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An emerging role for cysteine-mediated redox signaling in aging

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ABSTRACT

Reactive oxygen species (ROS) and hydrogen sulfide (H_2S) are naturally produced during metabolic processes. At physiological levels, they act as oxidation-reduction (redox) signaling molecules and regulate a myriad of cellular processes. Redox signaling occurs largely through rapid and reversible oxidation of reactive cysteine residues in target proteins, leading to changes in protein ligand binding affinity, subcellular localization, and function. Recent studies have demonstrated that ROS and H_2S play an essential role in various longevity models, and that a mild increase in ROS or H_2S levels is sufficient to extend lifespan in model organisms. Meanwhile, the number of aging-related proteins that are modulated by ROS- or H_2S-mediated post-translational modification is constantly growing. In this review, we aim to summarize key results that support cysteine-based redox regulation of organismal aging and lifespan. Better understanding of how mechanistically redox signaling controls aging will provide new perspectives for the development of targeted anti-aging strategies.

1. Introduction

Although it has been long known that excessive ROS impair redox homeostasis and accelerate aging, emerging evidence indicates that low levels of ROS serve as signaling molecules and modulate almost all aspects of cell function [1,2]. The reducing agent H_2S also functions as a signaling molecule at physiological concentrations, and controls a wide range of biological processes [3]. Both hydrogen peroxide (H_2O_2) and H_2S signals are transduced mainly through reversible modification of selective protein cysteines, which play a central role in the redox signaling network [4]. Substitution of a cysteine residue with the non-oxidizable serine or alanine disrupts redox signaling, whereas the aspartate can functionally mimic an oxidized cysteine [5–7]. Examinations of individual cysteine mutations have revealed that cysteine oxidation acts as a functional switch that regulates an array of proteins, including transcription factors, protein kinases, phosphatases, and metabolic enzymes [8–11].

Mildly or transiently increasing ROS or H_2S levels delays aging and extends lifespan in model organisms [12–14]. As an effort to decipher the redox network that regulates aging, pioneering studies have generated a collection of aging-associated cysteine proteomics datasets. Quantitative characterization of reversible protein cysteine oxidation in ten mouse tissues uncovered a multitude of tissue- and age-dependent changes in the cysteine redox proteome [15]. Meanwhile, it has been reported that multiple anti-aging interventions, such as dietary restriction (DR), reduced insulin/insulin-like growth factor-1 (IGF-1) signaling (IIS), and suppression of mechanistic target of rapamycin (mTOR) complex 1 (mTORC1), alter the cysteine redoxome in worms, flies, and rodents [16–20].

Aging is characterized with and driven by alterations in gene expression, impaired proteostasis, and deregulated nutrient-sensing [21]. An increasing number of aging-related proteins have been found to be modulated by redox reactions of cysteines, and specific cysteine oxidation events can affect organismal lifespan. For instance, oxidation of a redox-sensitive cysteine in LET-60, a small GTPase that regulates lifespan in nematodes, is required for longevity arising from increased

Abbreviations: ROS, reactive oxygen species; H_2S, hydrogen sulfide; H_2O_2, hydrogen peroxide; DR, dietary restriction; IGF-1, insulin-like growth factor-1; IIS, insulin/insulin-like growth factor-1 signaling; mTOR, mechanistic target of rapamycin; mTORC1, mechanistic target of rapamycin complex 1; ETC, electron transport chain; SOD, superoxide dismutase; NOX, NADPH oxidase; ERO1, ER oxidoreducin 1; ACOX, acyl-CoA oxidase; DAO, D-amino acid oxidase; GPX, glutathione peroxidase; Prx, peroxiredoxin; GSH, glutathione; GSSG, oxidized glutathione; GR, GSH reductase; Trx, thioredoxin; TrxR, thioredoxin reductase; FOXO, forkhead box class O; Nrf2, nuclear factor erythroid 2-related factor 2; CBS, cystathionine β-synthase; CGL/CSE/CTH, cystathionine γ-lyase; 3-MST, 3-mercaptopyruvate sulfur transferase; ATF4, activating transcription factor 4; SELENBP1, selenium-binding protein 1; NAC, N-acetylcysteine; HAT, histone acetyltransferase; HDAC, histone deacetylase; Keap1, Kelch-like ECH-associated protein 1; NF-κB, nuclear factor-κB; UPS, ubiquitin-proteasome system; PTEN, phosphate and tensin homolog; PTP1B, protein tyrosine phosphatases 1B; PI3K, phosphoinositide 3-kinase; PIP3, phosphatidylinositol-3,4,5-trisphosphate.

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ROS production [22]. In this review, we describe the metabolism of redox signaling molecules and principles of cysteine-dependent redox regulation, summarize pro-longevity interventions that depend on elevated ROS or H_2S levels, and highlight how individual cysteine oxidative modifications influence proteins that regulate hallmarks of aging.

2. Cysteine-mediated redox signaling

2.1. ROS production and elimination

ROS are a group of oxygen (O_2) derivatives that can be classified into non-radical species such as H_2O_2 and free radicals including superoxide anion ($O_2^{\cdot-}$) and hydroxyl radical (·OH). Compartmentalized ROS biosynthesis is an important mechanism that controls ROS availability and allows for localized redox regulation. Mitochondria are a main source of ROS production, where $O_2^{\cdot-}$ formed at the electron transport chain (ETC) is rapidly converted to H_2O_2 by superoxide dismutase 2 (SOD2) (Fig. 1a). Membrane-bound NADPH oxidases (NOXs) are another major source of ROS [23]. In response to various stimuli including growth factors, NOXs produce $O_2^{\cdot-}$ by transferring electrons from NADPH to O_2. ROS are also synthesized in the endoplasmic reticulum (ER) during oxidative protein folding. ER oxidoreducin 1 (ERO1) or quiescin-sulfhydryl oxidase (QSOX) drives protein disulfide bond formation by coupling oxidation of protein disulfide isomerases (PDIs) with reduction of O_2, leading to H_2O_2 generation [5,24]. Additionally, peroxisomes harbor several oxidases that are involved in H_2O_2 metabolism. For instance, acyl-CoA oxidase (ACOX) and D-amino acid oxidase (DAO) generate H_2O_2 as by-products during fatty acid β-oxidation or oxidative deamination of D-amino acids, respectively [25]. Overall, more than 40 human enzymes in multiple organelles have been characterized in terms of H_2O_2 or $O_2^{\cdot-}$ formation [1].

Despite the continuous production of H_2O_2, its intracellular concentration is maintained in the nanomolar range by a complicated ROS scavenging system composed of non-enzymatic small molecules and antioxidant enzymes. SODs constitute the first line of defense against ROS by transforming $O_2^{\cdot-}$ into O_2 and H_2O_2. H_2O_2 can be decomposed by catalase, glutathione peroxidase (GPX), and peroxiredoxins (Prxs) [2]. Catalase relies on the heme moiety for the breakdown of H_2O_2 into H_2O and O_2. GPX converts H_2O_2 to H_2O using glutathione (GSH) as a reductant, and oxidized glutathione (GSSG) formed in this process is later reduced by GSH reductase (GR). Prxs eliminate H_2O_2 through a catalytic cycle. Oxidation of their functional cysteines leads to the formation of an intra-molecular disulfide bond, which is subsequently restored by thioredoxin (Trx)/Trx reductase (TrxR) [26]. The levels of antioxidant proteins and cofactors are controlled by redox-sensitive transcription factors, such as forkhead box class O (FOXO) proteins and nuclear factor erythroid 2–related factor 2 (Nrf2) [27].

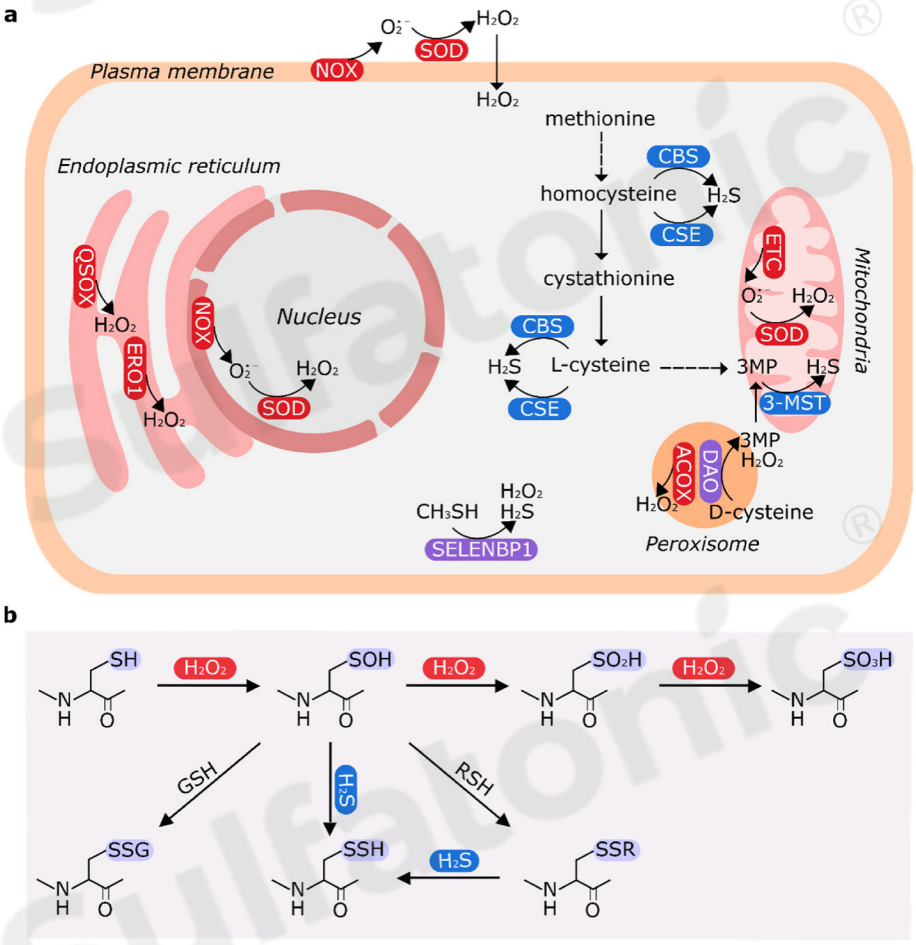


Fig. 1. H_2O_2 and H_2S serve as signaling molecules by modifying selective cysteine residues. (a) Major sources of H2O2 and H2S production in animal cells. H2O2 generation occurs at the plasma membrane, in the ER, mitochondria, and peroxisomes. H_2S is synthesized in the cytoplasm and mitochondria. Enzymes and protein complexes involved in H_2O_2 production are labeled in red, while enzymes that catalyze H_2S formation are in blue. DAO and SELENBP1 participate in the synthesis of both molecules and are labeled in purple. (**b**) A cysteine thiol or thiolate anion reacts with H_2O_2 to form a sulfenic acid. Sulfenic acids are relatively labile, and subsequent reactions that may occur include disulfide bond formation, glutathionylation, and persulfidation. These reversible modifications can be restored to the thiolate state by either the Trx/TrxR or glutaredoxin (Grx)/GR/GSH system [3]. Sulfenic acids can be further oxidized into sulfinic acids and sulfonic acids. In the range of physiological pH values, sulfinic acids, sulfonic acids, and persulfides exist almost completely as anionic species.

