



## Review

## Homeostatic interplay between FoxO proteins and ER proteostasis in cancer and other diseases

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## ABSTRACT

Cancer cells are exposed to adverse conditions within the tumor microenvironment that challenge cells to adapt and survive. Several of these homeostatic perturbations insults alter the normal function of the endoplasmic reticulum (ER), resulting in the accumulation of misfolded proteins. ER stress triggers a conserved signaling pathway known as the unfolded protein response (UPR) to cope with the stress or trigger apoptosis of damaged cells. The UPR has been described as a major driver in the acquisition of malignant characteristics that ultimately lead to cancer progression. Although, several reports describe the relevance of the UPR in tumor growth, the possible crosstalk with other cancer-related pathways is starting to be elucidated. The Forkhead Box O (FoxO) subfamily of proteins has a major role in cancer progression, where chromosomal translocations and deregulated signaling lead to loss-of-function of FoxO proteins, contributing to tumor progression. Here we discuss the homeostatic connection between the UPR and FoxO proteins and its possible implications to tumor progression and the acquisition of several hallmarks of cancer. In addition, studies linking a crosstalk between the UPR and FoxO proteins in other diseases, including neurodegeneration and metabolic disorders is provided.

## 1. Introduction

Tumor cells are exposed to several cell-intrinsic and microenvironmental perturbations that generate a selective pressure triggering adaptive mechanisms that favor cellular transformation. These conditions include nutrient deprivation, hypoxia, acidosis, oncogenic activation and exacerbated secretory capacity, all of which can alter the control of protein homeostasis or proteostasis through the accumulation of misfolded proteins at the endoplasmic reticulum (ER) lumen, a cellular state known as “ER stress” [1,2]. This condition engages an adaptive response termed as unfolded protein response (UPR), a signal transduction pathway that transduces information about protein folding status in the ER lumen to the nucleus and cytosol in order to increase protein folding capacity and the degradation of unfolded proteins via the ER-associated degradation (ERAD) pathway [3,4]. However, under irreversible ER stress, the UPR switches its signaling and induce apoptosis of damaged cells [5,6]. Accumulating evidence suggests that the UPR allows cancer cells to survive to adverse

environments, promoting cell survival and growth [7]. During the last decade, ER stress signaling has been described as a pro-oncogenic mechanism in tumorigenic processes and have been linked to most hallmarks of cancer [8].

Recent evidence has linked the activity of the UPR with members of the Forkhead Box (Fox) family of proteins and the maintenance of cellular proteostasis in the context of various diseases (see below) [9]. Fox proteins consists of a superfamily of transcriptional regulator factors that controls various biological processes composed by 5 subclass Fox A-C-M-O and P [10]. All the Fox transcription factors have been described as components of different signaling pathways and function either as tumor suppressor genes or oncogenes. FoxO proteins is the most studied subclass of Fox family members that altogether operate as regulators of cell proliferation and survival, including FoxO1, FoxO3A, FoxO4 and FoxO6 [11]. Deregulation of FoxO function has been observed in different cancer models, impacting tumorigenesis and cancer progression [12]. Here we overview available evidence supporting the contribution of UPR to cancer biology and other diseases and speculate

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about the possible relation with FoxO proteins.

1.1. ER stress and the unfolded protein response

Fast growing tumors undergo metabolic challenges that generates a dependency to the secretory capacity of the cell [13]. Intrinsic perturbations such as genetic mutations, activation of oncogenes, increased secretory demand and reactive oxygen species can result on the overload of the secretory pathway triggering ER stress [1]. Tumor cells engage a UPR as an adaptive mechanism to cope with misfolded proteins and sustain proteostasis [14]. The UPR activates transcriptional and post-transcriptional mechanisms in order to improve protein folding capacity [15]. When cells are unable to adapt to ER stress, the UPR engages a variety of apoptotic pathways to eliminate damaged cells [6,16]. ER stress generates a selective pressure to select cancer cells that can survive through the activation of the UPR [7]. Of note, ER stress is also emerging as a common feature in different pathological conditions such as neurodegeneration, inflammatory diseases and diabetes, among others (Reviewed in [17]).

The UPR is mediated by at least three stress sensors localized at the ER membrane: activating transcription factor 6 (ATF6) alpha and beta, the PKR-like ER kinase (PERK), and the inositol-requiring enzyme 1 (IRE1) alfa and beta [14,15]. Under basal conditions the luminal domains of these three sensors are constitutively bound to BiP (also known as GRP78). When unfolded proteins accumulate in the ER, BiP dissociates from the UPR sensors to bind misfolded proteins, leading to their activation [15]. PERK activation leads to inhibition of the global protein translation through the phosphorylation of the eukaryotic translation initiation factor (eIF2α), resulting in an instant reduction of protein synthesis and thus reducing ER load [18]. The phosphorylation of eIF2α allows the selective expression of activating transcription factor 4 (ATF4), which regulate genes involved in protein folding, antioxidant responses, autophagy, amino acid metabolism and apoptosis [19,20]. ATF6 is a type II transmembrane protein bearing transcription

