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Review

Interplay between FOXO, TOR, and Akt☆

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ABSTRACT

FOXO transcription factors have emerged as rheostats that coordinate the activities of Akt and targets of rapamycin complexes (TORCs). This review summarizes the regulatory circuits mediated by the activation of FOXO, which in turn modulate Akt and TORCs activities. The biological significance of these regulatory circuits is discussed in this article. This article is part of a Special Issue entitled: P13K-AKT-FoxO axis in cancer and aging.

1. Introduction

The phosphatidylinositol 3-kinase (PI3K)/Akt signaling pathway, which leads to the inhibition of the forkhead box O (FOXO) transcription factors is highly conserved across metazoans (Fig. 1). In both *Caenorhabditis elegans* and *Drosophila*, FOXO transcription factors are inhibited predominantly by the activation of insulin (Ins) or insulin-like growth factor receptors (Ins/IGF1R). Insulin and insulin-like growth factor receptors have similar functions across species. They exert their effects through the phosphorylation and activation of insulin receptor substrates (IRS), which provide docking sites for the interaction and activation of downstream effectors. In mammals, FOXO transcription factors are also inhibited by any extracellular signal that activates the serine/threonine kinase, Akt, which is also known as protein kinase B (PKB). Akt is activated by extracellular signals that activate PI3K. PI3K phosphorylates phosphoinositols to generate phosphatidylinositol 3′ phosphate (PIP3). The binding of PIP3 to the pleckstrin homology (PH) domain of Akt is the rate-limiting step in Akt activation. This binding elicits the translocation of Akt to the membrane, where it is fully activated by other kinases. Akt is phosphorylated at threonine residue 308 (Thr 308) by PDK1 and at a serine residue (Ser 473) by mTORC2, which is a rapamycin-resistant complex containing the mammalian target of rapamycin (mTOR) (for review, see [1]) (Fig. 2). Antagonizing PI3K activity negatively regulates Akt activity. For instance, Akt activity is negatively regulated by phospholipid phosphatases that dephosphorylate PIP3. The major phospholipid phosphatase that regulates Akt activity is the tumor suppressor PTEN, which dephosphorylates the 3′ phosphate of PIP3 and thereby negates the activity of PI3K. The most evolutionarily conserved downstream effectors of Akt are the FOXO transcription factors, which include FOXO1, 3, 4, and 6 in mammals [2]. Another conserved target of Akt is the target of rapamycin complex 1 (TORC1) (reviewed in [1], which is indirectly activated by Akt (Fig. 1)).

FOXO transcription factors, across species, have highly conserved phosphorylation sites that are phosphorylated by Akt. The phosphorylation of FOXOs by Akt in the nucleus creates a 14-3-3 binding site. The binding of 14-3-3 to FOXO masks the nuclear localization signal (NLS) and prevents nuclear translocation, thereby inhibiting the activities of FOXO (reviewed in [3]). FOXO transcription factors, across species, possess other phosphorylation sites that can be phosphorylated by the stress inducible kinases, Jun N-terminus kinase (JNK) and STE20-like protein kinase 1 (MST1). The activation of FOXO, initiated by the phosphorylation by JNK and MST1, is dominant to the inhibitory phosphorylation by Akt (reviewed in [3], Fig. 2).

The PI3K/Akt/FOXO pathway was delineated in *C. elegans* in a genetic screen for lifespan extension [4–7]. Mutations that attenuate the activities of the insulin receptor ortholog, DAF-2, and the PI3K ortholog, AGE-1, inhibit Akt activity and can also extend the lifespan of worms. The

