FOXO transcription factors in antioxidant defense

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Abstract
Forkhead box, class O (FOXO) family proteins are widely expressed and highly conserved transcriptional regulators that modulate cellular fuel metabolism, stress resistance and cell death. FOXO target genes include genes encoding antioxidant proteins, thus likely contributing to the key role FOXOs play in the cellular response to oxidative stress and supporting the cellular strategies of antioxidant defense, that is, prevention (of the formation of reactive oxygen species), interception (of reactive species prior to their reaction with cellular components), repair (of damaged biomolecules), and adaptation (i.e., the stimulation of signaling pathways allowing for the expression of protective proteins). FOXOs themselves are regulated by redox processes at several levels, including expression of FOXO genes and enzymatic as well as nonenzymatic posttranslational modifications of FOXO proteins. The latter include modifications of FOXO cysteine residues. Here, an overview is provided on (i) the contribution of FOXO target genes to cellular antioxidative strategies, and (ii) on the impact of thiol homeostasis and thiol modification on FOXO activity.

KEYWORDS
antioxidant strategies, C. elegans, stress signaling, Nrf2, diethyl maleate, glutathione, hormesis

1 INTRODUCTION: FOXO TRANSCRIPTION FACTORS

Forkhead box, class O (FOXO) proteins are transcriptional regulators involved in the modulation of numerous aspects of cellular metabolism, including fuel metabolism, stress resistance and cell death.1,2 Four FOXO proteins, FOXOs 1, 3, 4, and 6, are found in mammalian tissues (referred to as “FOXO isoforms” in this text). The first three are ubiquitously expressed in mammalian tissues,
albeit with varying isoform preferences; FOXO6 has been frequently described as being confined to brain, although Foxo6 in mice is expressed rather broadly, and data on FOXO6 expression in humans in tissues other than brain, such as in liver, accumulate.

All isoforms are similar in structure and domain organization (Figure 1), with an N-terminal conserved region, a forkhead box-DNA binding domain, a nuclear localization sequence (NLS), a nuclear export signal (NES) and one or more C-terminal conserved regions/transactivation domains. While FOXOs 1, 3, and 4 are rather similar in sequence, FOXO6 diverges and does not appear to harbor a functional NES, rendering it different from the other isoforms also in terms of its subcellular localization under basal conditions (Figure 2). Whereas FOXOs 1, 3, and 4 shuttle between nucleus and cytoplasm in response to various stimuli, FOXO6 appears to be constitutively nuclear. All FOXOs, acting as transcriptional regulators, recognize and bind to “forkhead-responsive DNA elements” (FHRE), such as the “insulin response element” (IRE, 5'-TT[G/A]TTTTG-3') or the “DAF-16-binding element” (DBE, 5'-TT[G/A]TTTAC-3').

As they share this recognition of the same specific DNA elements, it is not surprising that FOXO isoforms have some overlapping activities. However, there are also isoform-specific effects, as evident from the different properties of isoform-specific knockout mice, the most obvious being viability: whereas Foxo1-null mice die in utero, Foxo3- and Foxo4-null mice are viable, as are Foxo6-knockout mice. Functional differences between FOXO isoforms derive, in part, from their different expression patterns in different tissues as well as their regulation through posttranslational modification (PTM) and interactions with coregulators. An example of isoform-specific PTMs and interactions with coregulators has been convincingly established by comparing FOXO3 and FOXO4 as well as cysteine mutants thereof, and by identifying FOXO isoform-specific interaction partners forming mixed disulfides with FOXOs upon exposure of cells to hydrogen peroxide.