factor activity in its cytosolic domain and is located at the ER under basal conditions. Upon ER stress, ATF6 is transported to the Golgi apparatus where it is processed by S1P and S2P proteases, releasing the cytosolic fragment ATF6f, a potent transcription factor that regulates the expression of genes involved in to ERAD and ER proteostasis control [21,22]. Finally, IRE1α is a kinase and endoribonuclease that represents the most conserved branch in the UPR response. Upon activation, IRE1α catalyzes the unconventional splicing of X-box binding protein-1 (XBP1) mRNA removing a 26-nucleotide intron. This processing event changes the open reading frame of XBP1 mRNA leading to the translation of a new protein termed XBP1s (spliced form) [23]. XBP1s acts as a potent transcription factor and modulate the expression of several UPR-target genes involved in protein folding, glycosylation, and ERAD [24]. In addition, the IRE1α endoribonuclease activity can target other mRNAs and microRNAs through a process termed regulated IRE1-dependent decay (RIDD) [25]. Under prolonged or chronic ER stress the UPR triggers apoptosis through distinct mechanisms including the upregulation of the transcription factor CHOP through ATF4, the regulation of microRNAs, inflammation, RIDD, the upregulation of BCL-2 family members, calcium signaling, among other mechanisms [5,6,26]. Overall the UPR operates a central pathway determining cell fate under ER stress by integrating information about the duration and intensity of stress stimuli toward the establishment of adaptive programs or a terminal UPR that results in cell demise.

1.2. ER stress and cancer: an overview

Tumor growth involves the generation of microenvironmental challenges that alter the proper function of the cell including hypoxia, nutrient deprivation, acidosis, among others [27]. Tumorigenesis involves several molecular events including genome instability, amplification and mutations of genes, activation of oncogenes and increased secretory demands that ultimately results in a strong selective pressure toward malignancy [13,28]. Importantly, in addition to operate as a

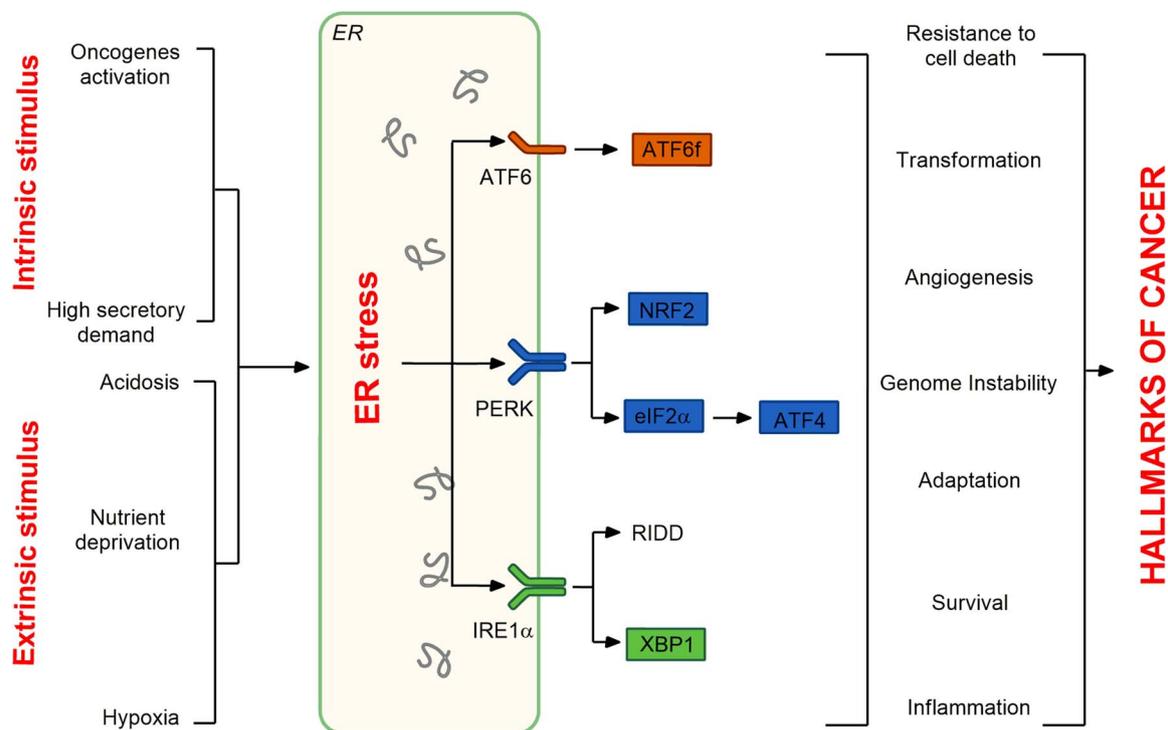


Fig. 1. The Unfolded protein response in Cancer tumorigenesis.

Different extrinsic and intrinsic stimulus that affects ER physiology generates a condition termed Endoplasmic reticulum (ER) stress. Tumor cells activates the unfolded protein response (UPR) to adapt and restore proteostasis. Upon ER stress, the IRE1α endoribonuclease activity regulates the expression of the transcription factor XBP1s, in addition to degrade several mRNAs by regulated IRE1-dependent decay (RIDD). PERK signaling blocks general translation through eIF2α phosphorylation and regulates de expression of ATF4. Upon ER stress, ATF6 protein is cleaved at the Golgi and generates de active transcription factor ATF6f. Altogether the UPR regulates a series of processes involved in cancer progression and pathogenesis.

survival pathway against the adverse microenvironment generated in solid tumors, recent studies have increased the complexity of the involvement of ER stress signaling in cancer, because it can impact the acquisition of several hallmarks of cancer (Reviewed in [8]) (Fig. 1).