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2.2. H_2S anabolic and catabolic pathways

The steady-state intracellular concentration of H_2S varies among different tissues, and is usually maintained in the sub-micromolar range [3]. Although H_2S can be produced non-enzymatically [28], it is primarily generated by three enzymes: cystathionine β-synthase (CBS), cystathionine γ-lyase (CGL/CSE/CTH), and 3-mercaptopyruvate sulfur transferase (3-MST) (Fig. 1a) [29,30]. CBS and CTH are critical enzymes in the transsulfuration pathway, and they utilize L-cysteine and homocysteine for H_2S biogenesis [30]. Both CBS and CTH are transcriptional targets of Nrf2 [31]. CTH is also positively regulated by the basic leucine zipper (bZIP) transcription factor activating transcription factor 4 (ATF4), which promotes CTH expression upon amino acid deprivation, ER stress, or DNA damage [32–34]. 3-MST catalyzes H_2S formation either in conjugation with cysteine amino transferase using L-cysteine as a substrate, or together with peroxisome-located DAO utilizing D-cysteine [35]. The methanethiol oxidase selenium-binding protein 1 (SELENBP1) can also generate H_2S, but the degree to which it contributes to total H_2S production is unknown [36]. Compared to H_2S generation, the removal of H_2S is less well understood. The canonical H_2S oxidation pathway involves a group of mitochondrial enzymes collectively named the sulfide oxidation unit (SOU), which converts H_2S to thiosulfate and sulfate [35]. Alternatively, H_2S oxidation can be catalyzed by globins. For example, red blood cells lack mitochondria, and utilize hemoglobin to oxidize H_2S into thiosulfate and hydropolysulfides [37].

2.3. Cysteine modification by ROS and H_2S

The human proteome contains ~210,000 cysteine residues, and mass spectrometry-based chemoproteomics analyses reveal that thousands of cysteines are oxidant-sensitive [7,38–40]. Reactive cysteines can undergo a variety of oxidative modifications (Fig. 1b), which do not need to reach a very high stoichiometry to mediate context-dependent regulation of protein function [15,41]. A redox-sensitive thiol group (-SH) can be oxidized into a sulfenic acid (-SOH) when H_2O_2 levels are low. Sulfenic acids are very reactive, and can rapidly form intra- or inter-molecular disulfide bonds (–SS–) with thiols nearby. In particular, formation of a mixed disulfide bond between a sulfenic acid and the low-molecular-weight thiol GSH leads to glutathionylation. H_2S can modify oxidized cysteines, and reactions of H_2S with a sulfenic acid or a disulfide yield a persulfide (-SSH). In the presence of excessive H_2O_2, oxidation of a sulfenic acid generates sulfinic acid (-SO_2H) and sulfonic acid (-SO_3H). Sulfinic acids can be reduced by sulfiredoxin [42–44], whereas sulfonylation is an irreversible modification.

Under physiological conditions, ROS and H_2S signaling are intrinsically connected via cysteine oxidation. For example, treating HeLa cells with EGF induces a transit increase in H_2O_2 production and promotes global sulfenylation, followed by a wave of proteome-wide cysteine persulfidation [10,18]. H_2O_2-mediated sulfenylation of the active site cysteine Cys797 enhances EGF receptor (EGFR) tyrosine kinase activity, which is suppressed by pretreatment with H_2S [18]. These results suggest that ROS- and H_2S-mediated cysteine modifications may play antagonistic roles in growth factor signaling, and raise an important question whether the crosstalk between ROS and H_2S also exists in other processes including aging. In the following sections, we will summarize our current knowledge of how cysteine modifications modulate aging-related proteins, with a focus on sulfenylation, persulfidation, disulfide formation, and glutathionylation.

3. Longevity models with increased redox signaling molecules

3.1. Pro-longevity interventions that require elevated ROS levels

The free-radical theory of aging by Harman back in 1956 first linked ROS to aging. It proposed that ROS indiscriminately damage macromolecules, and that accumulation of oxidative damage over time causes aging. Although the overall redox tone becomes more oxidized during aging [18,45,46], overexpression of antioxidant enzymes or treatment with antioxidants does not always extend organismal lifespan [47]. Now it has become apparent that the impact of ROS on aging is dependent on the concentration, type, and timing. In general, high doses of ROS are detrimental, but a modest or temporal increase in ROS levels promotes longevity in multiple species. Here we focus on longevity models that require ROS, and emphasize the beneficial effects of ROS on lifespan.

Genetic studies first revealed that mildly increasing mitochondrial

Table 1
Longevity models with escalated ROS levels.

Intervention	Elevated species	Organism	Lifespan extension	Ref
Genetic manipulation of ROS generation				
nuo-6(qm200)	$O_2^{\cdot-}$	*C. elegans*	80 % mean lifespan	[48]
isp-1(qm150)	$O_2^{\cdot-}$	*C. elegans*	84 % mean lifespan	[48]
ND75 knockdown	$O_2^{\cdot-}$	*D. melanogaster*	15 % mean lifespan	[50]
ero-1 knockdown	ROS	*C. elegans*	18 %–48 % mean lifespan	[5]
BLI-3 overexpression	H_2O_2	*C. elegans*	13 % mean lifespan	[52]
memo-1(gk345) or *memo-1* knockdown	H_2O_2	*C. elegans*	38 % mean lifespan	[52]
Reagents that increase ROS levels				
Arsenite 100 nM	H_2O_2	*C. elegans*	10 % median lifespan	[53]
Paraquat 0.1–1 mM	H_2O_2 and $O_2^{\cdot-}$	*C. elegans*	19 %–58 % mean lifespan	[45,48,54,56]
Epicatechin gallate 2.5 mM	ROS	*C. elegans*	6 % median lifespan	[57]
Epigallocatechin gallate 2.5–300 μM	H_2O_2	*C. elegans*	7 %–17 % mean lifespan	[57,58]
Metformin 50 mM	H_2O_2	*C. elegans*	31 % mean lifespan	[59]
Menadione 1 μM	$O_2^{\cdot-}$	*S. cerevisiae*	100 % median lifespan	[60]
α-KB 500 μM	H_2O_2	*C. elegans*	47 % median lifespan	[61]
Tetrathiomolybdate 1–4 μM	$O_2^{\cdot-}$	*C. elegans*	19 % median lifespan	[62]
Glucose restriction				
0.5 % glucose	H_2O_2	*S. cerevisiae*	80 % median lifespan	[65]
2-deoxy-d-glucose (DOG) 5 mM	ROS	*C. elegans*	17 % mean lifespan	[66]
mTORC1 inhibition				
tor1Δ	$O_2^{\cdot-}$	*S. cerevisiae*	180 % median lifespan	[60]
Rapamycin 200 mM	$O_2^{\cdot-}$	*S. cerevisiae*	200 % median lifespan	[60]
Reduced IIS				
daf-2(e1370)	$O_2^{\cdot-}$	*C. elegans*	138 % mean lifespan	[48]
daf-2 knockdown	H_2O_2	*C. elegans*	131 % mean lifespan	[67]
Other genetic models				
glp-1(e2141ts)	H_2O_2	*C. elegans*	43 % median lifespan	[55]
hlh-2 knockdown	H_2O_2	*C. elegans*	30 % mean lifespan	[68]
argk-1 knockdown	H_2O_2	*C. elegans*	29 % mean lifespan	[68]

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ROS generation positively regulates lifespan (Table 1). In *C. elegans*, defects in either the mitochondrial respiratory complex I subunit *nuo-6* or complex III subunit *isp-1* cause a rise in $O_2^{\cdot-}$ levels and extend lifespan [48,49]. The antioxidant N-acetylcysteine (NAC) severely shortens the lifespan of *nuo-6* or *isp-1* mutants, indicating that their longevity relies on ROS [48,49]. Likewise, in *D. melanogaster*, knocking down the mitochondrial respiratory complex I component ND75 in the muscle provokes superoxide generation and increases lifespan, while catalase overexpression abolishes the longevity phenotype of ND75-depleted flies [50]. The mitochondrial hydroxylase Coq7/CLK1 is essential for the synthesis of ubiquinone, a cofactor in mitochondrial respiration. In both worms and mice, depletion of Coq7 leads to an increase in mitochondrial ROS levels and lifespan [49,51], suggesting that mitochondrial-derived ROS play an evolutionarily-conserved role in lifespan regulation. Boosting ROS levels in the ER or by NOXs also promotes longevity. For example, upregulation of ROS production in the ER by knocking down *ero-1* prolongs lifespan in nematodes [5]. The *C. elegans* dual oxidase BLI-3 contains an NADPH oxidase domain, and overexpressing BLI-3 or depleting its upstream inhibitor MEMO-1 results in higher H_2O_2 levels and longer lifespan [52]. Treatment with the antioxidant GSH completely suppresses the lifespan extension caused by *memo-1* deficiency, suggesting an essential role for ROS in this longevity model [52].

