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REVIEW ARTICLE

Posttranscriptional regulation of *FOXO* expression: microRNAs and beyond

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Forkhead box, class O (FOXO) transcription factors are major regulators of diverse cellular processes, including fuel metabolism, oxidative stress response and redox signalling, cell cycle progression and apoptosis. Their activities are controlled by multiple posttranslational modifications and nuclear-cytoplasmic shuttling. Recently, post-transcriptional regulation of FOXO synthesis has emerged as a new regulatory level of their functions. Accumulating evidence suggests that this post-transcriptional mode of regulation of FOXO activity operates in response to stressful stimuli, including oxidative stress. Here, we give a brief overview on post-transcriptional regulation of FOXO synthesis by microRNAs (miRNAs) and by RNA-binding regulatory proteins, human antigen R (HuR) and quaking (QKI). Aberrant post-transcriptional regulation of FOXOs is frequently connected with various disease states. We therefore discuss characteristic examples of *FOXO* regulation at the post-transcriptional level under various physiological and pathophysiological conditions, including oxidative stress and cancer. The picture emerging from this summary points to a diversity of interactions between miRNAs/miRNA-induced silencing complexes and RNA-binding regulatory proteins. Better insight into these complexities of post-transcriptional regulatory interactions will add to our understanding of the mechanisms of pathological processes and the role of FOXO proteins.

LINKED ARTICLES

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Abbreviations

5-FU, 5-fluorouracil; AD, Alzheimer's disease; Ago2, argonaute 2; antagomiR/antimiR, synthetic miRNA inhibitor; ARE, AU-rich element; Bim, Bcl-2-interacting mediator of cell death; CAT-1, cationic amino acid transporter-1; FasL, Fas ligand; FOXO, forkhead box, class O; GlcNAcylation, O-linked-D-N-acetylglucosamine addition; HSC, haematopoietic stem cell; HuR, human antigen R; I/R, ischaemia/reperfusion; LAT, linker for activation of T cells; miRISC, miRNA-induced silencing complex; miRNA, microRNA; MITF-M, microphthalmia-associated transcription factor-M; MnSOD, manganese superoxide dismutase; oncomiR, miRNA associated with cancer; PTEN, phosphatase and tensin homologue; QKI, quaking; QRE, QKI response element; Sp1, specificity protein 1; UTR, untranslated region

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Tables of Links

TARGETS	
Enzymes[a]	**Other proteins**[b]
Akt	Bim, Bcl-2-interacting mediator of cell death
p38 kinase	**Transporters**[c]
PTEN, phosphatase and tensin homologue	CAT-1, cationic amino acid transporter 1, SLC7A1
Sirtuin 1	

LIGANDS
5-FU, 5-fluorouracil
all-trans-retinoic acid, tretinoin
FasL, Fas ligand

These Tables list key protein targets and ligands in this article which are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Pawson *et al.*, 2014) and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 ([a,b,c]Alexander *et al.*, 2015a,b,c).

Introduction

FOXOs and regulation of FOXO activity – posttranslational modification and beyond

Transcription factors of the forkhead box, class O (FOXO) family are major players in the regulation of metabolic processes and in the control of decisions on cellular life and death. FOXO targets include genes coding for proteins at crucial positions in fuel metabolism (such as the gluconeogenesis enzymes, glucose 6-phosphatase or phosphoenolpyruvate carboxykinase; Barthel *et al.*, 2005), in the regulation of cell cycle, apoptosis and autophagy (e.g. $p27^{Kip}$, Fas ligand (FasL) and beclin1, respectively – see Eijkelenboom and Burgering, 2013) and in stress response and antioxidant defence [such as manganese superoxide dismutase (MnSOD), catalase and certain selenoproteins; Klotz *et al.*, 2015].

There are four FOXO isoforms in humans, FOXO1, FOXO3, FOXO4 and FOXO6 – all of which are expressed in most human tissues and have overlapping target gene patterns. FOXO activity is regulated at several levels (Figure 1) – most acutely by posttranslational modification. FOXOs are substrates of various kinases (for a recent list of kinases and

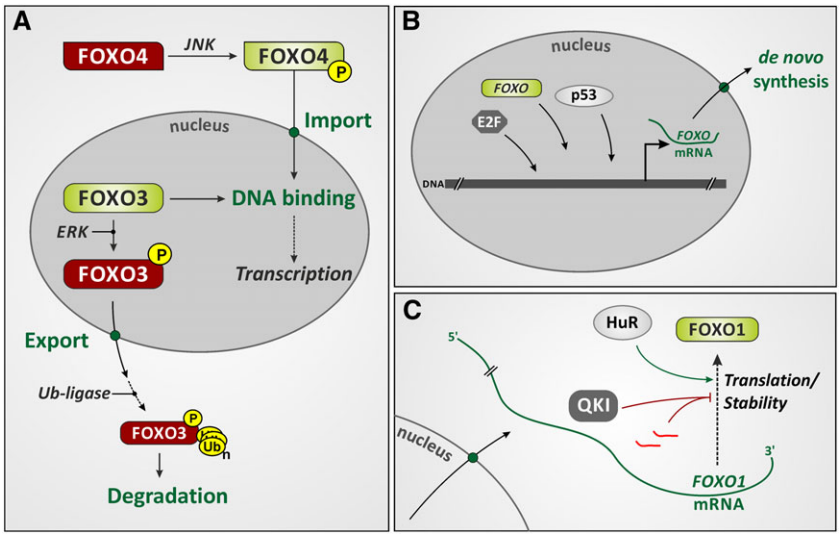

Figure 1

Levels of regulation of FOXO activity and expression. (A) Posttranslational modification of FOXOs affects their activity, subcellular localization and stability. The figure illustrates the effects of phosphorylation of two FOXO isoforms (FOXO3 and FOXO4) by two different kinases, c-Jun-N-terminal kinases (JNK) and extracellular signal-regulated kinases (ERK). The figure indicates consequences of FOXO phosphorylation: nuclear import and export, respectively, as well as increased or attenuated DNA-binding activity (red: inactive; green: active FOXO form). A consequence of FOXO3 phosphorylation by ERK is nuclear exclusion and ubiquitination (leading to proteasomal degradation). For further detail regarding FOXO posttranslational modification, see Klotz *et al.*, 2015. (B) Transcriptional regulation of *FOXO* expression. Transcription factors controlling *FOXO* expression include certain E2F isoforms, p53 and FOXOs (specifically, FOXO3 regulating *FOXO1* expression; see text). (C) *FOXO* mRNA stability and translation are affected by miRNAs (bright red) and RNA-binding proteins such as HuR and quaking (see text for details).

FOXO phosphorylation sites, see Klotz *et al.*, 2015) and are acetylated, ubiquitinylated (Eijkelenboom and Burgering, 2013), GlcNAcylated (Housley *et al.*, 2009) and even oxidized (Dansen *et al.*, 2009). These modifications, in turn, affect FOXO activity, that is, DNA binding and transactivation activity, FOXO subcellular localization and/or FOXO stability/degradation as well as interaction with transcriptional coregulators.