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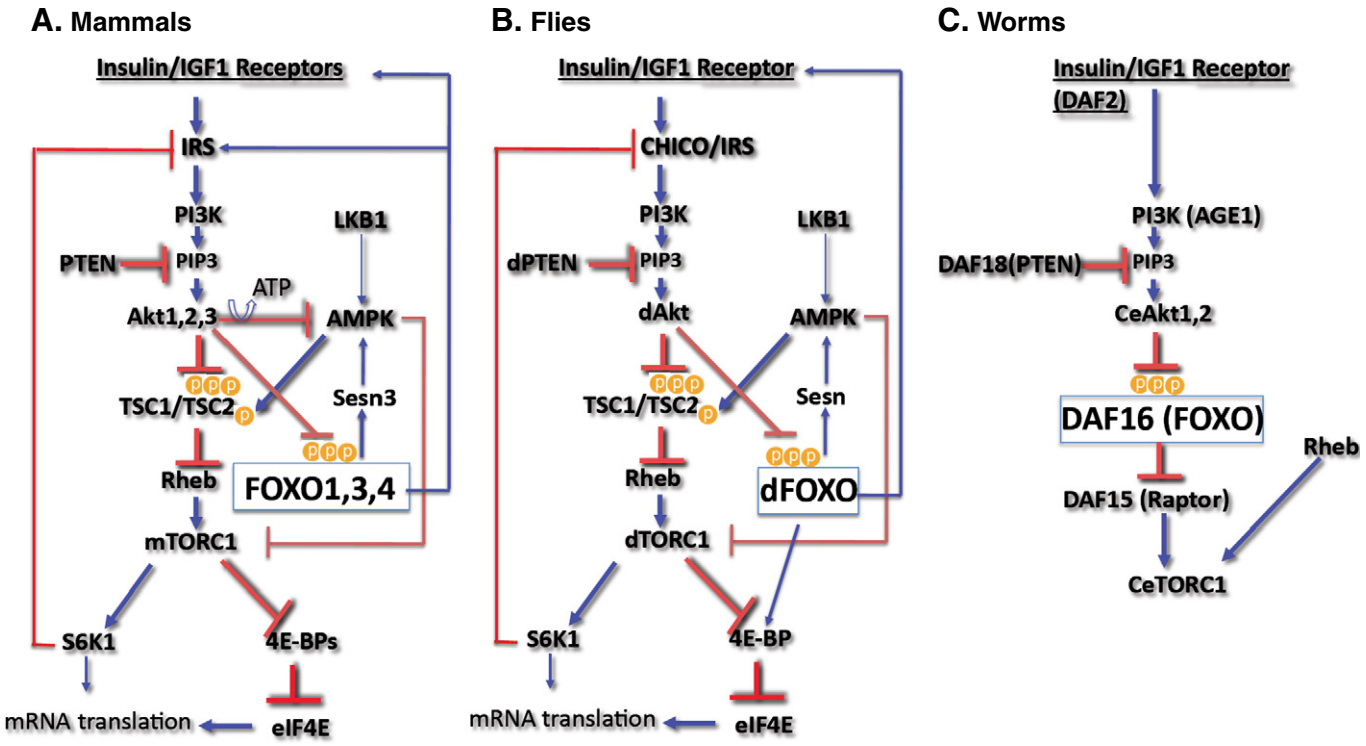

Fig. 1. The interplay between FOXO, TOR, and Akt. A. The signaling pathway from Insulin/IGF1 receptor through IRS, PI3K, and Akt in mammalian cells. Akt inhibits FOXO through direct phosphorylation, and indirectly activates mTORC1, which in turn elevates protein synthesis. mTORC1 and its downstream effector, S6K, elicit negative feedback loops to inhibit Akt. When activated FOXO induces the expression of Sestrin 3, which activates AMPK to inhibit mTORC1. FOXO also induces Insulin/IGF1 receptors, IRS2, and Rictor expression to activate Akt (see text for details). B. The signaling pathway from Insulin/IGF1 receptor through IRS, PI3K, and Akt in flies. The mechanisms of FOXO inhibition and mTORC1 activation by Akt are conserved in flies and mammals. In flies, the mechanism of TORC1 inhibition by FOXO through Sestrin and AMPK is conserved. In addition, FOXO elevates the expression of 4E-BP downstream of TORC1, and induces the expression of Insulin/IGF1 receptor to activate Akt (see text for details). C. The signaling pathway from the Insulin/IGF1 receptor through PI3K, and Akt in worms. The inhibition of FOXO by Akt is conserved in worms. However, the mechanism of TORC1 activation by Akt is not conserved. Akt can activate TORC1 through inhibition of FOXO because FOXO inhibits the expression of Raptor, which is required for TORC1 activity (see text for details).