PERK was the first ER stress pathway implicated in tumorigenesis [29,30]. Since then, fingerprints of UPR activation have been reported in most of human cancers [2]. For instance, overexpression of GRP78, a classical ER stress marker, has been extensively reported in tumors of patients with poor prognosis [31,32]. Also, the three UPR signaling branches have been described as pro-oncogenic pathways in many human tumors and preclinical models (reviewed in [1]). The less studied branch of the UPR in cancer is ATF6. However, data is available suggesting that protein levels of ATF6 are increased in recurrent tumors [33] and metastasis [34], in addition to promote the survival of dormant tumor cells [35].

In contrast to ATF6, the PERK pathway is implicated in many steps of the tumorigenic process [36]. Genetic ablation of PERK leads to reduced tumor size and aggressiveness [37,38]. Moreover, PERK signaling also enhances angiogenesis [38,39], metastasis [2,40,41], cell death resistance, DNA damage responses [42], and dormancy [43,44]. Most of these effects of PERK in cancer require eIF2 $\alpha$  phosphorylation [37]; and also an alternative target known as Nrf2, which regulates the redox status of the cell [45,46]. On the other hand, available data suggest a fundamental role of IRE1 $\alpha$  in cancer. IRE1 $\alpha$  is the fifth kinase presenting more driver mutations in human cancer [47,48]. Biochemical studies suggest that these somatic mutations alter the signaling properties of IRE1 $\alpha$  and may impact IRE1 $\alpha$  stability [49] and its ability to induce cell death [50]. The enzymatic activity of IRE1 $\alpha$  is highly increased in tumor cells and may determine the aggressiveness of cancer. Importantly, studies in patients with glioma [51], breast cancer [52], triple negative breast cancer (TNBC) [53] and pre-B acute lymphoblastic leukemia [54] indicated that high levels of XBP1s in tumors correlate with poor prognosis and decreased patient survival. Interestingly, a recent study suggested opposed functions of XBP1 mRNA splicing and RIDD in the progression of human glioma [55]. Tumors presenting high XBP1s or RIDD activity differentially regulates macrophages infiltration, angiogenesis and invasion, dictating the prognosis of Glioma patients: This report suggest a complex involvement of IRE1 $\alpha$  in tumor progression [55] and the interaction with the stroma [56]. Probably, the most studied cancer involving IRE1 $\alpha$  function are multiple myeloma [57] and Glioblastoma multiforme (reviewed in [58]). In brain cancer IRE1 $\alpha$  and XBP1s have been linked to tumor growth, angiogenesis and invasion [59,60]. XBP1s has been also shown to regulate immune responses against cancer cells [61], angiogenesis [62], and tumor survival through a crosstalk with HIF1 $\alpha$  [53].

In summary, available data suggests that PERK and IRE1 $\alpha$  are relevant players in cancer progression, suggesting that the pharmacological targeting of these stress transducers represent an attractive approach for future therapeutic interventions [17]. Small molecules to inhibit the kinase domain of PERK or the RNase activity of IRE1 $\alpha$  are available [63,64] and can provide beneficial effects in models of human pancreatic tumor xenograft [65,66] and multiple myeloma [67–71].

During the last years, the role of the UPR in cancer progression have gained more complexity due to a series of unanticipated findings linking the UPR to central aspects of tumor biology [72] including mitochondrial bioenergetics [73], immunogenicity, genomic instability and resistance to treatment (Reviewer in [28]) (Fig. 1). In addition, important crosstalk with cancer-related signaling pathways is emerging, including FoxO proteins.

### 1.3. FoxO proteins and regulation

#### 1.3.1. Fox family of proteins

The Fox proteins are transcription factors that play complex and important roles in various biological processes from development and organogenesis to the regulation of metabolism and the immune system

[10,74,75]. The Fox family is constituted by 50 genes in the human genome and 44 in mouse, divided into 19 subfamilies (from FoxA to FoxS) [76,77]. The nomenclature used to classify Fox family members seeks to ensure that the same name is used for orthologous genes in different species to reflect phylogenetic relationships [74].

One of the features that is conserved between all Fox proteins is the forkhead (FKH)-DNA binding domain (DBD) that consists in ~100 amino acids that folds in three  $\alpha$ -helices, three  $\beta$ -sheets and two 'wing' regions that flank a third  $\beta$ -sheet [78]. In contrast to most of helix–turn–helix DNA-binding proteins, forkhead proteins bind DNA as monomers and typically span asymmetrically between 15 and 17 bp [79]. The sequence specificity has been determined for several members of this protein family through selection of binding sites from pools of short and random-sequence duplexes [80]. A seven-nucleotide core corresponds to the best groove base contacts made by the recognition helix [79–81]. Fox protein expression is controlled at multiple levels, including modulation of transcriptional activity, mRNA processing, and post-translational modification of proteins [82,83]. The Fox transcription factors are modular proteins where distinct functions, such as DNA binding, trans-activation or trans-repression, are contained within separable domains [84].