Thus, phosphorylation is a major regulator of FOXO nucleocytoplasmic shuttling but also affects DNA binding of FOXOs. For example, phosphorylation elicited by the serine/threonine kinase Akt can cause FOXO nuclear exclusion and inactivation. These appear to be two independent consequences of FOXO phosphorylation, as suggested by studies on FOXO6: while phosphorylation of FOXO isoforms 1, 3 or 4 by Akt (e.g. upon stimulation of cells with insulin, which results in Akt activation via phosphoinositide 3′-kinase) results in their nuclear exclusion, this is not seen with FOXO6, which remains nuclear but nevertheless is inactivated (van der Heide *et al.*, 2005).

Modification of lysines to yield acetylated or ubiquitinylated FOXOs has consequences for FOXO activity and its stability, respectively. FOXO acetylation appears to attenuate its DNA binding and transactivation activity (different from acetylation of histones, which would support FOXO-dependent transcription), and it may render FOXOs susceptible towards phosphorylation and nuclear exclusion. However, it also stabilizes FOXOs by preventing ubiquitinylation of the same lysine residues and subsequent proteasomal degradation (Daitoku *et al.*, 2011).

Oxidation of FOXO cysteines mediates interaction with coregulators and may contribute to stress-induced changes in subcellular localization (Putker *et al.*, 2015). Moreover, it affects FOXO acetylation and activity. For example, FOXO4 was demonstrated to form mixed disulfides with p300 acetyltransferase upon exposure of cells to hydrogen peroxide and under conditions that cause endogenous generation of ROS; this disulfide formation was required for H_2O_2-induced FOXO4 acetylation and acetylation-induced loss of FOXO activity to occur (Dansen *et al.*, 2009).

Long-term regulation of FOXO levels and activity occurs through transcriptional regulation. Major transcriptional regulators of *FOXO* expression include E2F, p53 and FOXO3 itself (see Klotz *et al.*, 2015, for review).

More recently, post-transcriptional regulation of *FOXO* expression under different (patho-) physiological conditions has been of interest, focusing primarily on the effects of various microRNAs (miRNAs) on FOXO levels in various types of cancer. Because of their crucial role in the regulation and integration of metabolism, stress response, cell cycle progression and apoptosis (Furukawa-Hibi *et al.*, 2005; Eijkelenboom and Burgering, 2013; Klotz *et al.*, 2015), FOXO proteins are generally regarded as tumour suppressors (Dansen and Burgering, 2008); hence, their translational repression in some types of tumours seems to be essential to allow the uncontrolled proliferation of transformed cells.

A high metabolic rate in cancer cells supports their rapid proliferation and often comes with elevated steady-state levels of ROS as compared with untransformed cells, which is assumed – for example, through modulation of redox-sensitive signalling cascades – to contribute to their metabolic adaptation, proliferation and survival (Schieber and Chandel, 2014; Lennicke *et al.*, 2015). Moreover, redox signalling is involved in the regulation of quiescent and proliferative growth states. Intracellular ROS levels periodically change during the cell cycle, sometimes referred to as a 'redox cycle within the cell cycle' (Burhans and Heintz, 2009; Sarsour *et al.*, 2014). Interestingly, the activity of MnSOD, encoded by *SOD2*, a FOXO target gene, fluctuates during the cell cycle as well, and its loss generally leads to aberrant proliferation whereas its high activity is linked to the quiescent state (reviewed by Sarsour *et al.*, 2014).

We here present a brief overview of the literature on post-transcriptional regulation of *FOXO* expression, followed by a more detailed discussion of selected examples on physiological and pathological regulation of FOXOs by miRNAs, including regulation under oxidative stress conditions and in cancer. Moreover, we will discuss post-transcriptional regulation of *FOXO* expression by RNA-binding proteins and possible interactions of these proteins with miRNAs and miRNA-induced silencing complexes (miRISCs).

Post-transcriptional regulation of *FOXO* expression: overview

FOXO activity is controlled by posttranslational modification. As the expression of modifying enzymes, such as the deacetylase sirtuin 1 (Abdelmohsen *et al.*, 2007), may in turn be controlled at the level of mRNA stability, it can of course be argued that FOXO activity is also modulated by post-transcriptional regulatory processes. This article, however, will focus on post-transcriptional processes controlling *FOXO* expression by targeting *FOXO* mRNAs.

Many miRNAs have now been identified as regulators of *FOXO* expression, some of which will be dealt with in the following sections. Tables 1 and 2 provide a list of miRNAs identified as regulating the formation of FOXO isoforms, along with information on cell/tissue type and/or biological processes in which FOXOs and these miRNAs were involved.

Examples of such physiological and pathophysiological processes requiring post-transcriptional control of *FOXO* expression include clonal expansion of antigen-activated T_H lymphocytes (Stittrich *et al.*, 2010), maintenance of haematopoietic stem cells (HSCs) during ageing (Mehta *et al.*, 2015), cardiac hypertrophy (Ucar *et al.*, 2012) and certain aspects of neurodegeneration (Wong *et al.*, 2013). A number of miRNAs directly targeting *FOXO* mRNAs are also implicated in tumour promotion, growth or metastasis: for example, miR-182 targets *FOXO3* mRNA in lung cancer (Yang *et al.*, 2014b) and melanoma (Segura *et al.*, 2009); the same *FOXO3* mRNA is also targeted by miR-155, promoting oxidative stress in pancreatic cancer (Wang *et al.*, 2015c). Additionally, a polymorphism in a miR-137-binding site in the 3′-untranslated region (UTR) of human *FOXO1* mRNA has been described that decreases hereditary susceptibility to hepatocellular carcinoma (Tan *et al.*, 2015).

The following sections will focus on selected miRNAs and their role in regulating *FOXO* expression, followed by examples of multiple miRNAs affecting FOXO levels through concerted action. A final section will then highlight mRNA-binding proteins now known to control *FOXO* expression and their physiological relevance.

Table 1

A list of miRNAs demonstrated to target *FOXO* mRNA[a]