increase in lifespan by the inhibition of PI3K and Akt activities is largely a consequence of DAF-16 activation, which is the C-elegans ortholog of FOXO. Mutations that inhibit the activity DAF-16 revert the lifespan extension phenotype [8,9]. The role of the PI3K/Akt/FOXO signaling in longevity appears to be conserved across species (reviewed in [3,10]).

2. Regulatory circuits that mediate interplays between FOXO, TOR and Akt

Like FOXO transcription factors, TOR complexes, which share TOR as their catalytic subunit, are highly conserved across evolution. TOR

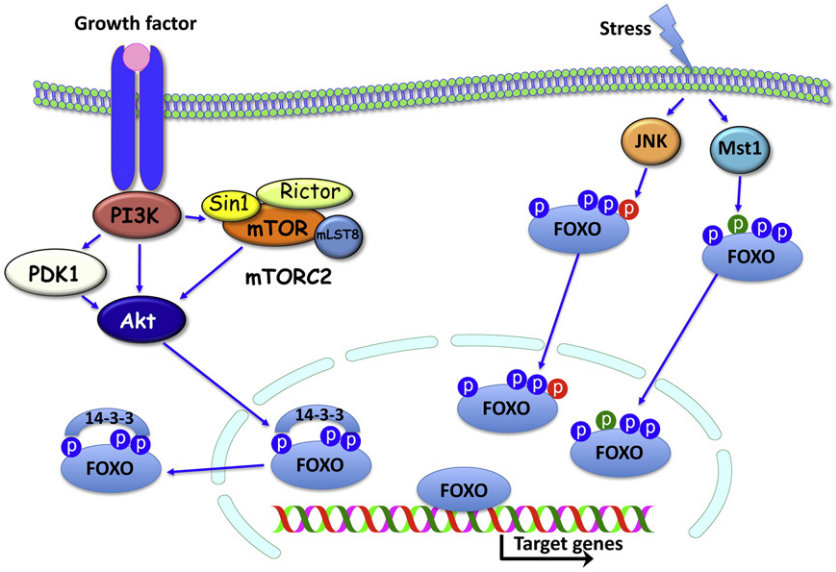

Fig. 2. The regulation of FOXO activity by Akt activation, and by JNK and MST1 activation. Akt is activated by PI3K downstream of tyrosine kinase growth factor receptors. PI3K also activates PDK1 and mTORC2, which are composed of mTOR, Rictor, Sin1 and mLST8. PDK1 and mTORC2 phosphorylate Akt for full activation. Upon activation Akt phosphorylates FOXO and creates docking site for 14-3-3. The binding of 14-3-3 to FOXO excludes FOXO from the nucleus. Oxidative and genotoxic stresses activate JNK and MST1. JNK and MST1 phosphorylate FOXO at two different sites. The phosphorylation by JNK or MST1 promotes the nuclear localization of FOXO despite phosphorylation by Akt (see text for details).

complex 1 (TORC1) is a conserved downstream effector of Akt, and TOR complex 2 (TORC2) is a conserved activator of Akt. The defining subunits of the two mammalian TORCs (mTORCs) are the regulatory associated proteins of mTOR (Raptor) in mTORC1 and Rapamycin-insensitive companion of mTOR (Rictor) in mTORC2, which are also evolutionarily conserved. mTORC1 is composed of mTOR, Raptor, mLST8 as the core kinase complex, and the accessory factors PRAS40 and Deptor [11]. One mechanism by which Akt activates mTORC1 is through direct phosphorylation of tuberous sclerosis complex 2 (TSC2), which otherwise inhibits mTORC1 activity (Fig. 1; reviewed in [12]). Tuberous sclerosis complex 1 (TSC1) and TSC2 form a heterodimer that possesses GAP activity and inhibits the activity of Rheb, a small GTPase required for mTOR activation (Fig. 1; reviewed in [1]). TSC2 can be activated when intracellular levels of ATP are reduced and AMPK activity is elevated. AMPK directly phosphorylates TSC2, leading to the induction of mTORC1 inhibition [13]. Additionally, AMPK inhibits mTORC1 through direct phosphorylation of Raptor [14], which is a conserved mechanism that might be the major pathway by which AMPK affects TORC1 in flies (Fig. 1). However, AMPK phosphorylation sites are not fully conserved in the *Drosophila* TSC2. Akt also activates mTORC1 by maintaining intracellular ATP levels and reducing AMPK activity [15].