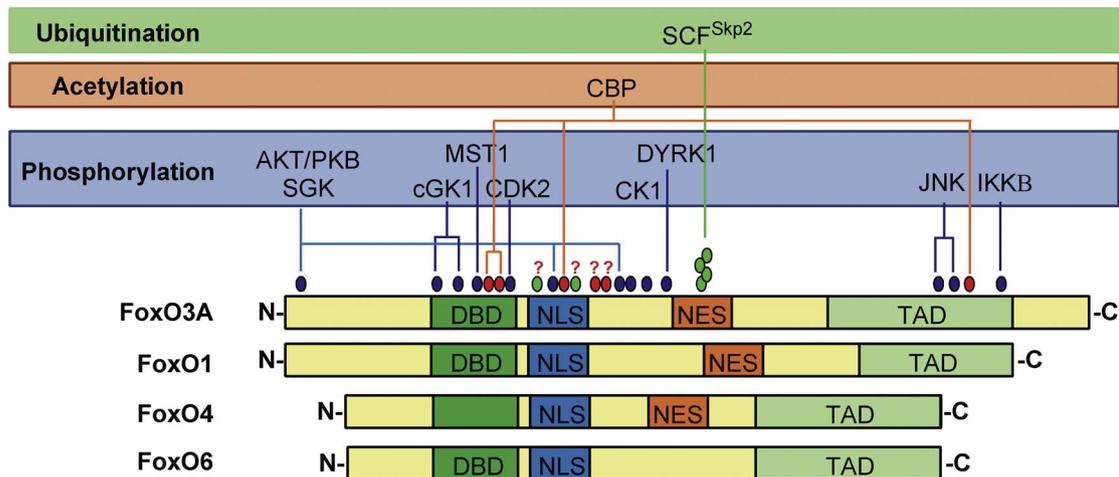
Historically, the first identified member of the forkhead/winged helix class factor transcription (*fkh*) was found in *Drosophila melanogaster* being essential for the formation of terminal structures of the embryo [85]. Since then, new components of this family were discovered with novel and unexpected functions. During the last years, the deregulation of Fox proteins has been reported contributing to cancer initiation, maintenance, and progression, in addition to drug resistance [10,77,86]. The Fox transcription factors FoxA, FoxC, FoxM, FoxO and FoxP proteins are essential components of oncogenic and tumor suppressive pathways; where the FoxO subfamily is better characterized [11].

#### 1.3.2. The FoxO subfamily: regulation and function

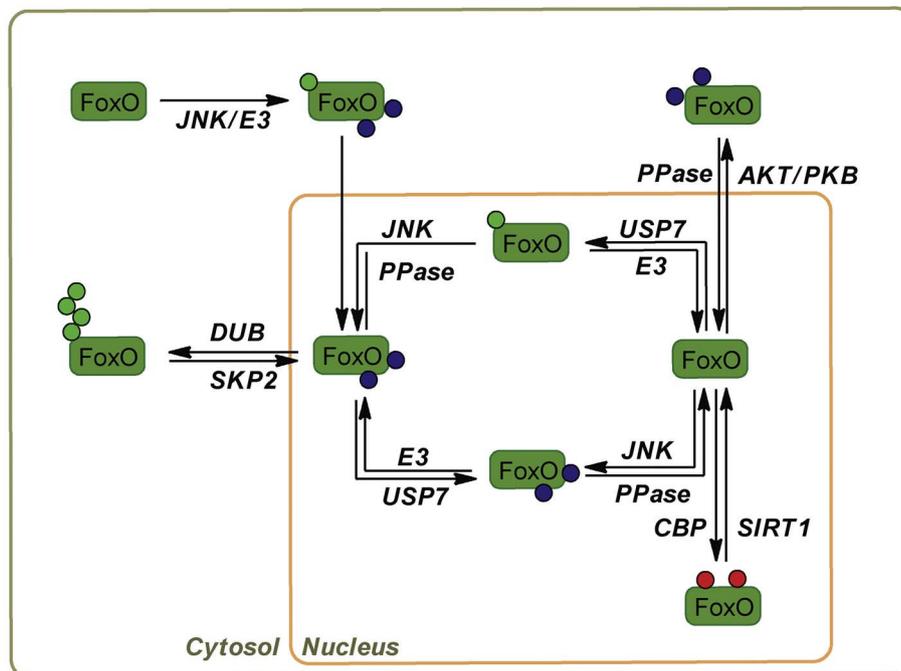
From *C. elegans* to mammals, the class O of forkhead box transcription factors, FoxO are conserved in evolution. In humans there are four members: FoxO1 (FKHR), FoxO3 (FKHRL1), FoxO4 (AFX), and FoxO6 that mainly differ in their tissue-specific expression [74,78,86]. The FKH-DBD of FoxO in humans, in particular helix three, binds at promoters containing the consensus motif 5'-TTGTTTAC-3' [87] that slightly differs from the other components of the Fox family. The FoxO transcription factors are composed by four major domains: forkhead domain (FKH-DBD), a nuclear localization signal (NLS), a nuclear export sequence (NES) and a transactivation domain (TA) (Fig. 2A). Interestingly, the FoxO6 protein does not contain the NES domain. The regulation of FoxO proteins is tightly associated to post-translational modifications that inhibit, misallocate or degrade FoxO [10]. The impact of FoxO in cell biology involves the transcriptional regulation of a wide range of genes involved in cellular processes regulating stress-resistance, metabolism, cell cycle arrest, apoptosis, proteostasis [11,88] (see below).

