2 domain of NRF2, to thereby reduce transcriptional activity. Triptolide inhibits the growth of A549 xenografts in nude mice. Triptolide exhibits selective cytotoxicity to patient-derived *IDH1*-mutated glioma cells *in vitro* and *in vivo* through targeting the NRF2 driven GSH synthesis pathway [470]. Clinical use may be limited as it induced liver injury in an NRF2-dependent manner through recruitment and polarization of macrophages in an LPS-challenged murine model [471]. IM3829 (4-(2-Cyclohexylethoxy)aniline) blocked the nuclear accumulation of NRF2 in H1299 human lung cancer cells and subsequent sensitivity to ionizing radiation [472]. ML385, identified from a large library screen from NCATS (National Center for Advancing Translational Science) in A549-ARE-luciferase reporter cells also inhibits downstream NRF2 target gene expression [473]. ML385 binds to the Neh1 domain of NRF2 and interferes with sMAF complex formation, thereby blocking the inception of transcription. Initial characterization of ML385 indicated the potentiation of the toxicity of platinum-based drugs, doxorubicin and taxol with specificity for NSCLC cells harboring a KEAP1 mutation. A combination chemotherapy study with carboplatin showed significant antitumor activity in an A549 orthotopic lung tumor model. ML385 has been used now as a NRF2 inhibitor in many cell culture and animal model studies, but the progression to clinical trials is not evident. Lastly, Modi et al. [474] have recently described a “stapled peptide” N1S as a direct cell-permeable inhibitor of NRF2-sMAF heterodimerization as a promising lead for the sensitization of NRF2-addicted cancers.

PROTAC has become a promising therapeutic strategy for treating diseases caused by overexpression or accumulation of proteins [475]. A PROTAC cassette consists of a small molecule that binds to the protein of interest, a ligand of an E3 ubiquitin ligase and a linker region that covalently connects the two ligands. The PROTAC then recruits E3 to facilitate proximity-induced ubiquitination of the target and its subsequent degradation by the 26S proteasome. The KEAP1 E3 ligase has been harnessed for targeted protein degradation [476–478]. Recently, ARE-based proteolysis-targeting chimeras (ARE-PROTACs) were constructed, targeting NRF2 using the ARE sequence as the ligand. Intriguingly, this led to a degradation of the NRF2-MAFG dimer and sensitization of NSCLC cells to ferroptosis [479].

New technologies such as cryogenic electron microscopy and machine-learning algorithms to interrogate protein structures at high resolution will illuminate the fine structure of transcription factors to facilitate the design of drugs that target them [454]. Direct interaction-based screening tools need to be adopted and coupled with functional assays for modulation of transcription factor activities. Lastly, potential crosstalk between NRF2 and other signaling pathways needs to be better defined to a level of cell-type specificity [452] to identify possible enhanced or untoward outcomes. Collectively, these tools will define the best candidates for specific (on-target) and effective drug candidates, features lacking in the small armamentarium of current NRF2 inhibitors.

4.5. Repurposing drugs to modulate NRF2 activity

4.5.1. Repurposing NRF2 activators

Despite novel advances in HTS, improvements in the reproducibility of *in vivo* models and increased understanding of the mechanism of disease, the number of approved novel drugs is much lower than expected [480]. The complexity and chronicity of many non-communicable diseases as well as strict regulation increases the time and cost of drug development. Drug repurposing has therefore become an alternative approach to bring effective treatments to the clinic by finding new uses and applications for already approved or investigational drugs in phase II or III clinical trials. Drug repurposing offers several advantages compared to the development of new drugs, especially a highly reduced risk of failure, as repurposed drugs have already completed toxicology and safety assessments. Another major advantage is time saving, as many steps in the drug development process have already been completed. As a result of these, the cost of development is significantly lower greatly facilitating the finding of effective drugs for unmet needs [481].