Pro-oxidants at low concentrations can promote longevity in model organisms. For instance, low doses of arsenite elicit H_2O_2 generation from multiple sources including mitochondria, and increase lifespan in nematodes in a ROS-dependent manner [53]. In addition, paraquat and green tea catechins at low levels induce mitochondrial ROS production, and their lifespan-extending effects require ROS [45,48,54–58]. Elevated mitochondrial respiration and H_2O_2 generation also contribute to longevity induced by the anti-diabetic drug metformin [59]. Intriguingly, increasing mitochondrial-derived ROS levels during development or early growth is sufficient to extend lifespan in worms and yeast [45,60]. Indeed, in an isogenic population, individuals with a more oxidized intracellular environment during development tend to live longer, suggesting that early-life ROS may have lifelong effects [45]. In addition to mitochondria ROS, pharmacologically elevating ROS levels in other subcellular compartments can also increase lifespan. Supplementation with the metabolite α-ketobutyrate (α-KB) prolongs lifespan by stimulating peroxisomal H_2O_2 production. In nematodes, α-KB upregulates peroxisomal fatty acid β-oxidation and H_2O_2 formation, leading to activation of transcription factor SKN-1 and extended lifespan [61]. This pathway is conserved in human fibroblasts, in which α-KB drives H_2O_2 generation, stimulates the nuclear translocation of SKN-1 ortholog Nrf2, and delays senescence [61]. The antioxidant enzyme SOD1 predominantly localizes in the cytosol and catalyzes superoxide removal. Recently, it was reported that the copper chelator tetrathiomolybdate promotes longevity in worms by inhibiting SOD1 activity and increasing superoxide levels [62].

DR, which refers to reduced total or specific nutrient intake without malnutrition, serves as a robust non-genetic intervention that extends healthspan and lifespan across evolutionary boundaries [63]. Suppression of nutrient-sensing pathways mTORC1 signaling and the IIS is sufficient to increase lifespan, and contributes to DR-induced longevity [64]. Intriguingly, ROS signaling plays a prominent role in longevity arising from DR or inhibition of nutrient-sensing pathways. For example, decreasing glucose availability promotes mitochondrial oxidative phosphorylation and ROS production, thereby extending lifespan in yeast and worms [65,66]. Lowering mTORC1 activity by depleting one of the two mTOR-encoding genes *tor1* or rapamycin also leads to an increase in mitochondrial superoxide generation in budding yeast [60]. SOD2 overexpression significantly curtails the extended chronological lifespan of the *tor1Δ* strain, suggesting an essential role for ROS in longevity arising from reduced mTORC1 signaling [60]. Moreover, acute depletion of the insulin/IGF-1 receptor DAF-2 elicits a temporary rise in mitochondrial ROS levels, and the lifespan-extending effect of impaired IIS is largely blocked by antioxidants [48,67].

ROS also play a vital role in several other longevity models. A subsequential increase in mitochondrial and cytosolic H_2O_2 levels has been reported in the long-lived germline-deficient *glp-1(e2*141ts*)* mutant worms, and antioxidant treatment shortens their lifespan [55,61]. In addition, RNAi-mediated depletion of transcription factor HLH-2 or its transcriptional target arginine kinase ARGK-1 leads to elevated H_2O_2 production and promotes longevity in nematodes [68]. NAC blocks the longevity resulting from loss of HLH-2 or ARGK-1, indicating that ROS are required for these manipulations to extend lifespan [68].

A few proteins that are modulated by reversible cysteine oxidation have been implicated in the longevity effects of ROS. Moderate levels of ROS activate transcription factors SKN-1 and DAF-16, which mobilize stress response pathways to prolong lifespan [5,52,53]. Activation of AMP-activated protein kinase (AMPK) and sirtuin 1 (SIRT1/SIR-2.1) also contributes to ROS-triggered longevity [58,69]. The SET1/MLL histone methyltransferase was recently identified as a ROS effector, as long-lived animals with higher endogenous ROS levels exhibit a global reduction in histone H3K4 trimethylation [45]. With the continuous identification of redox-regulated proteins, the molecular mechanisms by which ROS extend lifespan will be better understood.

3.2. Pro-longevity interventions that depend on increased H_2S levels

Since the discovery that exposure to 50-ppm H_2S (0.005 %) in the atmosphere increases lifespan and thermotolerance in *C. elegans* [70], H_2S has emerged as a positive regulator of lifespan in multiple model organisms (Table 2). In budding yeast, NaHS alone or in combination with the slow-releasing H_2S donor GYY4137 extends chronological lifespan [12,71]. In nematodes, H_2S-releasing compounds including GYY4137, FW1256, and mitochondrion-targeted AP39 improve health and promote longevity at low levels [72–74]. Additionally,

Table 2
Longevity models that rely on H_2S.

Intervention	Organism	Lifespan extension	Ref
Exogenous H_2S and H_2S donors			
50-ppm H_2S in the atmosphere	*C. elegans*	70 % mean lifespan	[70]
NaHS 5 μM + GYY4137 100 μM	*S. cerevisiae*	30 % median lifespan	[12]
NaHS 10~1000 μM	*S. cerevisiae*	32 %–74 % median lifespan	[71]
GYY4137 100 μM	*C. elegans*	20 %–59 % maximal lifespan	[72, 74]
FW1256 250 μM	*C. elegans*	51 % mean lifespan	[73]
AP39 100 nM	*C. elegans*	30 % maximal lifespan	[74]
Overexpression of H_2S-producing enzymes			
CBS-1 overexpression	*C. elegans*	26 % mean lifespan	[12, 75]
CBS overexpression	*D. melanogaster*	12~43 % mean lifespan	[13]
DR			
0.5 % glucose	*S. cerevisiae*	80 % median lifespan	[12]
eat-2(ad1116)	*C. elegans*	37.6 % mean lifespan	[12, 18]
0.4x AA+ 0.15 mM methionine	*D. melanogaster*	33 % maximal lifespan	[12]
5 % sugar/yeast	*D. melanogaster*	24 %–43 % median lifespan	[13]
mTORC1 inhibition			
raga-1(ok386)	*C. elegans*	31~44 % mean lifespan	[19]
mTORC2 suppression			
rict-1(ft7) or *rict-1* knockdown	*C. elegans*	24~31 % mean lifespan	[19]
ATF-4 overexpression			
ATF-4 overexpression	*C. elegans*	20 % mean lifespan	[19]
Germline removal			
*glp-1(e2*141ts*)*	*C. elegans*	43 % median lifespan	[55, 61]

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overexpressing the H_2S-producing enzyme CBS either ubiquitously or in selective tissues prolongs lifespan in both worms and flies [12,13,75,76].

In invertebrates, DR-mediated lifespan extension requires H_2S. For example, glucose restriction provokes H_2S generation and increases chronological lifespan in budding yeast [12]. In addition, the genetic DR-related model *eat-2(ad1116)* mutant worms have higher H_2S and protein persulfidation levels, and their longevity partially requires H_2S-producing enzymes CBS-1, CTH-1, and MPST-3 [12,18]. In flies, low-nutrient diets, such as sugar restriction or protein and methionine restriction, also stimulate CBS expression and boost H_2S production capacity [12,13]. RNAi-mediated knockdown of CBS or pharmacologically suppressing CTH activity partially reverses DR-induced lifespan extension in flies, suggesting that DR upregulates the transsulfuration pathway to promote longevity [13]. Induction of H_2S production by DR appears to be conserved in mammals. In mice, DR causes elevated CTH and H_2S levels, which is necessary for DR-mediated protection against hepatic ischemia reperfusion injury [12,17,19]. Reducing food consumption by 30 % for 6 months or longer also increases CBS and CTH expression in rats [77]. Despite the beneficial effects of H_2S discovered so far, whether H_2S contributes to the improved health and extended lifespan upon DR in vertebrates requires further investigation.

H_2S plays a crucial in longevity arising from suppression of mTORC1, mTOR complex 2 (mTORC2), or global protein synthesis [19]. All of these interventions converge on selective upregulation of ATF-4 translation, which promotes CTH-2 expression and H_2S production [19]. The ATF-4-CTH-2 pathway is required for the longevity effects of mTORC1 or mTORC2 inhibition [19]. Consistently, overexpression of ATF4 increases H_2S synthesis, global protein persulfidation levels, and lifespan in a CTH-2-dependent manner [19]. Longevity induced by germline loss also relies on H_2S. Removing germ cells results in the upregulation of CTH-1 and CTH-2 expression, as well as elevated H_2S production [55,61]. Depleting *cth-1*, *cth-2*, or *cbs-1* decreases H_2S levels and shortens the lifespan of germline-deficient *glp-1(e2*141ts*)* mutants [61].

Aging or pro-longevity interventions can dramatically alter cysteine persulfidation profiles in worms and rodents, suggesting that post-translational modification of cysteines may contribute to the lifespan-extending effects of H_2S [17–19]. Indeed, several redox-regulated proteins, such as DAF-16, SIR-2.1, and SKN-1, are required for H_2S-mediated longevity [55,70,74]. However, our knowledge of how H_2S increases lifespan is very limited, and more research is needed to elucidate the molecular mechanisms.

4. Redox-sensitive proteins that modulate hallmarks of aging

4.1. Histones and epigenetic modifiers

One of the most conserved aging hallmarks is epigenetic alterations. On the one hand, aging causes global and local changes in histone modification, DNA methylation, chromatin structure, and other epigenetic marks [78]. On the other hand, epigenetic factors modulate gene expression and thereby affect lifespan [79,80]. The epigenetic profile is sensitive to ROS levels, and redox control of the epigenetic landscape is in part through oxidative modification of histones and histone-modifying enzymes (Fig. 2a). Here we discuss how cysteine modification by ROS or H_2S affects epigenetic regulators and downstream pathways.