miRNA	Target mRNA (FOXO isoform)	Target cell/tissue or biological process (organism[b])	Reference
miR-9	FOXO1	Breast cancer cells (Hs)	Yang *et al.* (2014a)
	FOXO1	Neural stem cell differentiation (Mm)	Kim *et al.* (2015)
	FOXO1 and FOXO3	Haematopoietic cells (Hs and Mm)	Senyuk *et al.* (2013)
miR-10b	FOXO3	Glioblastoma multiforme (Hs)	Lin *et al.* (2012)
miR-21	FOXO1	Glioblastoma cells (Hs)	Lei *et al.* (2014a)
	FOXO1	Diffuse large B-cell lymphoma (Hs)	Go *et al.* (2015)
	FOXO1	Pancreatic ductal adenocarcinoma (Hs)	Song *et al.* (2015)
miR-23a	FOXO3	Cardiac hypertrophy (Mm)	Wang *et al.* (2012b)
miR-23b	FOXO4	Vascular smooth muscle cells (Hs and Rn)	Iaconetti *et al.* (2015)
miR-27a	FOXO1	Renal cell carcinoma (Hs)	Zhou *et al.* (2012)
	FOXO1	Liver cancer (Hs and Mm)	Sun *et al.* (2015a)
	FOXO3	Glioblastoma (Hs)	Ge *et al.* (2013)
miR-29a	FOXO3	Chondrogenic differentiation of mesenchymal stem cells (Hs and Mm)	Guerit *et al.* (2014)
miR-30d	FOXO3	Cardiomyocyte pyroptosis in diabetic cardiomyopathy (Rn and Hs)	Li *et al.* (2014d)
miR-96	FOXO1	Bladder cancer (Hs)	Guo *et al.* (2012)
	FOXO1	Prostate cancer (Hs)	Fendler *et al.* (2013)
	FOXO1	Prostate cancer (Hs)	Haflidadottir *et al.* (2013)
	FOXO1 and FOXO3	HepG2 hepatoma cells (Hs)	Xu *et al.* (2013a)
	FOXO3	Breast cancer (Hs)	Lin *et al.* (2010)
	FOXO3	Idiopathic pulmonary fibrosis fibroblasts (Hs)	Nho *et al.* (2014)
	FOXO3	Non-small cell lung cancer (Hs)	Li *et al.* (2015a)
	FOXO3	Prostate cancer (Hs)	Wang *et al.* (2015a)
miR-107	FOXO1	Gastric cancer cells (Hs)	Li *et al.* (2014b)
miR-126	FOXO3	Vascular smooth muscle cells (Hs and Mm)	Zhou *et al.* (2013)
miR-132	FOXO1	Gastric cancer cells (Hs)	Li *et al.* (2015b)
	FOXO3	Acute inflammatory lung injury (Mm)	Rao *et al.* (2015)
miR-132-3p	FOXO1	Alzheimer's disease (Hs)	Lau *et al.* (2013)
miR-135a	FOXO1	Spermatogonial stem cells in cryptochorid testes (Rn)	Moritoki *et al.* (2014)
	FOXO1	Bladder cancer (Hs)	Mao *et al.* (2015)
	FOXO1	Malignant melanoma cells (Hs)	Ren *et al.* (2015)
miR-135b	FOXO1	Anaplastic large cell lymphoma (Hs)	Matsuyama *et al.* (2011)
	FOXO1	Hepatocellular carcinoma (Hs and Mm)	Jung *et al.* (2014)
	FOXO1	Osteosarcoma cells (Hs)	Pei *et al.* (2015)
miR-137	FOXO1	Hepatocellular carcinoma (Hs)	Tan *et al.* (2015)
miR-139	FOXO1	Mouse hepatocytes (Mm)	Hasseine *et al.* (2009)
miR-145	FOXO1	White adipose tissue (Mm)	Lin *et al.* (2014)
miR-155	FOXO3	Breast cancer (Hs)	Kong *et al.* (2010)
	FOXO3	Hypoxic lung cancer cells (Hs)	Babar *et al.* (2011)
	FOXO3	Multifunctional Treg cell line (Hs)	Yamamoto *et al.* (2011)
	FOXO3	Vascular stem cell niche in bone marrow (Hs)	Spinetti *et al.* (2013)
	FOXO3	Glioma (Hs)	Ling *et al.* (2013)
	FOXO3	Ulcerative colitis (Hs)	Min *et al.* (2014)

Table 1

(Continued)

miRNA	Target mRNA (FOXO isoform)	Target cell/tissue or biological process (organism[b])	Reference
	FOXO3	Lymphoproliferation in linker for activation of T-cells (LAT) mutant mice (Mm)	Rouquette-Jazdanian *et al.* (2015)
	FOXO3	Pancreatic cancer (Hs)	Wang *et al.* (2015c)
miR-182	FOXO1	Activated helper T-lymphocytes (Mm and Hs)	Stittrich *et al.* (2010)
	FOXO1	Osteoblasts and skeletogenesis (Mm and Dr)	Kim *et al.* (2012)
	FOXO1	Rejecting cardiac allografts and mononuclear cell infiltrate (Mm)	Wei *et al.* (2012)
	FOXO1	Hydrogen peroxide-induced apoptosis in neuroblastoma cells (Hs)	Gheysarzadeh and Yazdanparast (2015)
	FOXO1 and FOXO3	Colon cancer – African and Caucasian Americans (Hs)	Li *et al.* (2014a)
	FOXO3	Melanoma metastasis (Hs and Mm)	Segura *et al.* (2009)
	FOXO3	Advanced ovarian carcinoma (Hs)	McMillen *et al.* (2012)
	FOXO3	Skeletal muscle (Mm and Rn)	Hudson *et al.* (2014)
	FOXO3	High-grade serous ovarian carcinoma (Hs)	Levanon *et al.* (2014)
	FOXO3	Ovarian cancer cells – orthotopic xenografts (Hs)	Xu *et al.* (2014a)
	FOXO3	Lung cancer (Hs)	Yang *et al.* (2014b)
miR-183	FOXO1	Human-specific miR-183 target site (Hs)	McLoughlin *et al.* (2014)
	FOXO1	Non-small cell lung cancer cells (Hs)	Zhang *et al.* (2015a)
miR-196a	FOXO1	Cervical cancer (Hs)	Hou *et al.* (2014)
miR-205	FOXO3	Lung squamous cell carcinoma (Hs)	Huang *et al.* (2014)
miR-217	FOXO3	Angiogenesis of cytomegalovirus-infected endothelial cells (Hs)	Zhang *et al.* (2013)
miR-223	FOXO1	Colorectal cancer, cervical cancer and hepatoma cells (Hs)	Wu *et al.* (2012a)
	FOXO1 and FOXO3	Analysis of decoy oligonucleotides as modulators of miRNA activity in various cell lines (Hs)	Wu *et al.* (2013)
miR-370	FOXO1	Prostate cancer cells (Hs)	Wu *et al.* (2012b)
	FOXO1	Gastric carcinoma (Hs)	Fan *et al.* (2013)
miR-374a	FOXO1	Osteosarcoma (Hs)	He *et al.* (2015)
miR-421	FOXO4	Nasopharyngeal carcinoma (Hs)	Chen *et al.* (2013)
miR-486	FOXO1	Cardiac and skeletal muscle (Mm and Rn)	Small *et al.* (2010)
	FOXO1	Muscle wasting in chronic kidney disease (Mm)	Xu *et al.* (2012)
	FOXO1	Cardiac/skeletal muscle cells in breast cancer and mouse models (Hs and Mm)	Chen *et al.* (2014)
miR-498	FOXO3	Ovarian cancer cells (Hs)	Liu *et al.* (2015)
miR-499-5p	FOXO4	Colorectal cancer (Hs)	Liu *et al.* (2011)
miR-582-5p	FOXO1	Monocytes (Hs)	Liu *et al.* (2013)
miR-664	FOXO4	Osteosarcoma cells (Hs)	Chen *et al.* (2015)
miR-708	FOXO3	Childhood acute lymphoblastic leukaemia (Hs)	Han *et al.* (2011)
miR-1269	FOXO1	Hepatocellular carcinoma (Hs)	Yang *et al.* (2014c)
miR-1274a	FOXO4	Gastric cancer (Hs)	Wang *et al.* (2015b)

[a]Only reports on FOXO regulation by a single miRNA are listed here. For reports on FOXO regulation by several miRNAs simultaneously, see Table 2.
[b]Hs, human; Mm, mouse; Rn, rat; Dr, zebrafish.