One of the earliest repurposed NRF2 activators is oltipraz, a member of the dithiolethione family used as an antischistosomal drug [482]. In 1987, Kensler *et* al., reported a protective effect of oltipraz against aflatoxin tumorigenicity as it was able to reduce 90 % of the tumor volume in liver. This effect was associated with the activation of the phase II antioxidant response and the specific activity of GST [483]. Further experimental reports have demonstrated its capacity to inhibit chemically induced carcinogenesis in bladder, stomach, colon, skin, and breast cancer models [484]. These results prompted its clinical evaluation in lung cancer (NCT00006457), non-alcoholic fatty liver disease (NCT04142749, NCT01373554, NCT02068339), and liver cirrhosis (NCT00956098).

Among natural compounds, UDCA, a secondary bile acid produced in the liver, was initially approved for the treatment of gallstone disease (1987) and primary biliary cholangitis (1996). It was described as an NRF2 inducer by Okada et al. [485], and has a capacity to improve mitochondrial dysfunction in a PD model, reestablishing membrane potential and recovering ATP levels [486]. Further evaluation has shown a potent neuroprotective effect against PD associated toxicity [487–489]. These results encouraged its clinical evaluation as a potential PD disease modifying drug in a small open-label prospective, multiple-ascending dose study [490] that demonstrated safety and a modest increase in ATP levels (NCT02967250) [491], although behavioral tests were not conclusive. UDCA has also been evaluated in several clinical trials of non-communicable diseases including T2D (NCT02033876), end-stage kidney disease (NCT02338635), ulcerative colitis (NCT03724175), rheumatoid arthritis (NCT05973370),

colorectal cancer (NCT01073202) and gastric cancer (NCT05410535), Huntington's disease (NCT00514774), and Barrett's oesophagus, a low-grade dysplasia (NCT01097304).

Ezetimibe (Zetia) was initially approved (2002) for the treatment of primary hyperlipidemia *via* sterol transporter Niemann-Pick C1-like 1 inhibition. It selectively inhibits cholesterol and phytosterol absorption in the small intestine, reducing its delivery to the liver, reduces hepatic cholesterol stores and activates cholesterol clearance from blood [492]. In 2016, Lee et al. evaluated the potential protective effect of ezetimibe in a NASH model and demonstrated that ezetimibe protected mice from NASH *via* NRF2. Ezetimibe activates AMPK that, in turn, phosphorylates p62 at S351 to potentiate KEAP1 interaction and its autophagosomal degradation resulting in NRF2 accumulation and phase II antioxidant response activation [493]. Clinical trials have been initiated to treat NASH (NCT01950884, NCT02244944), T2D (NCT04589351), acute kidney injury (NCT02547402), chronic kidney disease (NCT00125593), ischemic stroke (NCT03993236), endometrial (NCT02767362) and prostate cancers (NCT02534376), among others.

Metformin, orally used as a treatment for T2D, is also used to treat insulin resistance in polycystic ovary syndrome. It has been proposed to affect mitochondrial respiration *via* complex I [494] or complex IV inhibition [495]. Metformin activates AMPK evoking the phase II antioxidant response [496,497]. It also exerts potent anti-inflammatory responses, as demonstrated in cerebral ischemia models [498]. Conversely, metformin inhibits NRF2 expression and mRNA levels *via* Raf-ERK inhibition [499]. Its pleiotropic beneficial activities have encouraged several repurposing studies towards different non-communicable diseases [500], including breast cancer (NCT00984490), advanced prostate cancer (NCT03137186), colon cancer (NCT03359681), and endometrial cancer stage I (NCT04792749). Its effectiveness is also studied in Huntington's disease (NCT04826692), AD (NCT04098666), ischemic reperfusion injury (NCT05708053), and non-alcoholic fatty liver disease (NCT05521633), among many others.

4.5.2. Repurposing NRF2 inhibitors

Given the adverse effects of high NRF2 activity in many tumors, repurposing drugs for NRF2 inhibition is also of interest. Several approved drugs have been reported to act as NRF2 inhibitors and therefore candidates for repurposing. Clobetasol propionate, a corticosteroid approved for moderate to severe plaque psoriasis treatment and inflammatory pruritic manifestations of dermatoses, reduces nuclear localization of NRF2 and increases β-TrCP-dependent NRF2 degradation in NSCLC cell lines [501]. Currently, it is in clinical evaluation in refractory metastatic colorectal cancer (NCT02368886).