Regulation of FOXO transcription factors through redox processes occurs at several levels, including FOXO expression, which is controlled transcriptionally by redox-regulated transcription factors, including FOXOs themselves, as well as posttranscriptionally, for example through redox-sensitive RNA-binding proteins such as HuR.
Second, PTM of FOXOs, both enzymatic and non-enzymatic, is affected by redox-regulatory processes. As an example, the insulin-induced cascade resulting in Akt-dependent FOXO phosphorylation is affected by reactive oxygen species (ROS) at several levels (for review, see Reference 20), including oxidative inhibition of protein tyrosine phosphatase-1B (PTP-1B), or of the lipid and protein phosphatase, PTEN; even oxidative inactivation of Akt was described. Akt-dependent phosphorylation of FOXOs causes inactivation, and—in the case of FOXOs 1, 3, and 4, but not FOXO6—in nuclear exclusion (see Figure 2). Multiple other phosphorylation sites for kinases other than Akt exist in FOXOs, with various outcomes (see6). Further enzymatic PTMs were described for FOXOs, such as acetylation, methylation, ubiquitylation, GlcNAcylation, to name the most prominent (see6,21 for overview). Non-enzymatic modification of FOXOs will be discussed below.

Third, FOXO interaction partners, such as transcriptional co-regulators, were identified that rely on cysteine residues in FOXOs for their full impact on FOXO transactivation activity, rendering this interaction sensitive to cysteine modification, including oxidation.

Lastly, FOXO target genes include genes encoding proteins involved in cellular stress response, such as antioxidant proteins. The generation of antioxidant proteins in response to a FOXO activation resulting from oxidative events could be regarded as a feedback response that aims at alleviating the initiating stress.

Numerous excellent reviews outline the different FOXO target genes, with consequences for metabolism, cellular homeostasis and the regulation of cell death1,22–24; here, we will focus on target genes involved in cellular antioxidative approaches. A second focus of this short article will be on nonenzymatic posttranslational modifications of FOXO proteins and the impact of thiol homeostasis on FOXO activity.

2 FOXOS IN THE CELLULAR STRATEGIES OF ANTIOXIDANT DEFENSE

The role of FOXO transcription factors in cellular stress response and their contribution to stress resistance is conserved from nematodes, such as C. elegans, to mammals, as evident from the fact that not only the signaling cascades upstream of the respective FOXO proteins are largely conserved (see Figure 3), but in that also similar target genes exist, including genes encoding antioxidant proteins. In mammals, antioxidants encoded by FOXO target genes include proteins involved in direct interception and reduction of ROS, as well as more indirectly antioxidant proteins. It should be noted that FOXO activity may, for example as a consequence of pro-apoptotic activity, also contribute to the enhanced production of ROS; but even under conditions of FOXO-induced ROS generation, a parallel FOXO-dependent containment of ROS was observed.25

Mitochondrial Mn-containing superoxide dismutase (Mn-SOD)26 and catalase27 were among the first identified antioxidant proteins whose biosynthesis is transcriptionally regulated by FOXO transcription factors. A wealth of further antioxidant proteins has since been identified as transcriptionally controlled by FOXOs.

Such antioxidant proteins (see below for examples) are found both intra- and extracellularly (such as in plasma); moreover, these proteins are located in several subcellular compartments, including cytosol, mitochondria and peroxisomes. FOXO proteins, therefore, contribute to establishing a complex network of intracellular and extracellular antioxidative defense mechanisms.6

Applying the “strategies of antioxidant defense” concept by Helmut Sies28–31 it is obvious that all lines of defense are represented by the wealth of these different antioxidant proteins formed under control of FOXO transcription factors (Figure 4). While prevention includes measures of averting the formation of ROS in the first place, interception refers to chemical neutralization (in its broadest sense) of a formed ROS; for example, direct

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**FIGURE 3** Insulin signaling in mammalian cells and in C. elegans. FOXO transcriptional activity is inhibited by phosphorylation as catalyzed by the Ser-/Thr-kinase Akt, resulting in FOXO nuclear exclusion. Akt is activated by insulin via phosphoinositide 3’-kinase (PI3K); PTEN is a lipid phosphatase interfering with PI3K-dependent Akt stimulation by catalyzing the dephosphorylation of phosphoinositides. This figure was created with BioRender.com
scavenging of ROS is achieved by dedicated enzymes. Cellular mechanisms contributing to repair of oxidative damage elicited in cells upon exposure to ROS (i.e., under conditions of insufficient interception) are a crucial line of defense in the cellular antioxidant network. Finally, adaptation to oxidative stress includes the modulation of gene expression by ROS to alter cellular levels of proteins involved in cellular antioxidant defense.