In TSC2- or TSC1-null cells, mTORC1 is constitutively activated, independent of growth factors and Akt, which is consistent with an inhibitory role for TSC2. In contrast, Akt activity is markedly reduced in these cells. This reduction has been attributed to a negative feedback mechanism involving an inhibitory effect of S6 Kinase (a downstream effector of mTORC1) on insulin receptor substrate-1 (IRS1) or IRS2, which mediates PI3K activation by insulin and IGF-1 [23]. Additional negative regulatory loops elicited by mTORC1 that inhibit Akt activity may also exist [1].

The other mTOR complex, mTORC2, is composed of Rictor, mLST8 and mSin1 as the core kinase complex (Fig. 2), and the accessory factors Deptor and Protor-1 [11]. mTORC2 is the carboxy-terminus hydrophobic motif (HM) kinase for Akt and other AGC kinases.

One major conserved function of mTORC1 is to increase mRNA translation (Fig. 1) via the phosphorylation and activation of S6 kinase and by the phosphorylation and inhibition of the eukaryotic translation initiation factor 4E (eIF4E) binding protein (4E-BP), which is a repressor of mRNA translation [12]. The hypophosphorylated active form of 4E-BP binds eIF4E and blocks the interaction of eIF4E with eIF4G, thereby inhibiting cap-dependent mRNA translation. In addition to protein synthesis, mTORC1 has another conserved anabolic activity that involves fatty acid biosynthesis through the activation of the sterol-regulatory-element-binding protein (SREBP1) [16]. SREBP1 is a transcription factor that facilitates fatty acid synthesis by regulating the expression of enzymes associated with fatty acids synthesis. Finally, mTORC1 has a conserved function in inhibiting autophagy by phosphorylating proteins that are required for its initiation [17].

Unlike in mammals and flies, the insulin/IGF1-Akt axis has not been shown to regulate *C. elegans* TORC1 (CeTORC1). The *C. elegans* genome lacks readily identifiable homologs of TSC1 and TSC2 [18], which mediate the effect of Akt on mTORC1, but C. *elegans* Akt (CeAkt) can indirectly increase CeTORC1 activity via the phosphorylation and inhibition of the *C. elegans* FOXO transcription factor, DAF-16. DAF-16 has a potent negative effect on DAF-15 (*C. elegans* Raptor) expression [19], and therefore, the inhibition of DAF-16 by CeAkt could maintain the availability of Raptor/DAF-15 to form CeTORC1. Thus, in nematodes, Akt indirectly activates TORC1 through the inhibition of DAF-16 and the elevation of Raptor expression (Fig. 1). In contrast, the activation of DAF-16 by the stress inducible kinase, JNK, would inhibit TORC1. It is not known if, like in mammals and flies, the activation of CeTORC1 elicits a negative feedback loop to inhibit IGF1/insulin signaling and Akt. If such a negative feedback loop exists in *C. elegans*, it would imply that the activation of DAF-16 by oxidative stress would lead to the inhibition of TORC1 and the activation of Akt.