Pizotifen, a serotonin and tryptamine receptors antagonist used for migraine prophylaxis, has also recently been described as a NRF2 inhibitor for the treatment of oesophageal squamous cell carcinoma [502]. Its mechanism of action was associated with its ability to bind to the Neh1 domain of NRF2 blocking its binding to the ARE sequences.

Cetuximab is a recombinant chimeric monoclonal antibody towards the epidermal growth factor receptor (EGFR) thereby inhibiting EGF binding, and it is approved for the treatment of head and neck cancer and metastatic colorectal cancer. Cetuximab enhances the efficacy of the ferroptosis inducer RSL3 by inhibiting the NRF2/HO-1 axis [503]. This inhibition leads to increased lipid peroxide accumulation and heightened ferroptosis in KRAS mutant colorectal cancer cells. Mechanistically, the authors suggested that Cetuximab-induced p38 leads to suppression of NRF2 activity. However, the regulation of NRF2 by p38 may be indirect and contexxt dependent. Additionally, recent studies suggest that Cetuximab alone or conjugated with ribonuclease A, increases KEAP1 levels, further suppressing NRF2 activity [504]. Currently, there are 996 clinical studies on cetuximab, with a potential for further evaluation in other cancer types.

5. Biomarkers of NRF2 activation

5.1. Monitoring NRF2 activation in cancer

Given that NRF2 hyperactivity is prevalent in many cancers and associated with poor prognosis and therapy resistance, monitoring NRF2 activation in tumors has both prognostic as well as predictive significance. In NSCLC, head and neck and oesophageal cancers, somatic loss-of-function mutations of KEAP1 and gain-of-function mutations of *NFE2L2* are prevalent, and therefore sequencing of mutations from either tumor tissue [505,506] or cell free DNA from liquid biopsies [507] can be used to detect mutations resulting in aberrant NRF2 activation. Indeed, inactivating mutations in *KEAP1* have been associated with an aggressive NSCLC phenotype resistant to conventional chemotherapy [508,509], radiotherapy [510], EGFR kinase inhibition [511], PD-1 axis inhibitors [292,512] and most recently, KRASG12C inhibition [513]. However, using somatic mutations as markers of NRF2 activation has its limitations: the ambiguous functionality of rare variants, tumor heterogeneity, the tumor environment, and numerous other mechanisms of activation necessitate the use of alternative means to identify NRF2 overactive cancers. To this end, signatures based on transcriptomic data have been developed and used to identify NRF2 overactive tumors irrespective to the mechanism of activation [267,282,292,305,514–516]. While transcriptomic signatures can detect NRF2 activation with reasonable specificity and sensitivity, most of them are based on the expression of dozens of genes. This requires the use of high throughput transcriptomic analyses from tumor samples, which is often not practical for diagnostic use. However, the recently developed tissue-agnostic NRF2 activity score comprises of only 6 direct target genes, yet it robustly identifies NRF2 hyperactivity in tumors having functional *KEAP1* or *NFE2L2* mutations [305]. Intriguingly, there is an excellent correlation between mRNA and protein expression of these targets across cancers [517], indicating that they could be considered as universal markers of NRF2 activity.