i. Prevention—Synthesis of ceruloplasmin, the major plasma copper protein, is regulated by FOXO proteins in human and rat hepatocytes and affected by insulin accordingly. Its ferroxidase activity, through reduction of Fe$^{2+}$ released from cells to Fe$^{3+}$, not only allows for Fe$^{3+}$ transport by transferrin, but also helps prevent Fenton-type reactions. Metallothioneins, also the product of FOXO target genes in mammals and C. elegans, similarly contribute to prevention of oxidative processes, as their intracellular Cu(I) chelating activity prevents Fenton-like reactions contributing to lipid peroxidation. A peroxisomal protein that was proposed to prevent peroxidation of fatty acids, whose expression was detected early on as regulated by FOXOs, is sterol carrier protein 2 (SCP2).

ii. Interception—SODs and peroxidases, by catalyzing the dismutation of superoxide and the reduction of hydrogen peroxide and other peroxides, respectively, represent the level of interception, that is, the direct interference with reactive oxygen species prior to their interacting with other biomolecules. Next to SOD2 (mitochondrial Mn-SOD) and cytosolic SOD1 (Cu,Zn-SOD), enzymes catalyzing the reduction of peroxides are among the FOXO-dependently generated, such as catalase (see above), glutathione peroxidase-1 and peroxiredoxins (Prx3, Prx 5). Hepatic synthesis and release of selenoprotein P (SELENOP), the major plasma selenoprotein and selenium transporter from liver to extrahepatic tissue, is stimulated by FOXOs, contributing to interception of ROS both in a direct and an indirect fashion. SELENOP has some peroxidase activity per se, protecting LDL against oxidation. Moreover, as it is a known selenium delivery device providing selenium for the synthesis of cellular antioxidant selenoenzymes, including glutathione peroxidases or thioredoxin reductases, it contributes to rendering cells more resistant against oxidative stress.

iii. Repair—FOXO targets include genes encoding proteins involved in repair of oxidative DNA and protein damage. For example, activity of the 20S proteasome is modulated by FOXO1, which controls transcription of the gene encoding the catalytic β5 subunit. The 20S proteasome is a major contributor to cellular degradation of oxidized proteins. Some oxidized proteins, rather than degraded, can be reduced, and FOXOs contribute to the expression of enzymes catalyzing such reactions, including thioredoxin reductases, catalyzing the regeneration of thioredoxins, which themselves have protein disulfide reducing activity: the expression of mitochondrial thioredoxin (Trx2) and mitochondrial thioredoxin reductase (TrxR2) were demonstrated to be regulated by FOXO3a in bovine aortic endothelial cells. Accessory proteins such as sestrins (with three mammalian isoforms, sestrins 1–3, resulting from expression of the SESN1-3 genes) were identified as contributing to repair, that is, reduction, of oxidized peroxiredoxins—although SESN2 was later demonstrated to not have a sulfiredoxin-like activity of catalyzing the reduction of sulfenic acid-state Prx. SESN2 is also being discussed as a peroxidase itself (for a recent review on sestrin 2, see). SESN3 expression is stimulated by FOXOs, as is that of SESN2. Interestingly, SESN2 induction was also demonstrated to be stimulated by Nrf2. FOXO-dependent sestrin 3 production was demonstrated to cause mTOR complex 1 inhibition. As mTORC1 stimulates energy-consuming anabolic processes such as protein or lipid biosynthesis, this inhibition was hypothesized to...
contribute to repair processes occurring in afflicted cells indirectly, that is, by saving energy.59
As for DNA damage response, the FOXO target gene encoding Gadd45α was identified as a player in FOXO-dependent DNA repair.45 Recently, exposure of human or murine fibroblasts to bleomycin, a drug causing oxidative DNA damage, not only led to increased FOXO3 levels in these cells, but FOXO3 was then also shown to be required for repair of bleomycin-induced DNA double-strand breaks.62