In *Drosophila*, there are two major identified regulatory circuits by which FOXO regulates TORC1 and Akt activity (Fig. 1). It was shown that in *Drosophila*, 4E-BP is a transcriptional target of FOXO. Therefore, following the activation of FOXO in flies, 4E-BP is elevated and counteracts TORC1 activity on the initiation of cap-dependent mRNA translation. However, at the same time, FOXO upregulates the transcription of the insulin receptor (InsR) mRNA, which possesses an internal ribosome initiation site (IRES). Therefore, the high level of insulin receptor mRNA induced by FOXO is coupled to a high level of InsR protein through IRES-dependent mRNA translation, even though cap-dependent mRNA translation is inhibited. Consequently, the inhibition of cap-dependent mRNA translation by FOXO could be alleviated through the high levels of insulin receptor and the hyperactivation of Akt and TORC1 [20,21].

The upregulation of InsR by FOXO appears to be conserved in mammals, as it was found that FOXO activates InsR transcription, at least in liver and muscle cells [20]. It was also shown that FOXO elevates IRS2 mRNA levels, thereby potentially elevating signaling downstream of InsR or IGF1R. Notably, IRS2 protein is degraded by a mechanism that is dependent on mTORC1 or its downstream effector, S6K1 [22]. More recently, it was shown that FOXO elevates HER2/HER3 tyrosine kinase receptor expression in several cancer cell lines [23] in addition to InsR and IGF1R. The elevation of tyrosine kinase receptors by FOXO establishes feedback mechanisms that amplify growth factor signaling and limit prolonged FOXO activation.

Another regulatory circuit through which FOXO affects TORC1 in *Drosophila* was recently uncovered [24]. It was found that FOXO indirectly activates AMPK, which in turn activates TSC2 and inhibits TORC1 activity. FOXO activates AMPK through the transcriptional upregulation of Sestrin. Sestrins are a family of highly conserved proteins that were originally discovered in mammals as antioxidants [25,26]. However, it was found that they have an additional function that leads to the activation of AMPK, although the exact mechanism by which Sestrin activates AMPK is not fully understood [27]. This pathway, by which FOXO inhibits TORC1 in flies, manifests in conditions of oxidative stress, whereby FOXO is activated by stress inducible kinases, JNK or MST1.

The FOXO-Sestrin-AMPK-TORC1 axis is conserved in mammalian cells (Fig. 1). Mammalian FOXO1 was shown to bind to the promoter region of Sestrin 3, and transcriptionally elevate Sestrin 3 expression [28]. Sestrin 3 is one of three members of the Sestrin family. Sestrin 1 and 2 were shown to be transcriptional targets of p53 [27], whereas Sestrin 3 is induced by FOXO [28,29]. Sestrin 3 has a dual activity downstream of FOXO. In its role as a scavenger of ROS, Sestrin 3 mediates ROS detoxification by FOXO and inhibits cellular senescence [29], and as an activator of AMPK, it inhibits mTORC1 in a TSC2-depedent manner [28]. Thus, by analogy to p53, which induces the expression of Sestrin 1 and 2, reduces ROS levels and inhibits mTORC1, FOXO induces the expression of Sestrin 3 to reduce ROS and inhibit mTORC1 (Fig. 3). Notably, FOXO itself is subjected to regulation by the energy status of cells, as AMPK was shown to phosphorylate FOXO and facilitate its nuclear localization [30]. Therefore, the FOXO-Sestrin-AMPK axis could be further augmented by AMPK through a feed-forward mechanism.

The inhibition of mTORC1 by FOXO could lead to the activation of Akt via the inhibition of the negative feedback loop driven by mTORC1 and S6K1 (Fig. 1). However, FOXO also elevates transcriptional expression of Rictor through a DNA-binding independent mechanism. This elevation of Rictor by FOXO increases mTORC2 and Akt activity. The increase in Akt activity is due to the increase in assembly and activity of mTORC2, which occurs at the expense of the assembly and activity of mTORC1 [28]. Therefore, the elevation of Rictor by FOXO constitutes another mechanism by which FOXO could inhibit mTORC1 in a TSC-independent mechanism.