FoxO proteins function as transcriptional activators that can be inhibited by different signaling pathways (Fig. 2B). For example, in the presence of insulin and insulin-like growth factors (IGF), the phosphoinositide 3-kinase (PI3K) signaling pathway is activated and protein kinases such as protein kinase B (PKB/AKT) and the serum and glucocorticoid-induced kinase (SGK) can directly phosphorylate FoxO factors at three conserved residues, resulting in FoxO exclusion from the nucleus and repression of its transcriptional activity [86,89,90]. The AKT/PKB-mediated phosphorylation inhibits FoxO function by promoting its interaction with 14-3-3 proteins and its re-localization from the nucleus to the cytosol [91]. FoxO can be phosphorylated at diverse residues by several protein kinases (Reviewed in [90]). The mammalian sterile 20 kinase-1 (MST1) [92] or the c-Jun N-terminal kinase (JNK) can also phosphorylate FoxO3 and FoxO4 respectively to induce their nuclear translocation and activation [93,94]. On the other hand, the cyclin-dependent kinase-2 (CDK2) phosphorylates and inhibits FoxO1 upon

**A**



**B**



**Fig. 2.** FoxO subfamily and regulation.

(A) The subfamily of forkhead box transcription factor (FoxO) contains for mayor domains: forkhead domain (FKH-the DNA-binding domain), a nuclear localization signal (NLS), a nuclear export sequence (NES) and a transactivation domain (TA). (B) The regulation of FoxO proteins involves a series of posttranslational modification such as phosphorylation, acetylation and ubiquitination that regulate the transcriptional activity, degradation and localization of FoxO proteins (for a full list of modifications review [91]). The ubiquitination is mostly carried by the SKP1/cullin-1/F-box protein complex that contains the specific substrate-targeting F-box protein SKP2 (SCFSkp2). Acetylation of FoxO proteins is associated to the activity of cyclic-AMP responsive element binding (CREB)-binding protein (CBP). The phosphorylation is carried by a broad spectrum of protein kinases that involves AKT/protein kinase B (AKT/PKB); cGMP-dependent protein kinase-1 (cGK1); mammalian sterile 20 kinase-1 (MST1), cyclin-dependent kinase-2 (CDK2); casein kinase-1 (CK1); dual-specificity tyrosine (Y)-phosphorylation-regulated kinase-1 (DYRK1); c-Jun N-terminal kinase (JNK) and IκB kinase (IKKβ).

DNA damage impacting cell death [95]. Moreover, other phosphorylation events have been described through other protein kinases including cGMP-dependent protein kinase-1 (cGK1) [96], casein kinase-1 (CK1) [97], and dual-specificity tyrosine (Y)-phosphorylation-regulated kinase-1 (DYRK1) [98]. Remarkably, this phosphorylation's induce the export from the nucleus and accumulation of FoxO proteins at the cytosol. Therefore, the phosphorylation status of FoxO transcription factors is a key step in the regulation of gene expression.

Besides phosphorylation, the stability of FoxO proteins is regulated by ubiquitination at the NES and NLS domain (Fig. 2A). Poly-ubiquitination is a constitutive phenomenon that regulates the proteasomal degradation of FoxO proteins [99–101]. In addition, some

cellular perturbations such as oxidative stress can rapidly induce the mono-ubiquitination of FoxO inducing its nuclear translocation [102]. More recently, acetylation has been described as a new posttranslational modification that can regulate FoxO functions (Reviewed in [103]) (Fig. 2B). Histone acetyltransferase cyclic-AMP responsive element binding (CREB)-binding protein (CBP) acetylates and therefore inhibits FoxO activity [104]. However, the Sirtuin (SIRT1) deacetylase can counteract the effects mediated by CBP [105]. In addition, acetylation at residues in the NLS domain are associated with reduced binding to DNA and the translocation of FoxO to the cytosol [105]. In summary, the regulation of FoxO proteins is extremely complex involving multiple post-translational modifications (Fig. 2B).

**Box 1**

The mitochondrial UPR (UPR<sup>mt</sup>) and FoxO proteins: A new link in tumor cells.

Mitochondrial unfolded protein response (UPR<sup>mt</sup>) is a relevant node of the proteostasis network. The UPR<sup>mt</sup> is activated by different types of stress that alters mitochondria function, transducing information about mitochondrial status to the nucleus in order to repair and recover cellular function [169]. The activation of the UPR<sup>mt</sup> is mediated by ATFS-1 (activating transcription factor associated with stress). ATFS-1 is normally transported to healthy mitochondria where it is rapidly degraded. Any perturbation in the mitochondria that lead to the accumulation of misfolded proteins, reduces mitochondrial import of proteins and thus prevents the translocation and degradation of ATFS-1 [170]. Under these conditions, ATFS-1 is transported to the nucleus to trigger the UPR<sup>mt</sup>, modulating the expression of genes involved in import, oxidative phosphorylation complexes, chaperones and proteases [169,171]. Recently, the mammalian transcription factor ATF5 has been described as a new component of the UPR<sup>mt</sup> which is regulated similarly to ATFS-1 [172]. Remarkably, CHOP is also regulated by the UPR<sup>mt</sup> and is required for the induction of mitochondrial chaperones and proteases [173,174].