Table 2

A list of miRNAs demonstrated to target *FOXO* mRNA simultaneously

miRNA	Target mRNA	Target cell/tissue or biological process (organism[a])	Reference
miR-9, miR-27, miR-96, miR-153, miR-182, miR-183 and miR-186	FOXO1	Endometrial cancer (Hs)	Myatt *et al.* (2010)
miR-27a, miR-96 and miR-182	FOXO1	Breast cancer cells (Hs)	Guttilla and White (2009)
miR-27a and miR-24	FOXO1	Differentiation of embryonic stem cells (Mm)	Ma *et al.* (2015)
miR-96, miR-182 and miR-183	FOXO1	Classical Hodgkin lymphoma (Hs)	Xie *et al.* (2012)
miR-96, miR-182 and miR-183	FOXO1	Glioma (Hs)	Tang *et al.* (2013)
miR-96, miR-182 and miR-183	FOXO1	Granulosa cells (Bt)	Gebremedhn *et al.* (2015)
miR-96, miR-182 and miR-183	FOXO1	Hepatocellular carcinoma (Hs)	Leung *et al.* (2015)
miR-96 and miR-182	FOXO3	Ovarian cancer cells (Hs)	Xu *et al.* (2013b)
miR-132 and miR-212	FOXO3	Cardiac hypertrophy and cardiomyocyte autophagy (Mm and Rn)	Ucar *et al.* (2012)
miR-132 and miR-212	FOXO3	Alzheimer's disease (Hs, Mm and Rn)	Wong *et al.* (2013)
miR-132 and miR-212	FOXO3	Haematopoietic stem cell maintenance (Mm)	Mehta *et al.* (2015)
miR-182 and miR-223	FOXO3	Skeletal muscle – hormone replacement therapy (Hs and Mm)	Olivieri *et al.* (2014)

[a]Hs, human; Mm, mouse; Rn, rat; Bt, bovine.

Selected miRNAs regulating *FOXO* expression and their (patho-) physiological significance

miR-182

miR-182 was initially characterized as a member of an miRNA cluster (comprising the paralogues miR-96, miR-182 and miR-183), which is highly expressed in sensory organ tissues, such as the retina and olfactory epithelium (Kloosterman *et al.*, 2006; Weston *et al.*, 2006; Xu *et al.*, 2007). It is essential, together with miR-183, for sustaining outer segments of cone photoreceptors of the eye (Busskamp *et al.*, 2014) and contributes to the regulation of T-cell differentiation and osteogenesis (Stittrich *et al.*, 2010; Kim *et al.*, 2012). Furthermore, miR-182 is involved in the aetiology of multiple types of cancer and at various stages of cancerogenesis (see the following discussions, and Wei *et al.*, 2015). According to current nomenclature, the publications on FOXO1 and FOXO3 and miR-182 that are discussed in this section concern, more specifically, miR-182-5p (Kozomara and Griffiths-Jones, 2014).

A common function of down-regulation of *FOXO* expression by miR-182 under physiological conditions is to allow cell cycle progression and cell proliferation. Conversely, down-regulation of miR-182 may be required for protection against excessive oxidative stress, inhibition of proliferation, induction of cell cycle arrest and/or apoptosis by FOXO.

For example, FOXO1 controls the resting state of helper T-cells by inducing synthesis of the cell cycle inhibitor $p27^{Kip1}$, which in turn blocks cell cycle progression (Peng, 2008). Upon activation by antigen, transition of helper T-cells to a proliferative stage is achieved, which requires inactivation of FOXO1. FOXO1 is first inactivated by post-translational modification (by phosphorylation), resulting in its exclusion from the nucleus. However, the initial T-cell receptor-dependent signal resulting in FOXO phosphorylation is transient and stops within a day after antigen stimulation (Stahl *et al.*, 2002; Fabre *et al.*, 2005; Peng, 2008; Stittrich *et al.*, 2010). But what suppresses FOXO1 activity during the later phase of clonal expansion, when proliferation of helper T-lymphocytes is promoted by IL-2? Stittrich *et al.* (2010) showed that IL-2/IL-2 receptor-dependent signalling results in stimulation of transcription factor STAT5 and in binding of activated STAT5 to the regulatory region of the miR-182 gene, up-regulating its expression up to 200-fold. Mature miR-182, in turn, decreases formation of FOXO1 protein by interacting with a specific site in the 3′-UTR of its mRNA, hence enabling the replication of activated T_H lymphocytes (Stittrich *et al.*, 2010; reviewed in Haftmann *et al.*, 2012).

It was previously demonstrated that oxidative stress may inhibit the stimulation of JAK-STAT signalling by certain cytokines (Kaur *et al.*, 2005; Di Bona *et al.*, 2006; reviewed in Bourgeais *et al.*, 2013). In line with this notion, Gheysarzadeh and Yazdanparast (2015) have shown recently that, under conditions of oxidative stress, the STAT5 ↑/miR-182↑/FOXO1↓ axis can be altered to rapidly up-regulate FOXO1 activity (STAT5↓/miR-182↓/FOXO1↑). Exposure of human SK-N-MC neuroblastoma cells to 300 μM H_2O_2 led to inactivation of STAT5 and a 10-fold down-regulation of miR-182, which resulted in a fourfold increase in FOXO1 protein levels (while *FOXO1* mRNA levels did not change). This, in turn, led to an increased formation of the pro-apoptotic FOXO1 target gene products, Bcl-2-associated X protein and Bcl-2-interacting mediator of cell death (Bim), and to activation of caspase-3 (Gheysarzadeh and Yazdanparast, 2015).

The miR-182/FOXO axis was also shown to control early versus late stages of lung cancer progression; here, human *FOXO3* expression was attenuated by miR-182 (Yang *et al.*, 2014b). In their previous study, the authors had shown that transcription factor 'specificity protein 1' (Sp1) was highly

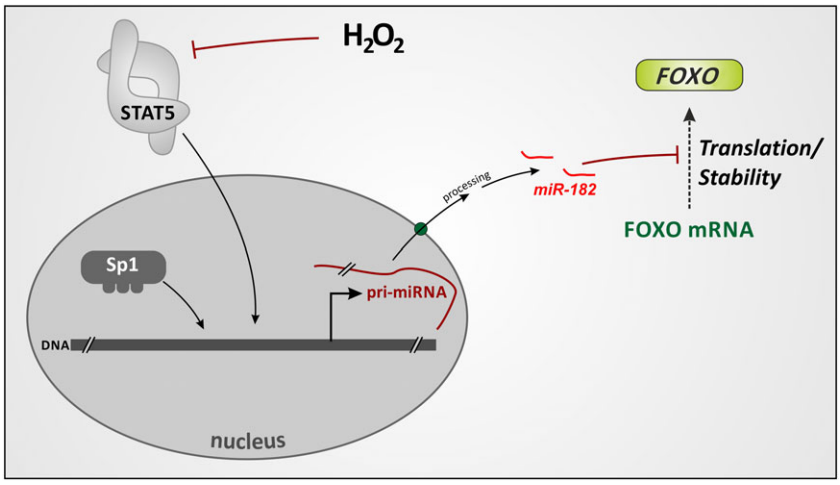

Figure 2

Regulation of FOXO synthesis through transcriptional control of microRNA formation. Transcription factors STAT5 or Sp1 stimulate miR-182 generation. MiR-182, in turn, blocks *FOXO1* and *FOXO3* mRNA translation or decreases its stability. Hydrogen peroxide was shown to attenuate STAT5 activation, thus up-regulating FOXO levels through preventing miR-182 production (see text).

expressed in early-stage lung adenocarcinoma, which was important for cancer cell proliferation and tumour growth (Hsu *et al.*, 2012). However, a decrease in Sp1 levels was observed in highly invasive and migratory late-stage lung adenocarcinomas. Sp1 overexpression in these late-stage cancers inhibited both migration and invasiveness of lung adenocarcinoma cells *in vitro* and their metastasis *in vivo*, while its knockdown enhanced these abilities (Hsu *et al.*, 2012). The authors then identified the gene coding for miR-182 as a target of Sp1 and demonstrated that expression of Sp1 inversely correlates with expression of *FOXO3*, the known target of miR-182 (Segura *et al.*, 2009). Hence, Sp1 was identified as another transcription factor stimulating the formation of miR-182, which in turn repressed translation of a *FOXO* mRNA (Yang *et al.*, 2014b) (Figure 2).