iv. Adaptation—One interesting feature of ROS-induced adaptation as an antioxidative strategy is that the very damage to biomolecules that antioxidants are supposed to prevent or revert may elicit those signaling processes in exposed cells that may then result in adaptation. Activation of signaling cascades resulting in FOXO modulation are part of this strategy, as are those resulting in Nrf-2 activation.20 Nrf-2 is a transcription factor held in check under basal conditions by binding to cytoplasmic Keap1, which couples Nrf-2 to cullin-3, a ubiquitin ligase, and allows for constant proteasomal degradation of newly formed Nrf2. A stimulus altering the three-dimensional structure of Keap-1, most often oxidants and electrophiles interacting with Keap-1 thiol groups, through abrogation of Keap-1/Nrf-2 interaction may cause release and nuclear translocation of Nrf-2 which then activates transcription of genes involved in cellular defense against oxidants and electrophiles, such as genes encoding glutathione biosynthesis enzymes, quinone reductases, and phase II xenobiotic metabolism proteins.63 The Keap-1/Nrf-2 system was proposed to establish a stress-induced transcription regulation floodgate in the cellular defense against oxidants and ROS-generating compounds, with other transcriptional regulators in place in case the gate is run over—including FOXO transcription factors.25 As Nrf-2 activation can be achieved by thiol-acting compounds, and as Nrf-2 and FOXOs are both involved in the cellular defense against oxidants, the link between FOXOs, Nrf-2 and thiols will be briefly dealt with in the following section.

3 | FOXOS AND THIOLS

3.1 | Hormetic effect of an Nrf-2 activator

Diethyl maleate (DEM) is a known activator of Nrf-2. It is so well known, in fact, that it is frequently used as a model compound, and the exact Keap-1-position (Cys151) is known that DEM interacts with to interfere with Keap-1/Nrf-2 interaction,64,65 causing the release of Nrf-2. In addition to alkylating suitable thiol moieties of proteins, it also interacts with the major cellular thiol, glutathione (GSH), causing GSH depletion, which may result in oxidative stress as the activity of cellular GSH-dependent antioxidant enzymes may be impaired.66,67 C. elegans is a model organism frequently employed in research on stress-induced effects, including aging processes and the development of stress resistance. Moreover, it has orthologs of both FOXOs and Nrf-2—called DAF-16 and SKN-1, respectively.

Exposure of C. elegans to DEM causes a moderate depletion of GSH; as expected, lifespan of C. elegans was significantly shortened (by approx. 10% relative to control conditions) when worms were held on agar containing 1 mM DEM. Interestingly, an exposure of worms to lower (up to 0.1 mM) concentrations elicited an extension of life span (by approx. 5%), pointing to a hormesis-like effect and an adaptive response elicited by such DEM concentrations.67 In fact, resistance to paraquat, a known redox-cycler, was also elevated in worms exposed to lower DEM concentrations. In line with expectations derived from DEM being an Nrf-2 activator, the same low DEM concentrations stimulated the expression of genes encoding antioxidative proteins. The lifespan extending effect of DEM was imitated by genetically induced thiol depletion: attenuation of glutathione biosynthesis through RNA interference with expression of C. elegans γ-glutamyl-cysteine synthetase caused moderate glutathione depletion and an adaptive response eliciting life span extension.67

Both DAF-16 and SKN-1 were involved in mediating DEM-induced life span extension, as only toxic but no positive effects of DEM remained in worm strains deficient in either DAF-16 or SKN-1.67