The UPR<sup>mt</sup> has been also linked to cancer progression [175] and several regulators of the pathway are involved in tumor growth through FoxO signaling. For instance, the sirtuin deacetylase SIRT1 [176] and SIRT3 [177] are reported to regulate the UPR<sup>mt</sup> independent of conventional signaling through the induction of the antioxidant machinery and mitophagy. In the case of SIRT1, this regulation of the UPR<sup>mt</sup> is dependent of the nuclear translocation of FoxO, inducing the expression of antioxidant programs [176]. The UPR<sup>mt</sup> and FoxO3a axis is implicated in bladder cancer [178] and gastric cancer [179].

#### 1.4. Role of FoxO in cancer biology

One of the first reported associations of Fox transcription factors with tumorigenesis was the presence of FoxO in chromosomal translocations linked to cancer [106]. The chromosomal translocation involving the FoxO1 and PAX3 and 7 gene has been associated with the occurrence of alveolar rhabdomyosarcoma (ARMS) [106]. In addition, FoxO2 and FoxO4 have been detected as fusion protein with the transcription factor MLL in leukemia, increasing its oncogenic potential [107]. Loss of function of FoxO1 has also been described through chromosomal deletion (13q14) in prostate cancer, ablating its role as tumor suppressor [108]. Although these genetic aberrations have been described as key factors in tumor progression, overexpression of these fusion proteins fails to induce tumors in transgenic mice, suggesting that additional factors are needed to enhance cancer progression [109].

Deregulation of FoxO signaling has been implicated in several tumor types including breast cancer [110], prostate cancer [108], glioblastoma [111], rhabdomyosarcoma [106], leukemia [112], cervical cancer [113], melanoma [114] and hepatocellular carcinoma [115]. In general, FoxO proteins are proposed to operate as tumor suppressors, thus the role of FoxO in cancer is associated with a loss-of-function [116]. The phosphorylation of FoxO by AKT/PKB induces the translocation of FoxO from the nucleus to the cytoplasm [90] followed by proteasomal-mediated degradation [99]. This signaling mechanism leads to decreased cell death of cancer cells [117]. Remarkably, several pathways involved in cancer inhibit FoxO proteins function and thus accelerate tumor progression. This is the case of ERK and IκB kinase

(IKK) that phosphorylates FoxO3, resulting in proteasomal-mediated degradation increasing cell proliferation and aggressiveness [118,119]. Other kinases such as SGK [120], Skp2 [99], AMPK [121] and CDK2 [95] also inhibit FoxO, potentiating tumor growth (reviewed in [77,116]).

In addition to the deregulation of FoxO proteins in cancer cells, new and complex roles of this transcription factors have been described through a crosstalk with other signaling pathways. For instance, FoxO acts as signal transducer downstream of Smad, PI3K, and FoxG1 pathways increasing cell proliferation in glioblastoma [111]. On the other hand, β-Catenin, a protein that mediates Wnt signaling and is involved in epithelial-mesenchymal transition of various cancers [122], directly binds to FoxO and enhances its transcriptional activity [123]. Moreover, the tumor suppressor p53 also interacts with FoxO3, and synergies in the control of gene expression, suggesting that they act in concert to prevent tumorigenesis [124,125].

Another important physiological process involved in cancer is autophagy, which has a dual role in promoting tumor suppression and supporting tumor growth under low nutrient conditions [126]. FoxO1 and FoxO3 enhances the transcription of a variety of autophagy-related genes (i.e., Atg5, Lc3, Beclin-1) [127], activating autophagy mechanisms in diverse cell types [90,124,127–131]. Remarkably, this phenomena has been demonstrated in several types of cancer models [132–135]. In addition, a negative regulation between XBP1 and FoxO1 has been described, which regulates autophagy [136] (see below).

Many transcriptional targets of FoxO are implicated in the regulation of several aspects of tumor progression, including angiogenesis, invasion, metabolism, drug resistance, DNA repair and stem cell renewal [10]. For example, FoxO1 and FoxO3 regulates the expression of VEGF in endothelial cells impacting angiogenesis [137,138]. In addition, FoxO1-3-4 impact cell invasion and metastasis by regulating the expression of metalloproteinases such as MMP2 [139], MMP9 [140] and MMP13 [141]. Thus, the role of FoxO proteins in cancer is not only related to the cell survival and proliferation, but also is implicated in the acquisition of several tumor characteristics (reviewed in [10]).

#### 1.5. The crosstalk between the UPR and FoxO subfamily: a possible role in cancer biology and other diseases

Although the intrinsic role of ER stress in cancer progression is well studied, the way in which the UPR impacts other cancer-related pathways in terms of crosstalk mechanisms is still poorly studied. During the last years, new links between the UPR with the FoxO family have emerged that might impact cancer progression and other diseases (Fig. 3).