In addition to using genomic data to infer NRF2 activity, protein expression data can be applied to identify NRF2 active cancers. For pathology, immunohistochemistry is a standard method used to localize and visualize biomarker protein expression, and it can be multiplexed allowing simultaneous detection of multiple markers on a single tissue slide. Immunohistochemical staining and quantification of NRF2 expression itself is problematic, given the issues regarding the specificity of anti-NRF2 antibodies [210]. Immunohistochemical detection of NQO1 is widely used as a marker of NRF2 activation; however, NQO1 is highly expressed in normal lung respiratory epithelium and endothelial cells, and the expression is variable within tumors and between patients [518,519]. This limits its use as a marker of aberrant NRF2 activity especially in lung cancer. However, there are other NRF2 targets that may be more suitable as markers of NRF2 activation. Many aldo-keto reductase family members (AKR1C1-3, AKR1B10) are highly NRF2-dependent and abundantly expressed in many cancers and are therefore promising biomarkers of NRF2 activity e.g. in NSCLC, kidney cancer and uterine leiomyomas [520–522]. Proteomic approaches may be used to further identify novel candidate biomarkers for NRF2 activity [517,523]. Finally, the NRF2-regulated cystine transporter xCT is a promising biomarker that can be assessed by [18F] FSPG PET imaging, which recently demonstrated to label $NRF2^{D29H}$ murine lung tumors and human patient-derived xenograft models readily [524].

5.2. Monitoring target engagement in clinical trials with NRF2 activators

Assessing the efficacy of NRF2 activators in clinical trials remains a challenge, given the limited accessibility of biological material from study subjects. In most cases, only blood (plasma and peripheral blood mononuclear cells, PBMCs) and urine are easily attainable, which restricts the repertoire of available markers to monitor target engagement. In most cases, NRF2 activation has been assessed using the analysis of

mRNA expression from PBMCs. In a phase I trial of bardoxolone methyl in patients with advanced solid tumors and lymphomas, increased NQO1 mRNA was assessed from PBMCs by qPCR 2 days and 22 days after the onset of treatment, in comparison to the baseline [525]. Transcriptional analysis of peripheral immune cells from a multiple sclerosis patients detected an increase in *NQO1* expression 4–6 weeks from the beginning of DMF therapy in a subset of patients, correlating with a favorable clinical outcome [526]. *NQO1* mRNA expression in PBMCs has also been used to monitor NRF2 activation in patients with autism spectrum disorder treated with sulforaphane [343]. Also, the mRNA expression of other NRF2-dependent genes such as *AKR1B10*, *AKR1C1*, *HMOX1*, *GCLC*, *CGLM*, *GPX1*, *UGT1* and various *GST* in PBMCs has been used as markers for NRF2 activity [343,526–528]. However, it is not known how well the expression of NRF2-dependent genes in cells derived from peripheral blood reflect the pathway activation in target tissues, nor is it well understood what factors affect interindividual variation in basal expression and inducibility of these genes. Also, the optimal combination of target genes is not well understood. Nevertheless, gene expression changes provide the most consistent, direct evidence of NRF2 activation, and this approach is likely to provide the best evidence for the activation of NRF2 for clinical trials.

6. Conclusions and future perspective

Since its discovery in the year 1994 [5], the role of NRF2 in combating stress in various disease pathologies has been well acknowledged. This is illustrated by the total number of papers on NRF2, which has increased exponentially over the years. While significant progress has been made in understanding its biology, several unresolved questions and challenges remain.

Under some circumstances NRF2 exhibits a dichotomous role that is incompletely understood. This is particularly evident in the case of cancer as discussed in this paper. Briefly, in early stages of chemically-induced carcinogenesis, NRF2 activation appears to be protective, probably because it favors biodegradation of the chemical mutagen. By contrast, in established cancers, somatic activating mutations of the NRF2 coding gene can promote tumor survival, progression, and resistance to therapy. The mechanisms underlying this dual role need to be more deeply understood in order to define the safety of strong activators of NRF2. It should be noted, however, that currently marketed NRF2 activators dimethyl fumarate and omaveloxolone do not seem to elicit a statistically significant increase in cancer risk.

It is important to note that these drugs present unwanted effects. For instance, some patients taking omaveloxolone exhibited hepatic effects, GI symptoms, headache, and fatigue among others [529]. Patients taking dimethyl fumarate also exhibited hepatic effects, GI symptoms, lymphopenia, and flushing [349]. However, the clinical trials with these drugs did not have a clear endpoint on the extent of NRF2 activation and they did not report the off-targets. These drugs, like most others reported in this paper, are electrophiles that can react with redox sensitive cysteines in many proteins. Further research is necessary to determine if the side effects are related to NRF2 activation or to the off-targets. Developing highly specific NRF2 activators remains a challenge that is now being addressed with the new generation of non-covalent disruptors of the NRF2/KEAP1 and NRF2/β-TrCP interaction.