4.1.1. Histone H3

Histones compromise the major protein components of chromatin, and can be divided into core histones (H2A, H2B, H3, and H4) and linker histone (H1). The only cysteine-containing histone H3 can be oxidized at Cys110, resulting in chromatin remodeling and changes in gene expression. H_2O_2 treatment induces sulfonylation of Cys110 [81], which may destabilize the DNA near the dyad and foster nucleosome disassembly [82]. Cys110 can also be glutathionylated, leading to a more

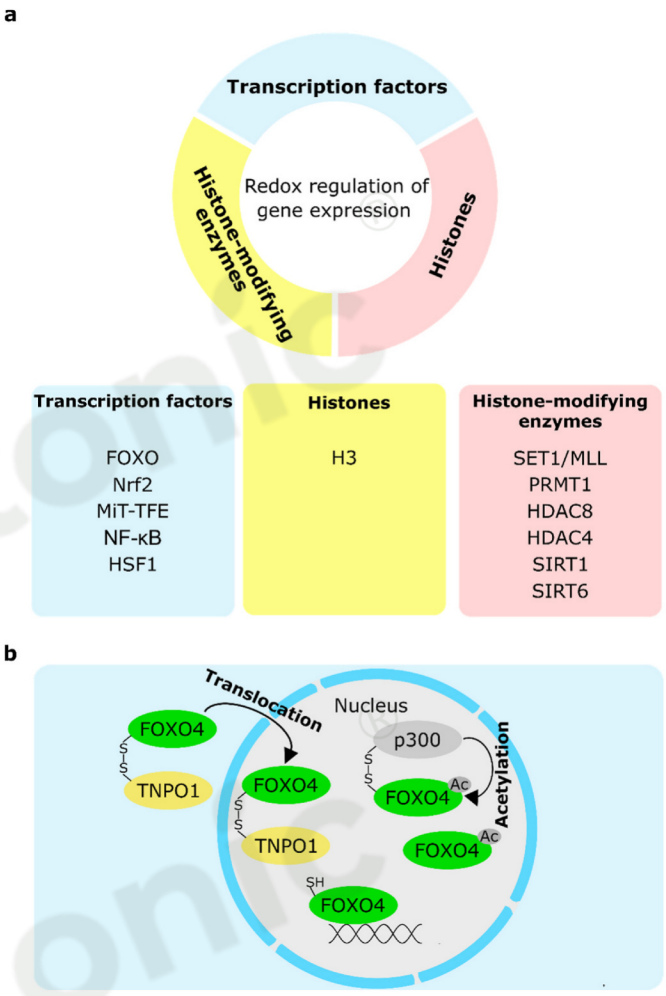


Fig. 2. Cysteine-dependent redox regulation of gene expression. (a) Redox signaling molecules can modulate gene expression by modifying cysteines in a collection of transcription factors, histone H3, and histone-modifying enzymes. (**b**) FOXO4 as an example showing the impact of cysteine oxidation on proteins that regulate gene expression. Oxidation of distinct cysteines in FOXO4 promotes its interaction with different binding partners. The inter-molecular disulfide bond with p300 leads to FOXO4 acetylation, whereas the disulfide bond with TNPO1 facilitates FOXO4 nuclear import and activation.

open chromatin structure that may assist DNA replication [83]. H3 has been associated with aging in different species. In yeast, H3 protein level drastically decreases during aging, while overexpression of H3 extends lifespan [84]. Glutathionylation of H3 at Cys110 declines with age in mouse livers [83], but whether it affects the aging process remains to be elucidated. Mammals express five H3 variants, among which the mammalian-specific H3.1 possesses a unique cysteine residue Cys96 that can be sulfenylated by H_2O_2 *in vitro* [85]. In breast cancer cells, oxidation of Cys96 in H3.1 promotes its exchange by H3.3, facilitates transcriptional activation of epithelial-to-mesenchymal genes, and increases metastasis [85]. Lowering nuclear H_2O_2 levels or mutating Cys96 of H3.1 into the redox-inert serine suppresses metastasis and resensitizes breast cancer cells to chemotherapy [85]. Interestingly, H3.3 exhibits age-dependent enrichment in the chromatin of various mouse somatic tissues, which is associated with alterations in global H3 methylation levels [86]. Given that ROS levels change during aging, understanding the relationship between post-translational modifications of H3 and aging might provide new insights into the redox regulation of epigenetic machinery and aging.

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4.1.2. Histone methyltransferases

Histone methylation is antagonistically controlled by histone methyltransferases and histone demethylases. Several histone methyltransferases are regulated by cysteine oxidation. For instance, H_2O_2 induces the formation of two intra-molecular disulfide bonds among cysteines in the SET domain of SET1/MLL histone methyltransferases and therefore suppresses SET1/MLL activity [45]. In addition, protein arginine methyltransferase 1 (PRMT1), which methylates histones and non-histone proteins, can be sulfenylated by H_2O_2 [87]. Oxidation of Cys101 and Cys208 attenuates the catalytic activity of recombinant PRMT1 proteins, and the Cys101Ser/Cys208Ser double mutant loses redox sensitivity [87]. PRMT-1 positively regulates lifespan in worms [88], but the relationship between post-translational modification of PRMT-1 and aging remains unknown.

4.1.3. Histone deacetylases

Histone acetyltransferases (HATs) and histone deacetylases (HDACs) play opposite roles in histone acetylation at lysine residues. Although no cysteine-mediated redox regulation of HATs has been reported, a few HDACs contain reactive cysteines and serve as well-characterized ROS and H_2S sensors. As one example, HDAC8, a class I HDAC, is inhibited by H_2O_2 in a dose-dependent manner *in vitro* [89]. The suppressive effect of H_2O_2 requires Cys102 and Cys153 of HDAC8, which are structurally close enough to form a disulfide bond [89]. Both cysteines are shared by class I HDACs, raising the possibility that other class I HDACs might be regulated in a similar way. As another example, HDAC4, a class IIA HDAC, can be modified by ROS. In cardiomyocytes, the ROS-generating hypertrophic stimulus phenylephrine promotes the oxidation and nuclear export of HDAC4 [90,91]. MS analysis of H_2O_2-treated HDAC4 proteins identified an intra-molecular disulfide bond between Cys667 and Cys669, which are shared by class II HDACs [90]. Cysteine oxidation is needed for proper localization of HDAC4, as both Cys667Ala/-Cys669Ala and Cys667Ser/Cys669Ser mutants are retained in the cytosol in myocytes without phenylephrine treatment [90]. Cardiac-specific overexpression of Cys667Ser/Cys669Ser mutant HDAC4 induces cardiac hypertrophy in mice, suggesting that the two cysteines are critical for the suppressive effect of HDAC4 on hypertrophy in the heart [90]. Interestingly, in HEK 293 cells, transiently transfected Cys667Ala/Cys669Ala mutant HDAC4 accumulates in the nucleus [92], indicating that the redox regulation of HDAC4 subcellular localization probably depends on cell type.

Class III HDAC sirtuins (SIRT1-SIRT7 in mammals) are a family of NAD^+-dependent deacetylases, among which SIRT1 and SIRT6 are oxidant-sensitive. Studies in zebrafish and mice show that SIRT1 activity is reversibly suppressed by glutathionylation *in vitro* and *in vivo* [93,94]. In zebrafish SIRT1, Cys204 in the catalytic domain close to the NAD^+-binding site serves as a main site for glutathionylation, and replacing it with a serine largely abolishes the inhibitory effect of glutathionylation [93]. Mouse SIRT1 can be glutathionylated in a glyceraldehyde 3-phosphate dehydrogenase (GAPDH)-dependent manner [94,95]. In cultured cells and mouse tissues, high fat and high sugar treatment causes glutathionylation of SIRT1 and reduces its deacetylase activity [94]. The oxidant-insensitive Cys61Ser/Cys318Ser/Cys613Ser triple mutant SIRT1 maintains active, and attenuates metabolic stress-induced apoptosis of HepG2 cells [94]. Interestingly, human SIRT1 can be persulfidated, which by contrast leads to its activation. Persulfidation at four cysteines (Cys371, Cys374, Cys395, Cys398) in the zinc-binding motif promotes zinc binding and the deacetylase activity of human SIRT1, both *in vitro* and *in vivo* [96]. Hyperactivation of SIRT1 and its ortholog SIR-2.1 increases lifespan in mice and worms [97,98]. SIR-2.1 is also indispensable for longevity arising from elevated H_2S levels [70]. These findings suggest that cysteine modification might mediate the lifespan-extending effects of SIRT1, which needs further investigation.

SIRT6 functions as a protein deacetylase and mono-ADP-ribosyl transferase [99]. It is also capable of removing long fatty acyl groups [100]. SIRT6 harbors multiple ROS-sensing cysteines. H_2O_2 treatment leads to sulfenylation of Cys18 in human SIRT6 and the formation of an inter-molecular disulfide bond with the transcription factor HIF1A [101]. The zinc-binding motif of SIRT6 contains four cysteines (Cys141, Cys144, Cys166, and Cys177) that are close to the catalytic site. These cysteines are functionally important, as mutating all of them into alanine residues abolishes SIRT6 demyristoylase activity [102]. Recent work discovered that SIRT6 is sulfenylated at Cys144 in monocytes during lipopolysaccharide (LPS)-induced inflammation [103]. The Cys144Ser mutation largely blocks SIRT6 sulfenylation and suppresses its deacetylase activity, leading to increased glycolysis in LPS-stimulated monocytes [103]. Increasing SIRT6 protein level or activity promotes longevity in mice [78,99], but whether its redox regulation contributes to lifespan determination remains to be understood.

4.2. Transcription factors

Aging is accompanied with extensive remodeling of the transcriptome landscape, and deterioration of transcriptional regulation is an early hallmark of aging [104,105]. By modulating gene expression, transcription factors regulate lifespan and healthspan across species [27]. ROS and H_2S can modify redox-sensitive cysteines in transcription factors and therefore alter the transcriptome (Fig. 2a). Here we summarize redox regulation of aging-related transcription factors, with a focus on how oxidative cysteine modification affects their stability, subcellular localization, and activity.

4.2.1. FOXO transcription factors

FOXO proteins represent a family of transcription factors that function downstream of the IIS [106]. They are activated by a wide range of stresses, and act as prominent regulators of stress response, immunity, metabolism, and aging. Invertebrates have a single FOXO gene, and overexpression of the only FOXO protein extends lifespan in worms and flies [107,108]. In mammals, there are four FOXO genes (FOXO1, FOXO3, FOXO4, and FOXO8), and certain SNPs in FOXOs have been associated with human longevity [109].