Whereas the FOXO ortholog DAF-16 mediated DEM-induced lifespan extension in C. elegans, no DEM-induced change in expression of FOXO target genes was observed in mammalian cells.66 At DEM concentrations eliciting Nrf-2 activation and upregulation of Nrf-2 target gene expression, a nuclear accumulation of FOXO1 was observed in human HepG2 hepatoma cells, yet without upregulation of FOXO1 target genes. Following DEM treatment, FOXOs (as FOXO-GFP fusion proteins) remain nuclear, even in the presence of insulin, which normally causes nuclear exclusion (Figures 2 and 3). It appears as if DEM traps inactive FOXO1 in the nucleus whereas it stimulates Nrf2-dependent gene expression (Figure 2).66

3.2 | FOXO cysteine modifications and their role in FOXO biology

Nonenzymatic PTMs include oxidative modification of amino acid side chains, the most prominent of which—
owing to their partial reversibility and hence potential involvement in regulatory events—are cysteine modifications. Of the possible cysteine oxidations a few have been described for FOXO proteins (Figure 5): of the smaller cysteine modifications, persulfidation of FOXO1 at Cys457 was demonstrated, with an impact on phosphorylation at Ser256; mechanistically, this implies sulfenylation prior to interaction with hydrogen sulfide; sulfenylation of FOXO3 has indeed been demonstrated in cells following exposure to hydrogen peroxide; S-glutathionylation of FOXOs has been postulated but never conclusively demonstrated. However, mixed disulfides between FOXOs and various other proteins were demonstrated in cells exposed to hydrogen peroxide, such as the histone acetyltransferase p300/CBP to Cys477 of FOXO4, which affects FOXO acetylation and activity and which is reversible by thioredoxin. Further mixed disulfides with proteins, both overlapping and isoform-specific, were identified for FOXO3 and 4 upon H₂O₂ treatment, including peroxiredoxins 1, 2 (FOXO3), and 5 (FOXO3 and FOXO4). As interaction with peroxiredoxins is rather frequently observed with redox-reactive cysteines in general, a term was coined that seems to apply to FOXOs as well: FOXOs are “S-peroxiredoxinylated”.

Mixed disulfide formation with transportin1 (FOXO4) and importins 7 and 8 (FOXO3), respectively, contribute to nuclear translocation of the respective FOXOs under oxidizing conditions. It was also implied by the authors that, following translocation, the lower nuclear redox potential may then contribute to a reduction of the mixed disulfide to release FOXOs. In addition to this isoform-specific mechanism, a more generic additional factor was suggested by Hwang et al., who demonstrated that Cys31 of FOXO3 (which is located in the N-terminal conserved region and is a cysteine conserved in all human FOXO isoforms) is oxidized in neural stem/progenitor cells upon treatment with H₂O₂ or paraquat. Subsequently, Akt-mediated phosphorylation of Thr32 is hindered and FOXO3 accumulates in the nucleus, where it transactivates some of its target genes.

Nuclear translocation of FOXO1, the isoform with the most cysteine residues among the human FOXOs, was achieved in cells exposed to DEM-induced stress. Interestingly, no change in nuclear translocation was observed in cells expressing a cysteine-deficient FOXO1 mutant, implying that no mixed disulfide needs to be formed with FOXO1 to cause its nuclear accumulation. Rather, the authors hypothesize that nuclear accumulation is a result of DEM blocking nuclear export. Nevertheless, FOXO1 cysteines are required for its full transactivation activity even under basal conditions: while not affecting DNA binding activity, the loss of its seven Cys residues, particularly of the C-terminal Cys612, does impair FOXO1 transactivation activity. A reason for the importance of Cys612 might be its contribution to FOXO1 interaction with its coregulators PGC-1α and CBP and, thereby, the induction of some target genes, even under non-stressed conditions.

**4 | CONCLUSIONS**

In summary, FOXO transcription factors are major players within the cellular antioxidative network. FOXOs, in turn, are regulated by redox processes at several levels, including (reversible) nonenzymatic post-translational modification of FOXO proteins: FOXO cysteine residues, through sulfenylation, persulfidation, and/or mixed disulfide formation in the presence of reactive oxygen species, contribute to subcellular distribution and transactivation activity of these transcriptional regulators.
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