Decreased levels of FOXO3 correlated with stimulated proliferation and tumour growth, possibly by down-regulation of $p27^{Kip1}$, whose gene is a FOXO3 target (Dijkers *et al.*, 2000; Medema *et al.*, 2000). Interestingly, Yang *et al.* (2014b) found that Sp1 also up-regulates *FOXO3* promoter activity – but any effect this might have on *FOXO3* transcription was overcome by the miR-182-mediated translational repression in terms of the FOXO3 protein level. In the late tumour stages, Sp1 and miR-182 were down-regulated, and FOXO3 protein expression up-regulated accordingly. Furthermore, the knockdown of miR-182 led to an increased expression of the N-cadherin gene and several other cancer metastasis-related genes. It also led to the enhanced cell migration and invasion *in vitro* and to the higher capacity to metastasize *in vivo* (Yang *et al.*, 2014b). In contrast, the simultaneous knockdown of miR-182 and *FOXO3* decreased invasive cell behaviour and expression of N-cadherin, indicating an important role of FOXO3 in cell migration and metastasis during late-stage lung adenocarcinomas. Peculiarly, miR-182 appears to function in lung adenocarcinoma both as an oncomiR for growth and as a suppressor of metastasis. Further experiments are required to ascertain whether *FOXO3*, generally considered to act as a tumour suppressor (Paik *et al.*, 2007; Dansen and Burgering, 2008; Kloet and Burgering, 2011), can also act as an oncogene during late stages of lung adenocarcinoma.

For melanoma cell lines, Segura *et al.* (2009) showed that overexpression of miR-182 increases their capability to migrate (*in vitro*) and to metastasize (*in vivo*). Down-regulation of miR-182, on the other hand, hindered invasion and induced apoptosis. Moreover, the pro-invasive effect of ectopically expressed miR-182 was shown to be a consequence of translational repression of FOXO3 formation and of another transcription factor, microphthalmia-associated transcription factor-M (MITF-M), by miR-182. Overexpression of either of the two transcription factors along with miR-182 blocked the pro-invasive impact of miR-182. In human tissue samples, the levels of miR-182 were significantly higher in metastatic melanoma as compared with primary melanoma and nevi. In metastatic tissues, they also inversely correlated with the FOXO3 and MITF protein levels, as determined by immunohistochemistry (Segura *et al.*, 2009).

The gene coding for miR-182 is located in the 7q32.2 human chromosomal region, in a cluster with two other miRNAs, miR-96 and miR-183 (Landgraf *et al.*, 2007; Xu *et al.*, 2007). The broader region 7q31–34 also includes genes coding for the c-MET and B-RAF proto-oncogenes and is often amplified in advanced human melanomas (Bastian *et al.*, 1998; Lin *et al.*, 2008). Indeed, copy number analysis performed by Segura *et al.* (2009) revealed seven cell lines with increased locus copy number out of 13 cell lines with elevated miR-182. High miR-182 levels in melanomas can thus be a consequence of locus amplification.

Taken together, miR-182 expression can be differentially regulated in various cancer types in the course of cancer progression. Furthermore, many groups have shown, outside the FOXO context, that miR-182 can act as an oncomiR or as a tumour suppressor, depending on the cell or tumour type. For example, the role of miR-182 in cancer progression and metastasis has been well established in breast cancer (Lei *et al.*, 2014b; Li *et al.*, 2014c), hepatocellular carcinoma (Wang

et al., 2012a; Du *et al.*, 2015; Leung *et al.*, 2015) and in primary (soft tissue) sarcomas (Sachdeva *et al.*, 2014; Dodd *et al.*, 2015). On the other hand, miR-182 can suppress proliferation and tumourigenicity of renal cell carcinoma (Xu *et al.*, 2014b), induce apoptosis in cervical cancer (Sun *et al.*, 2015b) and act as tumour suppressor in glioblastoma (Kouri *et al.*, 2015) and neuroblastoma (Rihani *et al.*, 2015). Its down-regulation has also been associated with the growth and invasion of osteosarcoma cells (Hu *et al.*, 2015). It will be interesting to explore the expression and possible roles of *FOXO* mRNAs as miR-182 targets in all these malignancies.

miR-132/miR-212

miR-132 and miR-212 are paralogous miRNAs encoded by a cluster on human chromosome 17. They play various roles in neuronal morphogenesis, maturation and function, while their deregulation is connected with neurological disorders. Additionally, accumulating evidence points to their involvement in the immune functions and inflammation (reviewed in Wanet *et al.*, 2012). According to current nomenclature, the publications discussed in this section are concerned with, more specifically, miR-132-3p and miR-212-3p (Kozomara and Griffiths-Jones, 2014).

FOXOs are known stress-responsive regulators of the cellular generation of antioxidant proteins (Klotz *et al.*, 2015). Likewise, they have an important role in the response of HSCs to physiological oxidative stress (Tothova *et al.*, 2007). Among the FOXO isoforms, FOXO3 is required for HSC self-renewal and for maintaining HSC quiescence and the HSC pool in aged mice (Miyamoto *et al.*, 2007). Moreover, FOXO3 is vital to drive a protective autophagy programme in HSC, including old HSCs, upon metabolic stress (starvation) in order to support HSC survival (Warr *et al.*, 2013). FOXO3 is also required for proper regulation of mitochondrial metabolism in HSCs (Rimmele *et al.*, 2015).

Mehta *et al.* (2015) identified the miR-132/miR-212 cluster as being responsible for controlling *FOXO3* expression in ageing HSCs, which in turn ensures balanced HSC maintenance, survival and function. The authors show that *FOXO3* mRNA is directly targeted by miR-132, and miR-132 regulates HSC cycling and function through FOXO3. Notably, miR-132 is up-regulated in HSCs with age (Mehta *et al.*, 2015). Taken together, the study demonstrates a molecular mechanism by which FOXO3 function is differentially regulated in the ageing organism. These findings are of particular interest, as several polymorphisms in the *FOXO3* locus have been shown to be associated with exceptional human longevity (reviewed in Morris *et al.*, 2015).