As indicated above, FOXO elevates both InsR and IRS2 mRNA but IRS2 protein is degraded by mTORC1. Therefore, the inhibition of

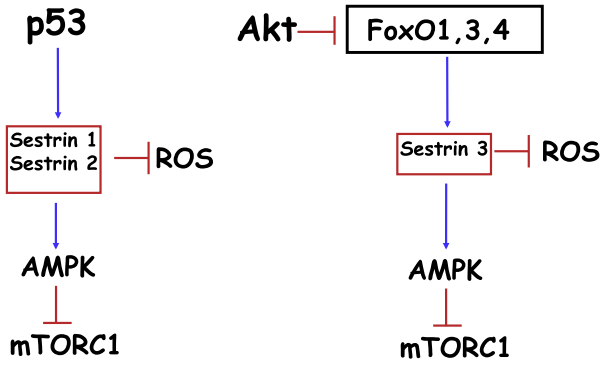

Fig. 3. Analogy between p53 and FOXO activities. By analogy to p53, which induces Sestrin1 and Sestrin2 transcriptionally, FOXO induces Sestrin3 transcriptionally. p53 reduces ROS and inhibits mTORC1 through the induction of Sestrin1 and 2 expression, while FOXO reduces ROS and inhibits mTORC1 through the induction of Sestrin3 expression.

mTORC1 by FOXO could further augment Akt activity through InsR and IRS2 (Fig. 1).

There are other potential mechanisms by which FOXO could regulate Akt and mTOR activities. For instance, FOXO suppresses the expression of the pseudokinase, tribbles 3 (Trb3) [31], and it was reported that Trb3 inhibits Akt activity [49]. Thus, by suppressing Trb3 expression, FOXO could activate Akt. It was also reported that FOXO elevates the expression of Bnip3 [50]. Because Bnip3 was shown to inhibit mTORC1 activity downstream of TSC2 by interfering with Rheb activity [51], FOXO could inhibit mTORC1 through the induction of Bnip3 expression. Finally, it was recently reported that FOXO3 induces the transcriptional expression of TSC1 and inhibit mTORC1 [32].

3. The biological significance of the FOXO, TOR, AKT interplay

The inhibitory effect of FOXO on TORC1 could explain, at least in part, some of FOXO activities that phenocopy TORC1 inhibition. For instance, the activation of FOXO extends lifespan, whereas the activation of TORC1 reduces it [33]. Thus, it is possible that one mechanism by which FOXO extends lifespan is through the inhibition of TORC1. Heterozygous DAF-15 (Raptor ortholog) worms and CeTOR RNAi-treated worms have an extended adult life span [19,34], similar to DAF-2, the ortholog of insulin/IGF1 receptor and age-1 (CePI-3kinase), mutant worms and DAF-16 (FOXO ortholog) overexpressing strains. In addition, DAF-15 and CeTOR homozygous mutant larvae accumulate lipids, similar to DAF-2 mutant dauer larvae [19,34]. Thus, at least some of the effects of the DAF-2/Akt/DAF-16 pathway (such as longevity) may be mediated through regulation of CeTOR/DAF-15.

In *Drosophila*, it was shown that 4E-BP extends lifespan and is required for the extension of lifespan by dietary restriction (DR) [33]. Although FOXO-null flies respond normally to DR, it cannot be completely excluded that the transcriptional induction of 4E-BP by FOXO, in flies, contributes to the ability of FOXO to extend lifespan. Supporting this possibility are the findings, which show that overexpression of 4E-BP in FOXO-null flies, which are sensitive to oxidative stress, restores oxidative stress resistance [35]. Furthermore, either the overexpression of 4E-BP or activation of FOXO delays proteostasis during muscle aging in flies, and FOXO exerts its effect on muscle aging through the induction of 4E-BP expression [36].

The FOXO-Sestrin-AMPK-TORC1 axis in flies was shown to alleviate several age-related pathologies in response to oxidative stress, such as muscle degeneration, cardiac arrhythmia, and lipid accumulation [24]. Because FOXO can also improve cardiac aging in flies by increasing 4E-BP levels [37], it could affect fly aging pathologies by both decreasing TORC1 activity and increasing 4E-BP levels.