While NRF2 activation is generally protective in age-related diseases, its efficacy diminishes with age. Mechanistically, it is unclear how, signaling pathways affecting stability, ARE-binders as BACH1, chromatin state, and epigenetic modifications modulate NRF2 dynamics. It seems that the short-term defensive NRF2 activation is progressively lost in some chronic diseases such as NASH [232,530]. The reasons for this decline and how to restore NRF2 function in aging tissues and in long-term chronic disease are unresolved but probably pharmacological intervention should focus on restoring NRF2 levels close to the physiological values, rather than eliciting a strong upregulation. Achieving the right balance between NRF2-defficieny and NRF2 activation is critical, particularly in chronic treatment.

Some other completely open questions include the role of NRF2 in infectious diseases, connecting host-pathogen interactions and the possible antimicrobial effects, for instance in Covid-19 [531]. Also, exciting new data connect NRF2 with the circadian clock probably connecting NRF2 stability with GSK-3 mediated phosphorylation [532]. Disruption of the circadian rhythms affect NRF2 activity.

Finally, a crucial issue that needs to be solved in the near future is to definitely find easily measurable and quantifiable biomarkers of NRF2 activity. This is crucial to define endpoints of NRF2 target engagement in patients, drug dosing and response, and monitor disease progression. Understanding the molecular mechanisms of NRF2 dependent gene regulation in more detail will ultimately provide a wealth of novel strategies for therapy.

CRediT authorship contribution statement

Antonio Cuadrado: Writing – review & editing, Writing – original draft, Visualization, Supervision, Conceptualization. **Eduardo Cazalla:** Writing – review & editing, Writing – original draft, Visualization. **Anders Bach:** Writing – review & editing, Writing – original draft. **Boushra Bathish:** Writing – review & editing. **Sharadha Dayalan Naidu:** Writing – review & editing. **Gina M. DeNicola:** Writing – review & editing, Writing – original draft. **Albena T. Dinkova-Kostova:** Writing – review & editing, Writing – original draft. **Raquel Fernández-Ginés:** Writing – review & editing. **Anna Grochot-Przeczek:** Writing – review & editing, Writing – original draft. **John D. Hayes:** Writing – review & editing, Writing – original draft. **Thomas W. Kensler:** Writing – review & editing, Writing – original draft. **Rafael León:** Writing – review & editing, Writing – original draft. **Karen T. Liby:** Writing – review & editing, Writing – original draft. **Manuela G. López:** Writing – review & editing, Writing – original draft. **Gina Manda:** Writing – review & editing, Writing – original draft. **Akshatha Kalavathi Shivakumar:** Writing – review & editing. **Henriikka Hakomäki:** Writing – review & editing. **Jessica A. Moerland:** Writing – review & editing. **Hozumi Motohashi:** Writing – review & editing, Writing – original draft. **Ana I. Rojo:** Writing – review & editing, Writing – original draft. **Gerasimos P. Sykiotis:** Writing – review & editing, Writing – original draft. **Keiko Taguchi:** Writing – review & editing, Writing – original draft. **Ángela M. Valverde:** Writing – review & editing, Writing – original draft. **Masayuki Yamamoto:** Writing – review & editing, Writing – original draft. **Anna-Liisa Levonen:** Writing – review & editing, Writing – original draft, Visualization, Conceptualization.

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Declaration of competing interest

A.B. is co-inventor on patent applications covering non-covalent Keap1-Nrf2 inhibitors. **K.T.L.** is a named inventor on patents issued to Dartmouth College for synthetic triterpenoids. **A.C.** is co-inventor of a patent covering the use of disruptors of the β-TrCP/NRF2 interaction and co-founder of Servatrix Biomed S.L.

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Data availability

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

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