FOXO transcription factors shuttle between the nucleus and cytoplasm, and the nuclear localization is a prerequisite for their transcriptional activity. Under oxidized conditions, post-translational modification of cysteines in FOXO proteins and upstream regulators in the IIS pathway drives their nuclear accumulation and promotes target gene expression. The first redox-sensitive cysteine identified in FOXO proteins is Cys477 in the transactivation domain of FOXO4. Oxidation of Cys477 is needed for H_2O_2-induced FOXO4 acetylation by p300/CBP acetyltransferase (Fig. 2b) [11]. This cysteine is highly conserved within the FOXO family, and the corresponding residue Cys612 in FOXO1 mediates its interaction with p300 and acetylation during oxidative stress [110]. Two other cysteines in FOXO4, Cys239 and Cys355, can also be modified by H_2O_2. Oxidation of either cysteine promotes the formation of an inter-molecular disulfide bond between FOXO4 and nuclear import receptor transportin-1/TNPO1, which facilitates FOXO4 nuclear translocation and activation (Fig. 2b) [111]. DAF-16, the FOXO ortholog in *C. elegans*, also binds to TNPO1 in via a disulfide bond, and requires TNPO1 for ROS-induced nuclear import [111].

By contrast, the subcellular localization of FOXO3 is affected by the redox states of two different cysteines Cys150 and Cys31. Cys150 is a FOXO3-specific cysteine. H_2O_2 treatment causes the formation of a disulfide bond between Cys150 of FOXO3 and nuclear import receptor Importin-7 (IPO7) or Importin-8 (IPO8), which is required for FOXO3 nuclear translocation [112]. H_2O_2 also triggers the formation of disulfide-linked heterotrimers containing monomeric FOXO3 and dimeric PRDX1, and replacing Cys31 or Cys150 of FOXO3 with a serine impairs H_2O_2-induced FOXO3-PRDX1 protein complex and FOXO3 nuclear import [113]. In summary, FOXO family members have both overlapping and unique disulfide-dependent interacting partners, and are differentially regulated by ROS signaling.

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4.2.2. Nrf2 transcription factor

The bZIP transcription factor Nrf2/SKN-1 controls the basal and inducible expression of proteins involved in antioxidant defense and xenobiotic metabolism [114]. It serves as a transcriptional master regulator of redox homeostasis, and positively regulates lifespan in multiple species. Overexpression of SKN-1 promotes longevity in nematodes [115], whereas Nrf2 depletion shortens lifespan in mice [116].

Under basal conditions, Nrf2 is sequestered in the cytoplasm and delivered to the ubiquitin-proteasome pathway by the E3 ubiquitin ligase adaptor Kelch-like ECH-associated protein 1 (Keap1) for rapid degradation [117]. H_2O_2 drives Nrf2 nuclear import and activation by modifying reactive cysteines in Nrf2 and Keap1. In human Nrf2, Cys183 in the nuclear export signal (NES)-like motif acts as a sensor for H_2O_2, and replacing it with an alanine partially attenuates Nrf2 nuclear translocation during oxidative stress [118]. Multiple cysteines in Keap1 are amenable to oxidation and contribute to ROS-induced Nrf2 accumulation and activation. Oxidation of Cys151 in human Keap1 promotes disulfide-dependent Keap1 homodimerization, leading to the dissociation of Keap1-Nrf2 complex and stabilization of Nrf2 [119]. Mouse Keap1 can also be modified by H_2O_2, and forms intra-molecular disulfide bonds among four other cysteines (Cys226/Cys613/Cys622/Cys624) [120]. The Cys151Ser or Cys226Ser/Cys613Ser mutant Keap1 retains the ability to target Nrf2 for proteasomal degradation regardless of ROS levels, suggesting that these cysteines serve as critical ROS sensors [119,120]. Cys151 in Keap1 also acts as a target of H_2S. Persulfidation of Cys151 in Keap1 suppresses its interaction with Nrf2, enhances Nrf2 nuclear localization, and stimulates the transcription of Nrf2 target genes [121,122]. Keap1 persulfidation mediates the protective effects of H_2S on cellular senescence and diabetes-associated atherosclerosis [121,122], and whether it influences organismal aging is currently unknown.

4.2.3. MiT-TFE transcription factors

The MiT-TFE family of basic helix-loop-helix leucine zipper (bHLH-ZIP) transcription factors play a vital role in lysosomal biogenesis, cellular energy homeostasis, and autophagy. In response to cellular stresses, such as nutrient deprivation and oxidative stress, they transport from the cytoplasm to the nucleus and control gene expression [123]. The MiT-TFE proteins are conserved through evolution, and include four closely related members in vertebrates: TFEB, TFE3, TFEC and MITF. In *C. elegans*, the only MiT-TFE family member HLH-30 is indispensable for multiple mechanistically distinct longevity models, and HLH-30 overexpression extends lifespan [124,125].

An important mechanism that regulates MiT-TFE transcription factors involves the shuttling between lysosomal surface, the cytoplasm, and the nucleus. H_2O_2 oxidizes a conserved cysteine in MiT-TFE proteins (Cys212 of TFEB, Cys322 of TFE3, and Cys281 of MITF), resulting in their rapid nuclear translocation and target gene expression [126]. Mutating the conserved cysteine into an alanine in individual MiT-TFE transcription factors abolishes their nuclear import after acute H_2O_2 treatment [126]. Interestingly, following prolonged stresses such as 1 h of sodium arsenite treatment, the same cysteines in TFEB and TFE3 form inter-molecular disulfide bonds that result in homo- and hetero-oligomerization of these transcription factors [127]. Compared to monomers, those oligomers are more stable and less accessible to mTORC1-mediated phosphorylation and inactivation, thereby exhibiting increased transcriptional activity [127]. Cysteine-dependent oligomerization of MiT-TFE proteins is conserved in nematodes, and replacing the only cysteine Cys284 with a serine in HLH-30 eliminates its oligomerization [127]. Although mutant worms expressing Cys284Ser mutant HLH-30 display no obvious difference in median lifespan compared to wild-type animals, they are more susceptible to the pathogen *Staphylococcus aureus*, indicating that Cys284 is needed for HLH-30 function under certain conditions [127]. Several pro-longevity interventions rely on elevated HLH-30 activity, and whether the redox-inert mutation in HLH-30 blocks lifespan extension needs future investigation. In addition to oxidation, the subcellular localization of MiT-TFE transcription factors is largely affected by phosphorylation [123]. Interestingly, kinases that act upstream of MiT-TFE proteins such as AKT and mTOR are susceptible to oxidative modification, and may also contribute to the redox regulation of these transcription factors.

4.2.4. Nuclear factor-κB (NF-κB)

NF-κB comprises a family of transcription factors that control a diverse array of physiological processes, including immune response, inflammation, cell survival, and differentiation. Transcriptional activity of NF-κB increases with age in various tissues [128], and hyperactive NF-κB induces premature aging in mice [129,130]. By contrast, suppressing NF-κB signaling promotes longevity in flies [131].

The canonical pathway that activates NF-κB signaling involves the inhibitory IκB proteins and IκB kinase (IKK). Under basal conditions, NF-κB is retained in the cytoplasm by IκB family members and stays inactive. In response to oxidative stress and other stimuli, IKK-mediated phosphorylation triggers IκB ubiquitination and proteasomal degradation, enabling the nuclear transport of NF-κB [132]. The most abundant form of NF-κB activated by the canonical pathway, the p50/p65 heterodimer, is regulated by the redox status of specific cysteines. For instance, reduction of Cys62 in p50 is required for NF-κB activation. This cysteine is highly oxidized in the cytosol, but becomes reduced in the nucleus by the nuclear protein Ref-1, leading to elevated DNA-binding activity of p50 [133]. Additionally, Cys38 in p65 can be persulfidated in mouse liver and peritoneal macrophages following TNF-α treatment, which elevates endogenous H_2S production [134]. Persulfidation of Cys38 promotes p65 binding with the coactivator ribosomal protein RPS3 and increases its transcriptional activity [134]. The Cys38Ser mutant p65 fails to be persulfidated, resulting in decreased DNA binding activity and increased susceptibility to TNF-α-induced cell death [134].

4.2.5. HSF1

The evolutionarily conserved heat shock transcription factor 1 (HSF1) plays a central role in the transcriptional activation of heat shock proteins (HSPs). Proteotoxic stresses such as elevated temperature and oxidative stress promote trimerization and nuclear translocation of HSF1, which drives chaperone gene expression to maintain proteostasis [135]. HSF-1 overexpression extends lifespan in *C. elegans* through multiple mechanisms, including transcriptional upregulation of HSPs, induction of autophagy, maintenance of cytoskeletal integrity, and alterations in mitochondrial morphology [136–139].

Under non-stressed conditions, HSF1 exists as inactive monomers and localizes in the cytoplasm. During short-term heat stress or H_2O_2 treatment, Cys36 and Cys103, two conserved cysteines in the DNA-binding domain of human HSF1, rapidly form an inter-molecular disulfide bond that leads to HSF1 homotrimerization [140,141]. Mutating either cysteine into a serine abolishes stress-induced HSF1 trimerization, nuclear import, and DNA binding, indicating a critical role for the Cys36-Cys103 disulfide bond in HSF1 activation [140,141]. Persistent heat or oxidative stress triggers the formation of disulfide-linked HSF1 oligomers at HSP gene loci to modulate their transcription [142]. Oxidative oligomerization of HSF1 relies on Cys153 in the leucine zipper 1–3 domain, and the Cys153Ser mutation significantly reduces HSF1 oligomerization [142]. Oxidation-mediated activation of HSF1 protects cells from heat- or ROS-induced apoptosis [140], but any relationship between HSF1 oxidation and aging remains to be examined.

4.3. Proteostasis network

The proteostasis network is composed of cellular machineries for protein biogenesis, folding, and degradation. Loss of proteostasis is a common feature and major driver of aging, whereas improving proteostasis retards the aging process and extends lifespan [143]. Mildly increasing ROS levels protects the integrity of the proteome by inhibiting global translation, activating selective molecular chaperones, and

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inducing degradation of damaged proteins [144,145]. Here we focus on cysteine-based redox control of proteostasis pathways and oxidant-sensitive proteins in the proteostasis network.

4.3.1. Translation machineries

Aging is accompanied with and affected by changes in protein synthesis [146,147]. Pharmacologically or genetically reducing translation rates can increase lifespan and healthspan across many species [148–150]. In addition, improving translational fidelity promotes longevity in yeast, worms, and flies [151], whereas high levels of translational errors result in premature aging in mice [152].