Recently, two groups have implicated miR-132/miR-212 and FOXO3 in two serious pathological conditions. Wong *et al.* (2013) found that both miRNAs are down-regulated in temporal cortical areas and CA1 hippocampal neurons of human Alzheimer's disease (AD) brains. The authors identified phosphatase and tensin homologue (PTEN), FOXO3 and p300 as direct targets of miR-132/212 in primary neurons and PC12 cells and showed that specific inhibition of miR-132/212 with anti-miRs (antagomirs) led to apoptosis of these cultured cells, which was counteracted by siRNA-induced down-regulation of PTEN, FOXO3 and p300. In contrast, overexpression of miR-132 and miR-212 rendered cultured hippocampal neurons less sensitive to hydrogen peroxide. Furthermore, mRNA and protein levels of PTEN, FOXO3 and p300 and of FOXO3 target genes coding for pro-apoptotic factors were increased in AD brains. The authors suggest that a 'miR-132/miR-212/PTEN/FOXO3' axis exists that contributes to the neurodegeneration in AD (Wong *et al.*, 2013).

In a second report, Ucar *et al.* (2012) uncovered the role of miR-132/212 in cardiac hypertrophy and cardiomyocyte autophagy. Myocardial stress induces pathological hypertrophy (Barry and Townsend, 2010), and miR-132/212 expression is up-regulated by pro-hypertrophic stimuli. Both miRNAs are necessary and sufficient for hypertrophic cardiomyocyte growth (Ucar *et al.*, 2012). Overexpression of the two miRNAs leads to down-regulation of FOXO3, which results in impairment of the autophagic response upon starvation. Intriguingly, antagomir injection in mice to block miR-132 function prevents cardiac hypertrophy and heart failure (Ucar *et al.*, 2012).

Simultaneous regulation of FOXO levels by several miRNAs

The real scenario within cells is likely to be more complicated, as commonly one mRNA can be simultaneously regulated by multiple miRNAs (Krek *et al.*, 2005). For example, some studies showed that miR-182 regulates *FOXO1* expression in concert with several other miRNAs. Among these, miR-27a and miR-96 (which has the same seed region as miR-182) were identified as regulating *FOXO1* expression together with miR-182 and to be highly expressed in MCF-7 (miR-27a/miR-96/miR-182) and MDA-MB-231 (miR-27a/miR-182 only) breast cancer cells, causing down-regulation of FOXO1 protein levels and thus contributing to maintenance of a proliferative state while impairing apoptotic responses (Guttilla and White, 2009). In line with this, *FOXO1* mRNA was significantly down-regulated in breast tumours of various stages compared with normal breast tissue.

Interestingly, *FOXO3* and *FOXO4* mRNA levels were not significantly altered in these tumour samples (Guttilla and White, 2009), although *FOXO3* mRNA has been shown to be the target of miR-27a or of miR-182 in multiple cell types (Table 1). One explanation for this discrepancy may be that the accessibility of a miRNA-binding site in the respective 3′-UTR may be affected by other 3′-UTR interacting factors, depending on cell/tissue type and its developmental, physiological or pathological state.

For *FOXO1* mRNA, two regions were identified in the 3′-UTR (nucleotides 204–492 and 1907–2247 of the 3′-UTR, which correspond to nucleotides 2557–2845 and 4260–4600, respectively, of the whole mRNA depicted in Figure 3), each containing one binding site for miR-27a, miR-96 and miR-182. In functional assays using luciferase reporter constructs, a higher repression was observed with the construct containing both 3′-UTR regions, as compared with the two constructs with one or the other 3′-UTR region only, suggesting the combined action of multiple miRNA target sites in the *FOXO1* 3′-UTR (Guttilla and White, 2009).

An array of seven miRNAs that cooperate in repressing FOXO1 protein levels, including miR-27, miR-96 and miR-182, was identified in endometrial cancer (Myatt *et al.*,

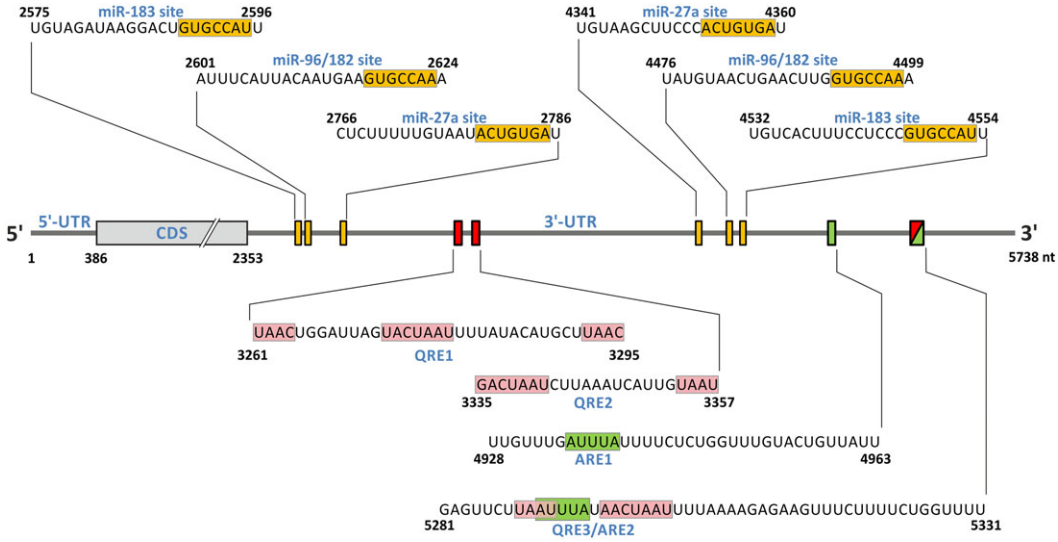

Figure 3

Position of microRNA, HuR and quaking target sites within the human *FOXO1* 3′-UTR. Position of microRNA target sites is depicted as orange boxes on the RNA; the sequences interacting with the respective miRNA are shown above the RNA, with sequences pairing with the respective miRNA seed region boxed in orange. For miR-96/182, the orange-boxed sequence indicates pairing with the miR-96 seed region, whereas pairing with the miR-182 seed region would be 1 nt shorter at the 5′ end (Guttilla and White, 2009; McLoughlin *et al.*, 2014). Quaking response elements (QRE1/2/3) (Yu *et al.*, 2014) are shown as red boxes on the RNA and the actual sequences given underneath; the 'core' and 'half site' sequences corresponding to the bipartite consensus target RNA motif (Galarneau and Richard, 2005) are boxed in pink. Note that the 'half site' can be located downstream or upstream of the 'core' sequence. QRE1 appears to have two consensus-corresponding 'half sites'. HuR-responsive AU-rich elements (ARE1/2) are shown as green boxes on the RNA, and the corresponding sequences are shown underneath (Li *et al.*, 2013), with the ARE consensus pentamer AUUUA boxed in green. Note that QRE3 and ARE2 overlap (see text for details). The scheme and sequences numberings are according to the human *FOXO1* mRNA sequence entry in the National Center for Biotechnology Information Reference Sequence Database (O'Leary *et al.*, 2016), NM_002015.3 (GI:133930787).