The PERK signaling pathway have been linked to FoxO in diabetes and insulin resistance. For example, PERK can activate mTOR and Akt/PKB activation impacting FoxO phosphorylation and inhibiting its transcriptional activity [142]. Interestingly, it was recently suggested that PERK can directly phosphorylate FoxO3 at serines 261, 298, 301, 303 and 311 increasing its activity in a model of insulin resistance reprogramming cells from anabolic to catabolic energy supply [143]. Thus, PERK can have opposite effects on FoxO regulation through the UPR signaling pathway independently of AKT/PKB in different cell types. The activation of the PI3K-AKT pathway by PERK has pro-survival effects and protects cells from ER stress-induced apoptosis [144,145]. In addition, upon ER stress CHOP, a key transcription factor downstream of PERK, can synergistically interact with FoxO3 to induce the expression of pro-apoptotic genes such as BIM and PUMA in neurons [146]. Remarkably, a similar effect was described in apoptosis of cancer cells induce by rhein where FOXO3a and CHOP can act together to regulate the expression of BIM [147].

XBP1 has been shown to regulate the stability of FoxO1 in various experimental systems. The XBP1 unspliced form (XBP1u) regulates FoxO1 degradation by recruiting FoxO1 for the 20S proteasome. This physical interaction between FoxO1 and XBP1u depends on the

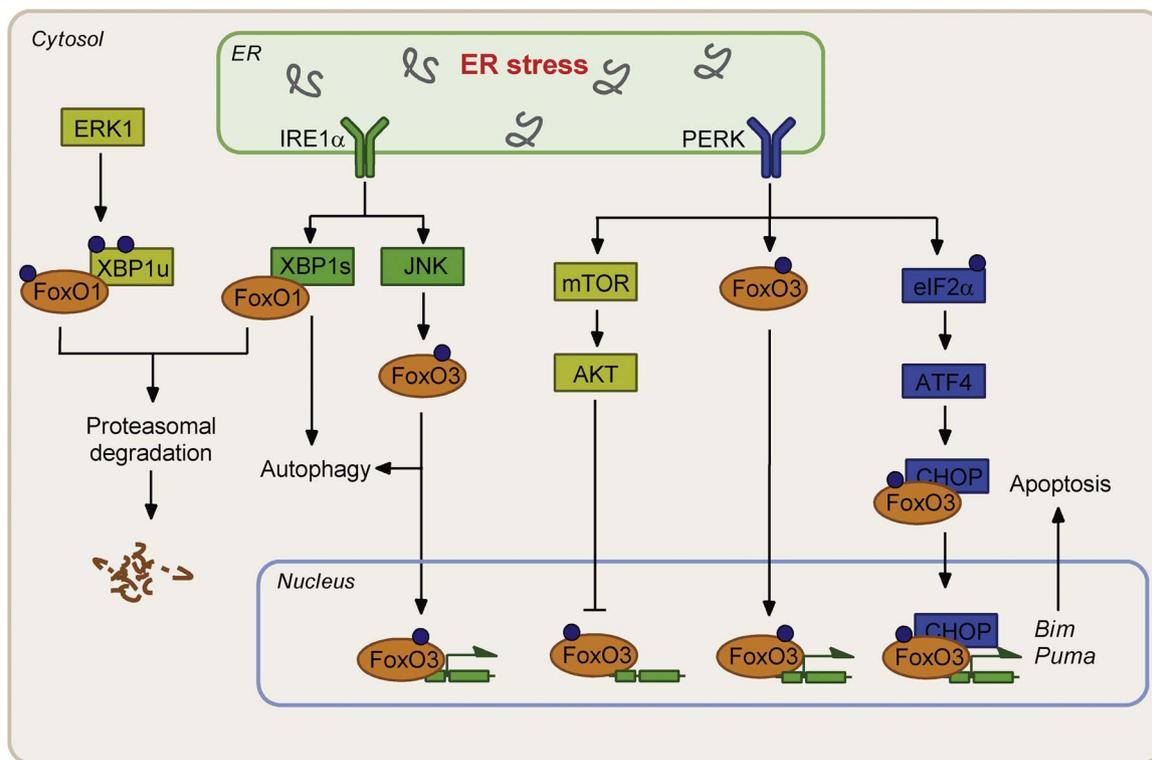


Fig. 3. The crosstalk between FoxO and the UPR.

Tumor cells have increased ERK1 activity that correlates with the phosphorylation of FoxO1 and XBP1u. This leads to the interaction of both proteins that are then targeted for proteasomal degradation. Similar mechanisms have been described for XBP1s that have also linked to autophagy induction through FoxO1. Remarkably, JNK activation downstream of IRE1 $\alpha$  induces the phosphorylation of FoxO3 that regulates the translocation to the nucleus and the transcriptional activity. The PERK signaling pathway has opposite effects in the regulation of FoxO3. PERK can engage mTOR and AKT/PKB activation that phosphorylates FoxO3 and induces the translocation to the cytoplasm and thus reducing the transcriptional activity. On the other hand, PERK can directly phosphorylate FoxO3 inducing the translocation to the nucleus and the transcriptional activity. Finally, CHOP can interact with FoxO3 and induce the expression of proapoptotic genes such as *bim* and *puma*.