Oxidation of selective ribosomal proteins plays an important role in ROS-induced translation suppression (Fig. 3a). Ribosomal protein RPL40A is located on the surface of ribosomes, and can be oxidized by exogenous or mitochondria-derived ROS. Replacing Cys115 in RPL40A with a serine attenuates the inhibitory effect of H_2O_2 on translation without affecting basal protein synthesis rates, suggesting that this cysteine acts as a redox switch for translation [153]. H_2O_2 also sulfenylates ribosomal proteins RPS26 and RPL10 [154]. Oxidation of Cys74 and Cys77 in RPS26 promotes its removal from mature ribosomes by chaperone proteins, allowing for ribosome repair [154]. Similarly, sulfenylation of Cys105 in RPL10 results in chaperone-dependent

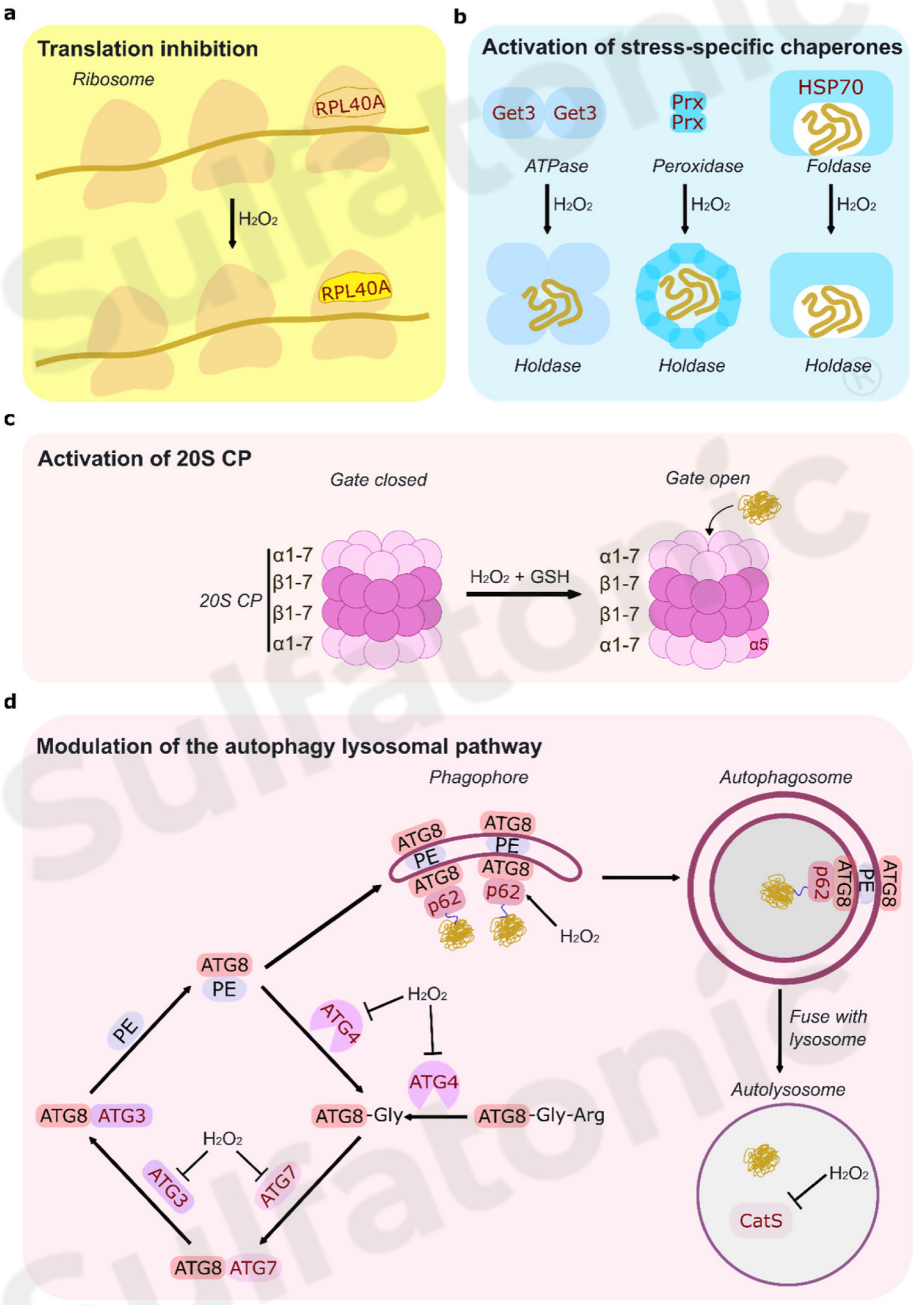


Fig. 3. Oxidative modification of specific cysteine residues regulates the proteostasis network. (**a**) Oxidation of Cys115 in ribosomal protein RPL40A mediates the inhibitory effect of H_2O_2 on protein synthesis. (**b**) During oxidative stress, H_2O_2-mediated cysteine oxidation converts Get3, Prxs, and HSP70 family members into ATP-independent holdases to prevent protein aggregation. (**c**) (**d**) The two major protein degradation pathways in eukaryotes, UPS and the autophagy lysosomal pathway, are both redox-regulated. (**c**) Glutathionylation of Cys76 and Cys221 in the 20S proteasome subunit α5 promotes gate opening of 20S CP. (**d**) Cysteine oxidation modulates multiple proteins involved in autophagy and lysosomal degradation. For example, H_2O_2 post-translationally suppresses several ATG proteins and the lysosomal protein cathepsin S. By contrast, oxidation of Cys105 and Cys113 in the autophagy receptor p62 promotes its oligomerization and enhances autophagy activity. In all panels, peptides and proteins are shown in dark yellow.

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dissociation of oxidized proteins and repair of damaged ribosomes [154]. RPS-26 maintains a fast turnover rate over the course of aging, and negatively regulates lifespan in worms [155,156]. Interestingly, abolishing RPL10 or RPS26 turnover impairs cell growth [154], but any relationship between ribosome repair and aging remains to be determined.

4.3.2. Chaperones

Molecular chaperones are classified into foldases and holdases based on their functions. Foldases facilitate protein folding in an ATP-dependent manner, while holdases bind to unfolded/misfolded proteins independently of ATP and prevent their aggregation during stressed conditions. Molecular chaperones are key players in the proteostasis network, and upregulation of selective chaperones extends lifespan in invertebrates [157–159].

Oxidative modification of cysteines can turn non-chaperone proteins into stress-specific holdases (Fig. 3b). As one example, the yeast ATPase Get3 mediates the integration of tail-anchored proteins into the ER membrane under non-stressed conditions, but becomes an ATP-independent chaperone during oxidative stress [160]. Oxidation of two conserved cysteines, Cys240 and Cys242 in the CXC motif, promotes Get3 oligomerization and functional switch [160]. ASNA-1, the Get3 ortholog in nematodes, exhibits the same mutually exclusive redox-modulated activities, and replacing cysteines Cys285 and Cys288 with serine residues increases worm sensitivity to cisplatin-triggered oxidative stress [161,162]. As another example, sulfinylation of the peroxidatic cysteines induces oligomerization of 2-cys Prxs and transforms these peroxidases into holdases [43,163]. Sulfiredoxin catalyzes the reduction of sulfinylated Prxs and restores their peroxidase activity [43].

The 70-kDa heat shock proteins (HSP70s) are a group of highly conserved molecular chaperones. Oxidation of selective HSP70 family members converts them from foldases into holdases (Fig. 3b). For instance, sulfenylation or glutathionylation of the yeast chaperone Kar2 at a conserved cysteine Cys63 in the ATP-binding pocket disrupts its ATPase activity and stimulates the holdase activity [164,165]. Elevated ROS production in the ER suppresses the growth of yeast cells expressing Cys63Ala mutant Kar2, which can be alleviated by wild-type or Cys63Asp mutant Kar2, implying that oxidation of Cys63 may protect cells against oxidative stress [164]. The ER luminal chaperone Grp78/BiP, a mammalian ortholog of Kar2, can also be oxidized, and the Cys41-Cys420 disulfide bond increases its ATP-independent chaperone activity [166]. Additionally, the human HSP70 protein HSPA1A/HSP72 contains multiple reactive cysteines, and is differentially affected by distinct oxidation events. Substitution of either Cys267 or Cys306 in the ATPase domain of HSPA1A with an aspartate reduces its ATPase activity and increases the holdase activity [167]. Interestingly, HSPA1A can also be glutathionylated at Cys574 and Cys603 located in the substrate-binding domain, which by contrast boosts its ATPase activity [168].

4.3.3. Proteasomal subunits

The ubiquitin-proteasome system (UPS) selectively degrades cellular proteins and serves as one of the major proteolytic pathways in eukaryotes. The 26S proteasome is a large protein complex comprising two major subcomplexes, the 20S core particle (CP) and the 19S regulatory particle (RP). Proteasome activity decreases with age, whereas hyperactivation of the proteasome increases lifespan in model organisms [169–171].

An important mechanism by which ROS regulate proteasomal degradation is by modifying cysteines in 20S proteasome subunit α5. The 20S CP is a barrel-shaped chamber that consists of four stacked heptameric rings made of α and β subunits, and the α-rings function as a gate for substrate entrance (Fig. 3c). Glutathionylation of Cys76 and Cys221, two highly conserved cysteines in α5, triggers gate opening of free 20S proteasomes and promotes their proteolytic activity [172]. Mutating either cysteine into a serine fosters gate closing of 20S proteasomes and shortens chronological lifespan in yeast, suggesting a critical role for oxidation-induced gate-opening of proteasomes and substrate degradation in aging [172,173].

4.3.4. Proteins in the autophagy lysosomal pathway

Autophagy is a fundamental cellular process that delivers damaged or unwanted macromolecules and organelles to lysosomes for degradation and recycling. Autophagy occurs at a low basal level under normal conditions, and is induced in response to starvation and other stresses. Autophagy is closely associated with aging. One the one hand, lysosomal morphology, motility, function, and autophagic activity undergo dramatic changes during aging [174–176]. On the other hand, autophagy affects lifespan from yeast to mammals. Suppressing autophagy accelerates aging, whereas enhancing autophagic flux promotes longevity [177,178]. Lately, a regulatory role for lysosomal morphology and signaling pathways in aging has also been uncovered [179–182].