FOXO transcription factors, across species, promote resistance to oxidative stress, premature aging, and cellular senescence. This activity of FOXO was attributed largely to its ability to induce the expression of antioxidants. By contrast, the anabolic activities of TORC1 induce oxidative stress, and chronic activation of mTORC1 induces premature senescence [33,38–40]. Thus, the inhibition of TORC1 by FOXO, which occurs across species by different mechanisms, could add another way by which FOXO reduces oxidative stress and inhibits premature aging and cellular senescence.

FOXO transcription factors are thought to have tumor suppressive activity [41] whereas mTORC1 is frequently activated in cancer cells [1]. Both the activation of FOXO and the inhibition of mTORC1 elicit cell cycle arrest or attenuation of cell proliferation. Thus, the inhibition of mTORC1 could account for some of FOXO's tumor suppressor activities.

Other consequences of FOXO activation and mTORC1 inhibition that phenocopy each other include cellular atrophy and autophagy. Both the activation of FOXO and the inhibition of mTORC1 elicit cellular atrophy [42–45]. Therefore, it is possible that the inhibition of mTORC1, by activated FOXO, contributes to cellular atrophy. The activation of mTORC1 is known to inhibit autophagy, and it was also shown that autophagy could be mediated by the activation of FOXO [46].

As described above, the inhibitory effect of FOXO on TORC1, at least in flies and mammals, is associated with simultaneous direct or indirect Akt activation, indicating that under normal physiological conditions, the effect of FOXO on TORC1 may occur in a temporal manner. In flies, at the organismal level, the induction of 4E-BP by FOXO in combination with the induction of Insulin/IGF-1 receptor transcription and mRNA translation was considered to be an adaptive response to nutrient availability (reviewed in [47]). When nutrients are limiting, insulin secretion is reduced and FOXO is activated. This inhibits cell proliferation and growth by elevating 4E-BP expression as well as Sestrin expression that inhibits TORC1. Consequently, cap-dependent mRNA translation and the other anabolic activities of TORC1 are repressed.

The anabolic activities of TORC1 consume nutrients and cellular energy, and thus, reducing these activities reduces demand for nutrients. The simultaneous induction of Insulin/IGF-1 receptor mRNA by FOXO, in conjunction with its IRES-dependent mRNA translation, increases the number of receptors at the cell surface, thereby increasing sensitivity to insulin. Thus, when nutrients become abundant, the cells are hypersensitized to the concomitant increase in insulin levels, which inhibit FOXO and promote cell growth and proliferation. A similar scenario could occur under other stress conditions, such as oxidative stress when FOXO is activated by the stress inducible kinases. If the stress conditions are prolonged, the inhibition of TORC1 by FOXO could induce autophagy as a rescue mechanism.

In mammalian cells, the activation of FOXO under stress conditions promotes the inhibition of mTORC1 by inducing the expression of Sesn3 and Rictor, which also leads to the activation of Akt. This mechanism was shown to maintain cellular energy homeostasis under stress conditions [28]. By shutting down the anabolic activities of mTORC1, such as protein synthesis and lipid biosynthesis, which consume energy, and by activating Akt, which increases energy production, FOXO maintains cellular energy homeostasis (Fig. 4). Through this mechanism, FOXO uncouples Akt and mTORC1 activities and prevents energy crisis. Under normal physiological conditions, this mechanism could constrain high mTORC1 activity. Under conditions of reduced growth factors, FOXO is activated due to reduced Akt activity. The regulatory circuit induced by FOXO, under these conditions, acts in a temporal manner since it does not permit prolonged FOXO activation and mTORC1 inhibition because of Akt activation. However, under oxidative stress conditions, the activation of FOXO by the stress inducible kinases is dominant to the inhibition of FOXO activity by Akt and, thus, could induce prolonged mTORC1