2010; Lam *et al.*, 2012) (see also Table 2), the most common uterine cancer (Amant *et al.*, 2005). FOXO1 is expressed in the normal human endometrium and up-regulated during differentiation of endometrial stromal cells into decidual cells. Decidualization is induced by progesterone and cAMP signalling and accompanied by increased ROS levels and oxidative stress. FOXO1 has been shown to be an important regulator of this process (Christian *et al.*, 2002; Kajihara *et al.*, 2006; Labied *et al.*, 2006; Takano *et al.*, 2007).

FOXO1 protein levels were much lower in endometrial hyperplasia and carcinoma samples than in the normal endometrium (Myatt *et al.*, 2010). Consistent with previous reports (Burney *et al.*, 2007; Goto *et al.*, 2008; Ward *et al.*, 2008), *FOXO1* mRNA levels were also lower in the cancer than in the normal tissue, although not markedly so – suggesting post-transcriptional regulation of FOXO1 synthesis.

Using several miRNA target prediction programmes and quantitative RT-PCR analysis, the authors then identified a collection of evolutionarily conserved miRNAs that were significantly up-regulated in endometrial tumours. To verify *FOXO1* targeting by these miRNAs, two endometrial cancer cell lines with profoundly different FOXO1 protein levels were used. As reported previously (Goto *et al.*, 2008; Ward *et al.*, 2008), HEC-1B cells abundantly expressed FOXO1 protein, whereas its level was very low in the Ishikawa cell line. Although *FOXO1* mRNA was substantially lower in Ishikawa cells, compared with the HEC-1B cells, the difference in mRNA levels was clearly not reflected in the difference in protein levels, analogous to the picture observed in cancer tissue samples versus normal endometrium. Remarkably, most of the miRNAs that were up-regulated in the endometrial tumours were also at very high levels in the Ishikawa cells but very low in HEC-1B cells (Myatt *et al.*, 2010).

In a series of miRNA overexpression and antagomir experiments, it was then demonstrated that a cooperative action of multiple miRNAs is essential to effectively repress the translation of *FOXO1* in endometrial cancer cells (Myatt *et al.*, 2010).

In Ishikawa cells, miRNA repression using antagomirs resulted in FOXO1 up-regulation and induced cell cycle arrest and apoptosis. Simultaneous depletion of FOXO1 using siRNA targeting the *FOXO1* mRNA coding region decreased cell death, confirming involvement of FOXO1 in this process (Myatt *et al.*, 2010).

The additive effect of three of the miRNAs identified in these studies – miR-96, miR-182 and miR-183 – on FOXO1 down-regulation has also been reported in human glioma-derived cell lines (Tang *et al.*, 2013). This miRNA cluster is strongly up-regulated in glioma tissue compared with the normal cerebrum. Further overexpression of the three miRNAs in glioma cells, individually or as a pool, led to a decreased *FOXO1* expression and increased cell proliferation. Conversely, knockdown of these miRNAs resulted in up-regulated *FOXO1* expression and increased apoptosis. Interestingly, overexpression of miRNAs was correlated with lower ROS production (although FOXO proteins are usually connected with cellular antioxidant protein production), whereas their knockdown was accompanied by the rise of ROS levels (Tang *et al.*, 2013). It is unclear, however, how and to what effect ROS levels are modulated by these procedures.

Regulation of *FOXO* expression by RNA-binding proteins

Post-transcriptional regulation of *FOXO* expression not only occurs through miRNA-mediated modulation of mRNA stability or translation but is also regulated by RNA-binding proteins, such as human antigen R (HuR) and quaking (QKI), which have recently been shown to control the levels of *FOXO1* transcript and protein (Li *et al.*, 2013; Guo *et al.*, 2014; Yu *et al.*, 2014).

HuR

HuR is an AU-rich element (ARE)-binding regulatory protein that interacts with a wide repertoire of mRNAs involved in cell survival, cell division, immune response and differentiation. It commonly acts as mRNA-stabilizing or translation-promoting factor (Srikantan *et al.*, 2012). Abundantly present in the nucleus, it responds to diverse stressful stimuli by shuttling to the cytoplasm. These stimuli include conditions that induce oxidative stress, such as UV radiation (Wang *et al.*, 2000; Fernau *et al.*, 2010), exposure to arsenite (Bhattacharyya *et al.*, 2006), *tert*-butylhydroquinone (Song *et al.*, 2005) or hydrogen peroxide (Wang *et al.*, 2000; Tran *et al.*, 2003)) or induce endoplasmic reticulum stress (thapsigargin; Bhattacharyya *et al.*, 2006) or conditions of amino acid deprivation (Bhattacharyya *et al.*, 2006). Exposure to these stimuli results in activation of p38-MAPK, which directly or indirectly (e.g. via MAPK-activated protein kinase-2, MK2) triggers HuR phosphorylation, which in turn leads to binding of its target mRNAs and cytoplasmic accumulation. Furthermore, HuR itself was hypothesized to function as redox sensor. HuR attains its full activity as a homodimer, and a cysteine residue in the first of the three HuR RNA recognition motifs was suggested to contribute to homodimerization through formation of an intermolecular disulfide bond (Benoit