Recent findings have demonstrated that autophagy and lysosomal function are modulated by post-translational oxidation of protein cysteines. Autophagy initiates with nucleation of the cup-shaped membrane structure phagophore, which eventually expands into autophagosome [183]. Several autophagy-related (ATG) proteins that drive autophagosome biogenesis are redox-regulated (Fig. 3d). One example is the cysteine protease ATG4, which plays a dual role in autophagy. It cleaves nascent ATG8/LC3/GABARAP to expose a glycine required for phosphatidylethanolamine (PE) binding; it also catalyzes the deconjugation of ATG8-PE to recycle ATG8 [184]. Oxidative modification of distinct cysteines in ATG4 inhibits its ATG8 cleavage or delipidating activity. H_2O_2-induced Cys338-Cys394 disulfide bond in yeast ATG4 suppresses ATG8 processing, and replacing either cysteine with a serine restores ATG8 cleavage [185]. By contrast, oxidation of human ATG4A or ATG4B at a conserved cysteine (Cys81 of ATG4A or Cys78 of ATG4B) near the catalytic site blocks ATG8 delipidation [186]. Consistently, either Cys81Ser mutant ATG4A or Cys78Ser mutant ATG4B dramatically reduces starvation-induced GABARAPL2 or LC3 lipidation [186]. Cys292 and Cys361 in human ATG4B also mediate the inhibitory effect of H_2O_2 on LC3 delipidation, by forming inter- and intra-molecular disulfide bonds [187]. Following H_2O_2 treatment, HeLa cells expressing the Cys292Ser/Cys361Ser double mutant ATG4B exhibit lower lipidated LC3 (LC3-II) levels than those expressing wild-type ATG4B [187].

In addition to ATG4, two other ATG proteins involved in autophagosome formation, ATG3 and ATG7, are ROS targets. Sequential actions of ubiquitin-activating enzyme E1 ATG7 and E2-like enzyme ATG3 are required for ATG8-PE conjugation on the autophagosomal membrane (Fig. 3d). When autophagy is inactive, covalent binding with LC3 protects ATG3 and ATG7 from being oxidized in mammalian cells [188]. Upon autophagy induction, such interactions become transient, and the active thiols of ATG3 and ATG7 are exposed [188]. H_2O_2 triggers the inter-molecular disulfide bond between Cys264 of ATG3 and Cys572 of ATG7, which prevents LC3 binding and suppresses starvation-induced LC3 lipidation [188]. Importantly, there is an increase in ATG7 oxidation and a decrease in starvation-induced LC3-II in mouse aorta during aging, suggesting that altered redox states of ATG proteins might contribute to aging [188].

Autophagy receptors connect specific cargos with the autophagosomal membrane to facilitate cargo degradation. The mammalian autophagy receptor SQSTM1/p62 contains two oxidant-sensitive cysteines in a disordered region that are highly conserved among vertebrates. Oxidation of Cys105 and Cys113 promotes disulfide-linked oligomerization of p62, leading to increased autophagosome biogenesis and cell survival during oxidative stress (Fig. 3d) [189]. Substitution of both cysteines in p62 with alanine residues causes more cell death in the presence of excessive H_2O_2 [189]. *Drosophila* p62 lacks oxidant-sensitive cysteines and does not form disulfide-linked conjugates in response to H_2O_2 [189]. Interestingly, introducing the corresponding cysteines into *Drosophila* p62 elevates autophagic flux and promotes stress resistance,

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implying that the redox-sensitivity of p62 may have evolved in vertebrates as a mechanism to maintain cell viability during stressed conditions [189].

Several lysosomal proteins are controlled by ROS-mediated cysteine oxidation. For example, cathepsins, a group of lysosomal cysteine proteases, are differentially modulated by oxidation. Sulfenylation of the catalytic cysteine in cathepsin S inhibits its auto-maturation and activity in a dose-dependent manner *in vitro* (Fig. 3d) [190,191]. The activities of

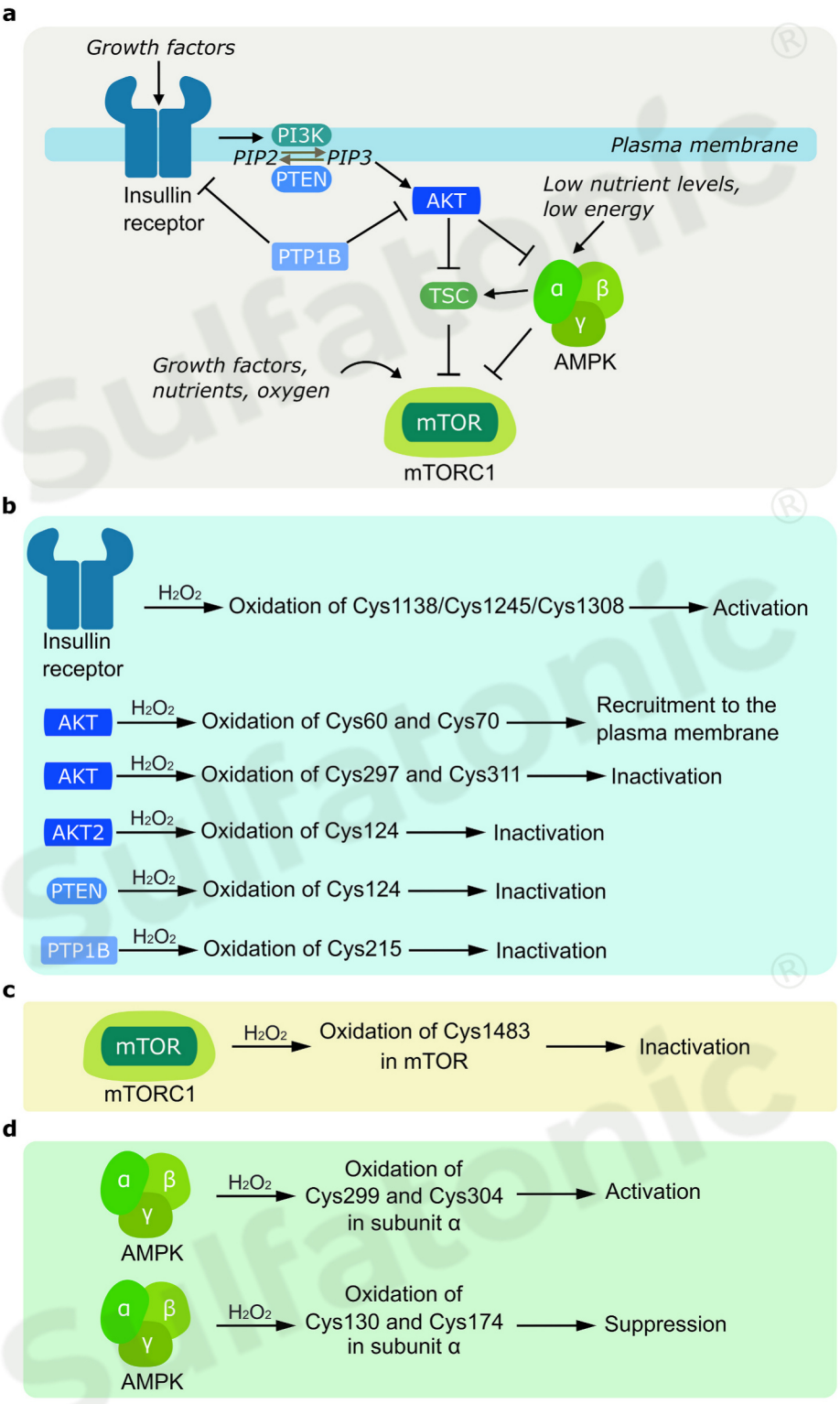


Fig. 4. A schematic diagram of the regulation of inter-connected nutrient-sensing pathways by H_2O_2. (a) High nutrient levels activate the IIS and mTORC1 signaling, but inhibit AMPK activity. mTORC1 is activated downstream of the IIS, and negatively modulated by AMPK. All these pathways are modulated by post-translational cysteine oxidation of critical kinases and phosphatases. (b) The IIS pathway contains H_2O_2-sensing kinases insulin receptor and AKT, as well as H_2O_2-targeting phosphatases PTEN and PTP1B. **(c)** H_2O_2 suppresses mTORC1 kinase activity by modifying Cys1483 of mTOR. (d) AMPK can be oxidized at multiple cysteines in the α subunit, which differentially affects its kinase activity.

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cathepsins B, K, and L are also suppressed by H_2O_2, whereas cathepsin D is activated by H_2O_2 [192,193]. As another example, Rab7, a small GTPase that regulates lysosome biogenesis, fusion, and transport, is oxidized by low-dose H_2O_2 [194,195]. Replacing Cys83 and Cys84 into serine residues enhances Rab7 GTP-binding activity without affecting protein abundance or subcellular localization, implying that oxidative modification of these cysteines might impair Rab7 activity [195].

4.4. Proteins in nutrient-sensing pathways

The ability to detect and respond to fluctuations in intracellular and extracellular levels of sugars, amino acids, and lipids is essential for life. Evolutionarily-conserved nutrient-sensing pathways, including the IIS, mTORC1 signaling, and AMPK, regulate lifespan across diverse species. Dysregulation of nutrient-sensing impairs metabolic homeostasis, and serves as an important hallmark of aging [196]. Importantly, limiting nutrient intake or manipulating nutrient-sensing pathways to mimic DR conditions delays aging and extends lifespan.

Recent studies have revealed that there is extensive crosstalk between the nutrient-sensing network and redox metabolism. Nutrient and growth factor levels affect ROS and H_2S production [12,66,197]. Meanwhile, nutrient-sensing pathways contain redox-sensitive proteins that ensure proper responses to both nutrient and redox signals. Here we provide an overview of current advances in the redox regulation of major nutrient-sensing pathways.

4.4.1. The IIS pathway components

The IIS pathway connects nutrient levels to metabolism, growth, development and aging. Following insulin binding, insulin receptor activates the phosphoinositide 3-kinase (PI3K)-AKT signaling cascade, culminating in the inactivation of FOXO transcription factors [198]. This process is counteracted by two phosphatases, phosphate and tensin homolog (PTEN) and protein tyrosine phosphatases 1B (PTP1B). PTEN antagonizes the PI3K-AKT signaling through its lipid phosphatase activity, whereas PTP1B dephosphorylates insulin receptor and AKT (Fig. 4a). Insulin induces intracellular H_2O_2 production, which amplifies insulin-mediated signal transduction by oxidizing reactive cysteines in kinases and phosphatases in the IIS pathway (Fig. 4b).