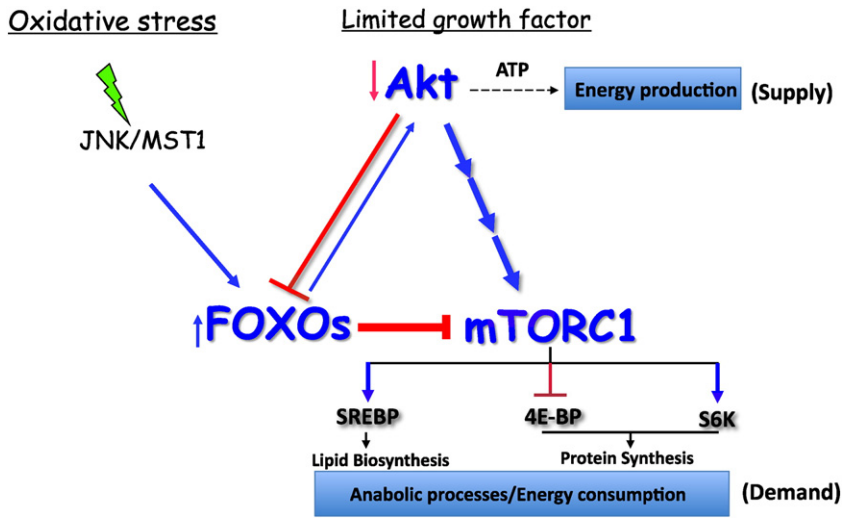

Fig. 4. FOXO maintains cellular energy homeostasis by coordinating cellular supplies and demands. Under conditions of growth factor limitation or other cellular stresses, FOXO transcription factors are activated, and inhibit the anabolic energy consuming functions of mTORC1, while activating Akt to facilitate energy producing processes. Prolonged stress conditions and activation of mTORC1 could induce autophagy (see text for details).

inhibition. By analogy to what was shown in flies, if stress conditions persist, the activation of mTORC1 by the FOXO-Sestrin3-AMPK axis could induce autophagy. Notably, as was recently reported, AMPK activation alone is sufficient to induce autophagy through the direct phosphorylation and activation of the ATG1 ortholog ULK1, which initiates the autophagic cascade [48]. Thus, the FOXO-Sestrin3-AMPK-mTORC1 axis could initiate autophagy both by inhibiting mTORC1, which otherwise inhibits ULK1, and by activating AMPK, which activates ULK1.

4. Concluding remarks

The picture that has emerged from the studies described in this review is that FOXO acts as a rheostat that, through fine-tuned mechanisms, coordinates intracellular supplies and demands. FOXO senses extracellular environment and responds accordingly. In the absence of extracellular stress, FOXO maintains a cellular homeostatic balance by preventing the hyperactivation of TORC1 relative to the activity of Akt. However, because in absence of extracellular stress FOXO executes this activity in a temporal manner, it would be difficult to follow this FOXO activity in a cell population, as this activity might not be synchronized. Consequently, if FOXO activity is followed in a population of cells in the absence of extracellular stress, it might be concluded that FOXO is relatively dormant. Therefore, to follow and quantify this oscillatory activity of FOXO, experiments should be designed to monitor the effect of FOXO on TORC1 and Akt at the single cell level using systems biology.

In response to environmental stress, FOXO may act in a temporal manner, but if the environmental stress is prolonged, FOXO activity might be shifted toward the inhibition of TORC1 to limit cellular demands under these conditions. In this respect, FOXO acts as a "gate keeper" that prevents cellular crisis. The activities of FOXO are consistent with its role in cellular lifespan and aging. It remains to be determined how much of FOXO's effect on aging is determined by its effect on TORC1. Similarly, it should be determined how much of FOXO's role in cellular atrophy, autophagy, and cell cycle is attributed to its effect on TORC1.

In light of the studies described in this review, the definition of FOXO as a tumor suppressor, in that its activation has a therapeutic advantage for cancer, becomes questionable. The suppressive effect of FOXO activation on mTORC1 could potentially have a positive impact on cancer therapy. However the coupling to the activation of Akt and upstream signaling, and in particular tyrosine kinase receptors activation, as was shown recently [23], poses the question of whether the inhibition of FOXO is preferred over it activation for cancer therapy.

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