phosphorylation of XBP1u by the extracellular signal-regulated kinases 1/2 (ERK1/2) [148]. A similar mechanism has been shown to control the inactivation of the UPR under prolonged ER stress. This mechanism is mediated by the physical interaction between XBP1u and XBP1s to target it for proteasome-mediated degradation [149,150]. Interestingly, XBP1u has been proposed to be one of the most unstable proteins in the human proteome [151]. However, although XBP1u is highly unstable and it is rapidly degraded by the proteasome. During its translation the nascent chain of XBP1u docks the ribosome to the ER membrane through a highly conserved hydrophobic domain [152,153] that, together with a translation pausing sequence [154], allows the efficient processing of the XBP1 mRNA in the cytosol to generate the spliced form [16]. In the context of insulin resistance in the liver, XBP1 was shown to inhibit the activity of FoxO1 through a physical interaction that triggers the degradation of FoxO1 by the proteasome and impact glucose metabolism [155]. We also reported that XBP1 deficiency is neuroprotective in models of ALS, Parkinson and Huntington's disease due to the upregulation of adaptive processes such as autophagy [129,156,157]. At the molecular level, we showed that XBP1 deficiency leads to the upregulation of FoxO1 in the brain, which may explain the enhancement of autophagy levels, providing protection to experimental Huntington's disease [129]. In other studies, the knockdown of XBP1 was also shown to augment the level of FoxO1 resulting in the persistent activation of autophagy [148]. Interestingly, an inverse correlation between XBP1u levels and FoxO1 expression has been also observed after the analysis of the expression profiles of 229 cases of human colorectal cancer tissues [148]. More recently, the interaction of FoxO1 and XBP1 has been observed in auditory cells impacting autophagy [158].

A few reports also suggest that FoxO1 and FoxO3 expression influences the susceptibility of cells to ER stress. For example, in beta cells,

FoxO1 has been shown to protect cells against ER stress [159]. Several studies have linked FoxO transcription factors to proteostasis control in *C. elegans*. For example, the phenotype observed in *Ire1* mutant worms in terms of secretion and metabolism can be fully rescued by the expression of the FoxO3 orthologous named Daf16 [160]. In other studies, using *C. elegans* a complementation between FoxO transcription factors and the UPR was reported to handle ER stress [161]. Similar findings were reported in failed dendritic morphogenesis in *Ire1* defective mutants, where Daf16 and IGF1 can bypass IRE1 $\alpha$  deficiency restoring normal phenotype [162]. The orthologous of mammalian FoxO proteins in *C. elegans* is an essential mediator of the effects of insulin on longevity [86,163]. More importantly, the effects of XBP1 deficiency in longevity have been linked with the activity of insulin growth factors and FoxO in this animal model, observing a negative correlation between both pathways. Importantly ER proteostasis control has a great impact on aging and aging-related diseases [164,165]. Proteostasis mechanisms are proposed to decrease with age, resulting in the accumulation of damaged, misfolded, and aggregated proteins [166]. Alterations in proteostasis are also associated with several aging-related diseases, including neurodegeneration [167]. Thus, a crosstalk between the UPR and the FoxO subfamily of transcription factors is emerged as a reostat that controls the aging process, however the implications in cancer biology are still poorly studied.

## 2. Concluding remarks

Increasing evidence supports a connection between the UPR and FoxO proteins in metabolic and neurodegenerative disorders, in addition to cancer. Overall evidence linking the crosstalk between the UPR and FoxO transcription factors in cancer is still poor. Although it is clear that IRE1 $\alpha$ /XBP1 and PERK/ATF4 branches of the UPR are implicated

in the regulation of FoxO through the control of its stability and activity, only a few examples suggest that this crosstalk is also relevant to tumor growth. The mechanism mediating the degradation of FoxO1 by XBP1 to suppress autophagy is the best described pathway in the context of tumor biology [148,168].

As discussed, the UPR has a major role in tumorigenesis enhancing the acquisition of several hallmarks of cancer [8]. Thus, targeting the UPR is proposed as a suitable therapeutic strategy to delay cancer progression [17]. In fact, in models of multiple myeloma models, small molecules that inhibit IRE1 $\alpha$  or PERK have beneficial effects by decreasing tumor growth and aggressiveness [69–71]. On the other hand, FoxO subfamily of transcription factors have also been widely associated to the acquisition of several hallmarks of cancer [10]. A tightly crosstalk between the UPR and FoxO is emerging in the control of gene expression in cancer cells, and examples for bidirectional regulations are available as discussed here. Remarkably, FoxO (Daf16) can rescue phenotypes of observed in IRE1 defective mutants in *C. elegans* models, supporting the idea of a functional relationship. In addition to ER proteostasis, the FoxO family can impact mitochondria proteostasis in order to act together to adapt cancer cells to energetic imbalances and also modulates the mitochondrial UPR (Box 1). Since FoxO proteins can be regulated by multiple signaling pathways and protein kinases, it remains to be determined if the protective effects of UPR targeting drugs also involve the modulation of FoxO transcription factors. Thus, a more systematic analysis is needed to provide a comprehensive view to explain the interrelation between the UPR and FoxO proteins and its relation to human disease.

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