The insulin receptor is embedded in the plasma membrane, and acts as a ROS sensor. As a receptor tyrosine kinase (RTK) family member, it becomes autophosphorylated after insulin binding. H_2O_2 dramatically enhances the autophosphorylation and activation of insulin receptor [199,200]. Three cysteines Cys1138, Cys1245, and Cys1308 are required for the regulatory effect of H_2O_2 on insulin receptor, and mutating either cysteine into an alanine lowers its kinase activity [199,200].

The AGC serine/threonine kinase AKT serves as a major signaling hub in the IIS. AKT activation initiates with its recruitment to the plasma membrane by phosphatidylinositol-3,4,5-trisphosphate (PIP3), and maximal AKT activity requires phosphorylation at T309 and S474 [41]. Post-translational oxidation of cysteine residues modulates AKT activity by affecting its subcellular localization and phosphorylation levels. Vertebrates have three AKT isoforms, AKT1, AKT2, and AKT3. AKT2 contains two oxidant-sensitive cysteines Cys60 and Cys77 in the N-terminal PH domain, which are shared by all AKT isoforms. Upon insulin treatment, Cys60 and Cys77 form a disulfide bond that augments AKT2 translocation to the plasma membrane [41]. Replacing both cysteines with serine residues abolishes insulin-induced AKT2 recruitment to the plasma membrane and phosphorylation, thereby suppressing cell proliferation and animal growth [41]. Recently, it was reported that Cys77 is persulfidated in the brains of Alzheimer's disease (AD) patients, leading to decreased interaction with its substrate GSK3β [201]. The Cys77Ala mutation largely abrogates AKT persulfidation, restores GSK3β phosphorylation, and improves cognitive functions in a mouse model of AD [201]. AKT1-3 harbor four conserved cysteines in the kinase domain. Crystal structure of inactive AKT2 proteins revealed that Cys297 and Cys311 in the activation loop form an intra-molecular disulfide bond [202]. The Cys297-Cys311 disulfide bond is present in cultured cells during oxidative stress, which promotes AKT dephosphorylation by serine/threonine protein phosphatase 2A (PP2A) and inhibits its kinase activity [41,203]. AKT2 also contains an isoform-specific cysteine Cys124 in the linker region between the PH domain and kinase domain. Cys124 becomes sulfenylated after growth factor stimulation, resulting in lower AKT2 activity [204]. Together, these findings indicate that oxidative modification of different cysteines mediates the context-dependent and isoform-specific redox regulation of AKT proteins.

Exogenous H_2O_2- or growth factor (insulin, PDGF, or EGF)-induced cysteine oxidation suppresses PTEN activity [203,205–207]. In the presence of H_2O_2, Cys124 at the active site of PTEN forms a disulfide bond with Cys71. Replacing Cys124 with a serine or reducing the Cys124-Cys71 disulfide bond with Trx abolishes the inhibitory effect of H_2O_2 and restores the PIP3 phosphatase activity of PTEN [8,208,209]. DAF-18, the ortholog of PTEN in *C. elegans*, acts downstream of the insulin/IGF-1 receptor DAF-2 to regulate lifespan. Mutating Cys150 in the phosphatase domain into a tyrosine impairs DAF-18 lipid phosphatase activity, and partially suppresses the longevity and stress resistance of *daf-2* mutant worms [210]. Cys150 is highly conserved, and whether the corresponding cysteine in mammalian PTEN also modulates lifespan requires future investigation.

Low levels of H_2O_2 modify PTP1B at the catalytic cysteine Cys215. Oxidized Cys215 forms sulfenyl amide with S216, which inhibits PTP1B binding with its substrate insulin receptor [211,212]. Such intermediate state is stabilized by the protein 14-3-3, which may protect PTP1B from overoxidation [211,213]. Consistently, reversibly oxidized PTP1B is reduced and re-activated by Trx1 [209,214]. PTP1B also undergoes persulfidation under conditions of elevated H_2S production, including insulin stimulation [215,216]. Persulfidation decreases PTP1B phosphatase activity, and the cysteines modified by H_2S remain to be determined [215,216].

4.4.2. The mTORC1 complex

The serine/threonine protein kinase complex mTORC1 is a central regulator of cell growth and metabolism [217]. Nutrients, growth factors, and oxygen control mTORC1 activity via two sets of small GTPases, Rag heterodimers and Rheb. In the presence of amino acids and glucose, Rag GTPases become activated and recruit mTORC1 to the lysosome, its major site of activation [218]. Growth factors enhance GTP loading of Rheb, and GTP-bound Rheb activates mTORC1 on the lysosomal surface [219]. Active mTORC1 promotes anabolic processes and suppresses catabolic processes by phosphorylating a variety of protein substrates, including p70 S6 kinase 1 (S6K1), eukaryotic initiation factor 4E-binding protein 1 (4E-BP1), and unc-51-like autophagy-activating kinase 1 (ULK1) [219,241]. Reduced mTORC1 signaling contributes to multiple longevity models, and genetically or pharmacologically lowering mTORC1 activity is sufficient to extend lifespan from yeast to mammals [220].

H_2O_2-mediated oxidation of mTOR suppresses its kinase activity (Fig. 4c) [221–223]. In the presence of 100 μM H_2O_2, mTOR forms inter-molecular disulfide bonds within 30 min [224]. Replacing the conserved cysteine Cys1483 into a phenylalanine attenuates H_2O_2-induced mTOR oxidation and restores phosphorylation of mTORC1 substrates, indicating that this cysteine is critical for the redox regulation of mTORC1 [224]. In contrast to H_2O_2, thiol oxidants phenylarsine oxide (PAO) or diamide at low doses rapidly activate mTORC1, regardless of amino acid levels or nucleotide status of Rag GTPases [225,226]. Although the protein targets of these oxidants have not been identified, one possible candidate is the tuberous sclerosis complex (TSC). TSC functions as a GTPase-activating protein (GAP) towards Rheb, and its component TSC2 contains several CXXC motifs that can react with PAO. PAO and diamide also suppress mTOR interaction with the mTORC1 subunit raptor, raising the possibility that mTOR or raptor may be

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modified by these oxidants [225,226]. In summary, mTORC1 activity is modulated by oxidation, and distinct oxidants may oppositely affect mTORC1 by targeting different proteins and cysteine residues. Deciphering the redox regulation of mTORC1 can help gain more insights about the mechanisms of aging and human diseases associated with altered mTORC1 activity and redox homeostasis.

4.4.3. AMPK

The heterotrimeric protein complex AMPK is composed of a catalytic subunit (α) and two regulatory subunits (β and γ). In response to low nutrient levels or energy stress, AMPK is activated to restore energy homeostasis [227]. AMPK mediates the longevity effects of DR, intermittent fasting (IF), reduced IIS, and mTORC1 suppression [228–232]. Upregulation of AMPK is sufficient to extend lifespan and delay aging in worms and flies, whereas reducing AMPK activity shortens lifespan [233–235].

AMPK is activated during oxidative stress, and its α subunit is a sensor of H_2O_2 (Fig. 4d). Incubation with 100 μM H_2O_2 for 10 min promotes the autophosphorylation and kinase activity of purified recombinant AMPK *in vitro* [236]. In HEK 293 cells, treatment with 250 μM H_2O_2 induces glutathionylation of AMPKα and AMPKβ, and increases the phosphorylation levels of AMPKα and its substrate ACC in a time-dependent manner [236]. The effects of H_2O_2 are largely attenuated by mutating either Cys299 or Cys304 of AMPKα into an alanine, suggesting that oxidation of the two cysteines is needed for AMPK activation by H_2O_2 [236]. Interestingly, in primary cardiomyocytes treated with 100 μM H_2O_2, oxidation of two conserved cysteines Cys130 and Cys174 in AMPKα induces inter-molecular disulfide bonds, leading to its aggregation and suppression [237]. The opposite effects of exogenous H_2O_2 on AMPK activity in HEK cells and cardiomyocytes might be due to a difference in their ROS scavenging capacity. It is possible that HEK 293 cells can keep H_2O_2 at a relatively low level, which prevents AMPK aggregation and allows for its oxidative activation [237].

AMPK plays an important role in ROS-induced longevity in model organisms. In nematodes, low-dose paraquat or genetically elevating mitochondrial ROS levels promotes AMPK phosphorylation [54,238], and the lifespan-extending effect of paraquat requires active AMPK [54]. In rodents, an isocaloric high-fat diet increases lifespan [239], and a high-fat diet induces AMPK oxidation [237]. These findings imply that AMPK oxidation might contribute to lifespan extension by increased ROS levels.

5. Conclusions and future directions

Our understanding of how natural metabolites ROS and H_2S affect aging has evolved dramatically over the past two decades. It is now widely accepted that these redox signaling molecules are required for multiple pro-longevity interventions, and that modestly increasing their concentrations is sufficient to extend lifespan in model organisms. Changes in gene expression, loss of proteostasis, and dysregulated nutrient-sensing pathways are prominent hallmarks of aging. Importantly, many proteins that modulate those processes are direct targets of ROS or H_2S, supporting a critical role for redox signaling in aging.

Intriguingly, recent results have shown that pro-longevity interventions including germline removal and dietary restriction lead to the upregulation of both ROS and H_2S, raising the possibility that these signaling pathways may be inter-connected. Protein cysteines are amenable to multiple post-translational modifications, and mediate the redox regulation of different physiological processes. It has been found that cysteine sulfenylation and persulfidation exert opposite effects on the activity of EGFR, but whether the crosstalk between ROS and H_2S at the post-translational level broadly exists remains to be determined. More work is needed to elucidate how redox signaling molecules interact with each other mechanistically under various conditions.

With recent advances in chemoproteomics, our knowledge of the redox proteome landscape has greatly expanded, and much attention is shifting towards defining the physiological relevance of individual cysteine oxidation events. Although many protein cysteines were found to undergo aging-related changes in redox states, whether and how individual cysteine modifications affect aging and lifespan are understudied. Future in-depth analyses of the redox network that controls aging will help define the protein targets of redox signaling molecules in the context of aging, and may inspire the development of novel strategies that aim to slow down aging.

Declaration of competing interest

The authors declare no conflict of interest.

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Data availability

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

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