Redox Biology 6 (2015) 51–72

Contents lists available at ScienceDirect

Redox Biology

journal homepage: www.elsevier.com/locate/redox

Review Article

Redox regulation of FoxO transcription factors

Lars-Oliver Klotz [a,*], Cristina Sánchez-Ramos [b], Ignacio Prieto-Arroyo [b], Pavel Urbánek [a], Holger Steinbrenner [a], Maria Monsalve [b,*]

[a] Institute of Nutrition, Department of Nutrigenomics, Friedrich-Schiller-Universität Jena, Dornburger Straße 29, 07743 Jena, Germany
[b] Instituto de Investigaciones Biomédicas "Alberto Sols" (CSIC-UAM), Arturo Duperier, 4, 28029 Madrid, Spain

ARTICLE INFO

Article history:
Received 28 May 2015
Received in revised form
25 June 2015
Accepted 30 June 2015
Available online 3 July 2015

Keywords:
Forkhead box proteins
Oxidative stress
Stress signaling
Antioxidant proteins
DAF-16
C. elegans
Insulin signaling
Akt

ABSTRACT

Transcription factors of the forkhead box, class O (FoxO) family are important regulators of the cellular stress response and promote the cellular antioxidant defense. On one hand, FoxOs stimulate the transcription of genes coding for antioxidant proteins located in different subcellular compartments, such as in mitochondria (i.e. superoxide dismutase-2, peroxiredoxins 3 and 5) and peroxisomes (catalase), as well as for antioxidant proteins found extracellularly in plasma (*e.g.*, selenoprotein P and ceruloplasmin). On the other hand, reactive oxygen species (ROS) as well as other stressful stimuli that elicit the formation of ROS, may modulate FoxO activity at multiple levels, including posttranslational modifications of FoxOs (such as phosphorylation and acetylation), interaction with coregulators, alterations in FoxO subcellular localization, protein synthesis and stability. Moreover, transcriptional and posttranscriptional control of the expression of genes coding for FoxOs is sensitive to ROS. Here, we review these aspects of FoxO biology focusing on redox regulation of FoxO signaling, and with emphasis on the interplay between ROS and FoxOs under various physiological and pathophysiological conditions. Of particular interest are the dual role played by FoxOs in cancer development and their key role in whole body nutrient homeostasis, modulating metabolic adaptations and/or disturbances in response to low *vs.* high nutrient intake. Examples discussed here include calorie restriction and starvation as well as adipogenesis, obesity and type 2 diabetes.

Contents

1. Introduction . . . 52
2. FoxO target genes: antioxidant defense . . . 53
3. Redox regulation of FoxO activity . . . 54
   3.1. Endogenous and exogenous sources of ROS and their effect on FoxO phosphorylation . . . 54
   3.2. ROS control of FoxO activity by lysine modification: acetylation and ubiquitination . . . 56
4. Redox regulation of FOXO expression . . . 59
   4.1. Transcriptional regulation of FoxO gene expression . . . 59
   4.2. Posttranscriptional regulation of FoxO levels . . . 61
   4.3. FoxO transcriptional coregulators in redox regulation of FoxO activity . . . 61
5. Physiological and pathophysiological consequences of redox (dys)regulation of FoxOs: selected examples . . . 61
   5.1. Metabolic adaptation to low nutrient intake . . . 61
   5.2. Adipocyte differentiation . . . 62
   5.3. Obesity and diabetes . . . 63
   5.4. Cancer . . . 63
6. FoxOs and ROS in different organs . . . 64
   6.1. Liver . . . 64
   6.2. Skeletal muscle . . . 64
   6.3. Bone . . . 65
   6.4. Central nervous system . . . 65

* Corresponding authors.
E-mail addresses: lars-oliver.klotz@uni-jena.de (L.-O. Klotz), mpmonsalve@iib.uam.es (M. Monsalve).

http://dx.doi.org/10.1016/j.redox.2015.06.019
2213-2317/

6.5. Blood . . . 65
6.6. Kidney . . . 65
6.7. Skin . . . 65
7. Conclusions . . . 66
Acknowledgments . . . 66
References . . . 66

1. Introduction

"Fork head" was first identified in *Drosophila* as a potential transcriptional regulator [1], and demonstrated to harbor a so-called winged-helix DNA binding domain that was then recognized to be present in other transcriptional regulators, including the mammalian hepatocyte-enriched nuclear factor (HNF)-3A (now FoxA1) [2]. This domain was christened the fork head domain [2], and later the dozens of proteins with such a winged helix/fork head domain identified by then were categorized into different classes of forkhead box (Fox) proteins [3]. Fox proteins – specifically, the forkhead box, class O, proteins (FoxO) – were first linked to stress resistance when long-lived mutants of *Caenorhabditis elegans* were analyzed with respect to genetic traits contributing to their longevity. It was found that insulin-like signaling along the cascade orthologous to the mammalian insulin receptor/phosphoinositide 3′-kinase/Akt (InsR/PI3K/Akt) cascade was involved in that mutants with impaired signaling along this cascade had extended life spans [4] (Fig. 1). It was then demonstrated that the *daf-16* gene conferred this life span extension [5] and that DAF-16 (DAF, dauer formation) is a transcription factor of the Fox family (specifically, a FoxO orthologue) essential to this process [6,7].

Mutants with deficient *daf-2*, coding for a *C. elegans* InsR orthologue [8], were then shown to not only display a long-lived phenotype but also a phenotype ("Oxr") characterized by oxidative stress resistance: A *daf-2*-inactive mutant had an enhanced resistance towards redox cycling compounds such as paraquat or menadione [9]. Like the longevity phenotype, this Oxr phenotype was prevented by mutations in *daf-16*, suggesting that transcriptional targets of DAF-16 might be involved in conferring stress resistance. In fact, the expression of *sod-3*, the gene for one of the two manganese-containing superoxide dismutases of *C. elegans* (but neither *sod-1* nor *sod-2*, coding for Cu, Zn-dependent SOD and a second Mn-dependent SOD, respectively [10]), was upregulated in long-lived *daf-2* mutants, which was prevented by an additional *daf-16* mutation [9].

These findings suggested that the expression of genes coding for antioxidant enzymes such as superoxide dismutases might be under the control of forkhead-type transcription factors. In fact, expression of the human Mn-SOD (mitochondrial SOD-2 in humans) was demonstrated to be transcriptionally controlled by the human DAF-16 orthologue, the forkhead box transcription factor, FoxO3a [11]. Despite the fact that it was later demonstrated that SOD-3 is not essential to the longevity phenotype in *daf-2* mutants [12], a link was established between forkhead box transcription factors and cellular antioxidant defense.

The purpose of this review is to provide an overview on the role of FoxO transcription factors in the cellular response to (oxidative) stress – including antioxidant defense – and on the

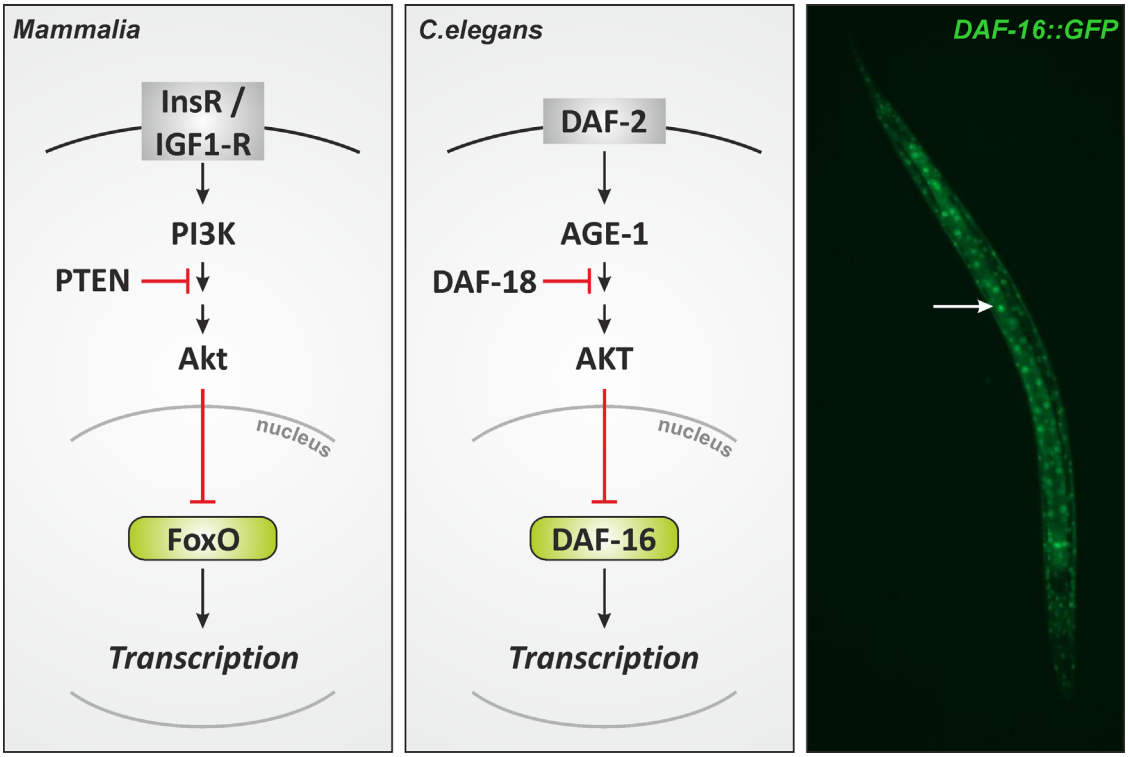

Fig. 1. Insulin signaling in mammalian cells and in *C. elegans*. See text for further details. Right panel: *C. elegans* transgenic strain TJ356 stably expresses a DAF-16::GFP fusion protein. DAF-16::GFP accumulates in nuclei upon exposure of worms to an oxidative stress (induced by diamide, a thiol oxidizing agent). Speckles (arrow) represent nuclei with DAF-16::GFP.