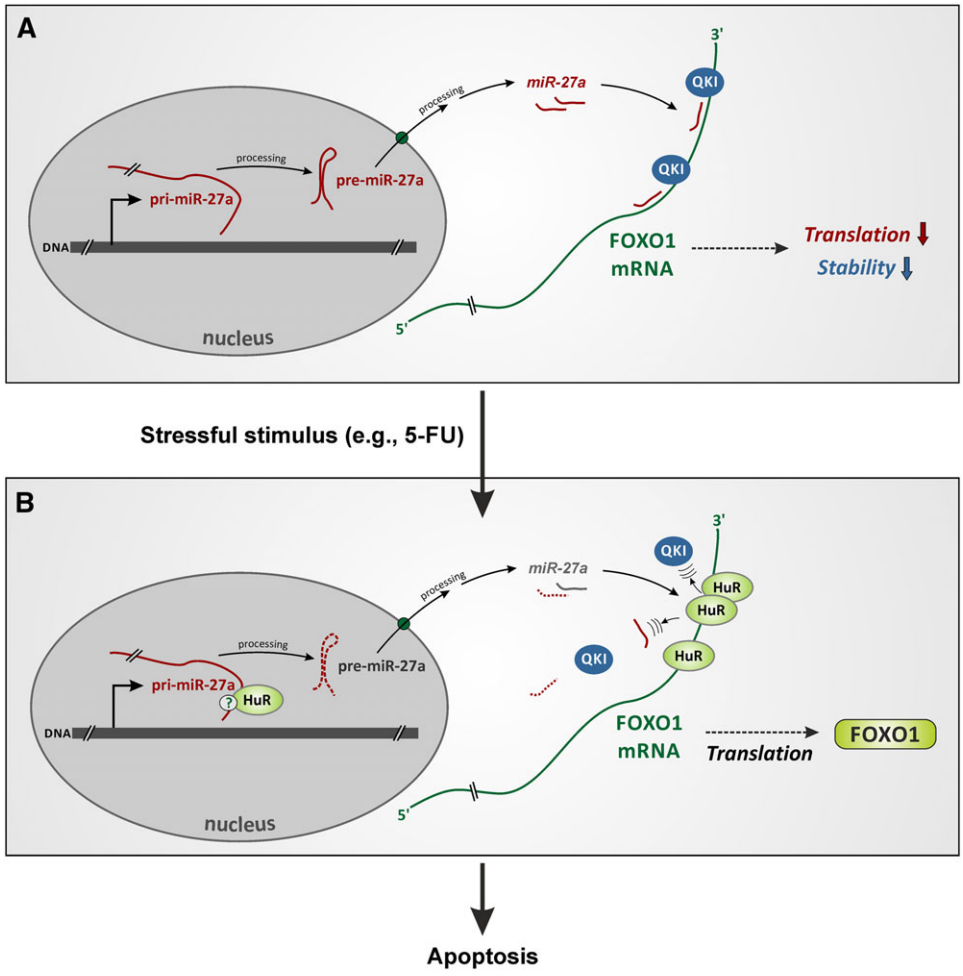

Figure 4

Hypothetical interactions between miRNAs, HuR and quaking in breast cancer cells upon stressful stimulus. (A) MiR-27a and miR-182 (not shown here), together with quaking (QKI), impair *FOXO1* mRNA translation and decrease its stability (Guttilla and White, 2009; Yu *et al.*, 2014). We hypothesize that QKI and miRNAs/miRISCs cooperate in this process. (B) Stressful stimuli, such as exposure to 5-fluorouracil (5-FU), up-regulate HuR and cause its accumulation in the cytoplasm; simultaneously, QKI is down-regulated. HuR binds *FOXO1* mRNA, which leads to miRNA and possibly also QKI dissociation, resulting in mRNA stabilization and up-regulation of its translation (Guttilla and White, 2009; Li *et al.*, 2013; Yu *et al.*, 2014). Notably, HuR may compete with QKI for one of their binding sites in this process (Figure 3). Additionally, a second synergistic level of miRNA regulation by HuR is proposed to take place. As HuR binds mature miR-27a and/or, for example, its pri-miRNA (Mukherjee *et al.*, 2011), it may inhibit miR-27a/RISC biogenesis. FOXO1 protein up-regulation in turn induces apoptosis in breast cancer cells (see text for details and references).

et al., 2010). As a redox-sensitive reactive cysteine, it would render HuR responsive towards oxidative stimuli, with an elevated HuR activity due to homodimerization (Benoit *et al.*, 2010; Benoit and Auer, 2011).

Using photoactivatable ribonucleoside-enhanced crosslinking and immunoprecipitation (PAR-CliP, Hafner *et al.*, 2010) and other high-throughput targeting techniques, thousands of putative HuR-binding sites were identified in the human transcriptome (Lebedeva *et al.*, 2011; Mukherjee *et al.*, 2011). The majority of binding sites were located in the 3′-UTRs and, surprisingly, in intronic regions of pre-mRNAs, indicating involvement of HuR in pre-mRNA processing and regulation of mRNA stability. HuR-binding sites were identified both in the 3′-UTR and in the intronic regions of *FOXO1* RNA (Lebedeva *et al.*, 2011; Mukherjee *et al.*, 2011), while only intronic HuR binding was found in *FOXO3* pre-mRNA (Mukherjee *et al.*, 2011).

Li *et al.* (2013) characterized two AREs recognized by HuR in the 3′-UTR of human *FOXO1* mRNA. Overexpression of HuR in MDA-MB-231 breast cancer cells stabilized *FOXO1* mRNA and elevated FOXO1 protein levels. Furthermore, stress-induced up-regulation of endogenous HuR levels using 5-fluorouracil (5-FU) also led to an increase in cellular FOXO1 levels. 5-FU-induced apoptosis was almost completely inhibited by simultaneous siRNA-mediated knockdown of endogenous HuR and restored by overexpression of ectopic FOXO1 in the presence of HuR-siRNA. Taken together, these data suggest a HuR-mediated up-regulation of FOXO1 upon exposure to a stressful stimulus, which in turn induces apoptosis in cancer cells (Figure 4).

Regarding FOXO1 up-regulation by HuR, an interaction between HuR and miRNA(s) bound to *FOXO1* 3′-UTR may contribute, analogous to findings by Bhattacharyya *et al.* (2006) who revealed that miRNA-mediated translational repression can be reversed by HuR under a variety of stress conditions. They showed that the mRNA of cationic amino acid transporter-1 (*CAT-1*) and reporter constructs containing the *CAT-1* 3′-UTR were subjected to repression by miR-122 in human Huh7 hepatocarcinoma cells. Upon conditions of amino acid deprivation, oxidative stress induced by arsenite, or endoplasmic reticulum stress, HuR binds an ARE located in the 3′-UTR of *CAT-1* mRNA and relieves CAT-1 from translational repression by miR-122. Notably, this derepression occurs despite the fact that the aforementioned ARE is located at some distance from miR-122-binding sites (Bhattacharyya *et al.*, 2006; Kundu *et al.*, 2012). The ability of HuR to oligomerize along RNA was suggested as a potential underlying molecular mechanism, leading to a dissociation of miRNA and associated proteins from the corresponding 3′-UTR site (Kundu *et al.*, 2012).

In addition to the direct removal of miRNAs/miRISCs by HuR from the 3′-UTR of a given mRNA, a second level of miRNA regulation by HuR has recently been described. HuR can bind primary transcripts of specific miRNA genes, thus inhibiting their processing and formation of mature miRNA (Lebedeva *et al.*, 2011; Choudhury *et al.*, 2013; Zhang *et al.*, 2015b). For instance, HuR, in complex with Musashi homolog 2 protein, suppresses maturation of miR-7 in non-neural cells (Lebedeva *et al.*, 2011; Choudhury *et al.*, 2013). Moreover, maturation of miR-199a is suppressed by HuR in hepatocellular carcinoma cells under hypoxic conditions, which contributes to the cancer cell switch to glycolytic metabolism (Zhang *et al.*, 2015b).

Notably, transcriptome-wide mapping of HuR-binding sites in human cells identified miR-27a as a HuR target (see Table S2 in Mukherjee *et al.*, 2011, under cluster ID: G71353.1). It is currently unclear, whether HuR binds mature miR-27a and/or any of its precursors, such as pri-miRNA-27a (as hypothesized in Figure 4). In any case, this finding raises a possibility that HuR employs two synergistic mechanisms to up-regulate FOXO1 protein under stress conditions described previously: (i) dissociation of miR-27a and miR-182 from *FOXO1* mRNA and (ii) inhibition of miR-27a/RNA-induced silencing complex (RISC) biogenesis (see Figure 4 for further details).

As outlined previously, *FOXO1* expression is likely to be repressed by miR-27a and miR-182 in MDA-MB-231 breast cancer cells (Guttilla and White, 2009). Their target sites are located in two regions of the 3′-UTR, with HuR-binding AREs positioned further downstream from these regions (see Figure 3 for the details). We therefore hypothesize that stress induced by 5-FU (Li *et al.*, 2013) and oxidative stress inducing HuR activity may lead to HuR-mediated dissociation of miR-27a and miR-182 from *FOXO1* mRNA, resulting in its translational derepression (Figure 4).

Quaking

A second RNA-binding protein involved in the post-transcriptional regulation of FOXO1 is QKI (Guo *et al.*, 2014; Yu *et al.*, 2014), a regulator of mRNA splicing, transport, stability and translation. It is essential for embryogenesis and for myelination during postnatal development. It coordinates differentiation and cell cycle and functions as tumour suppressor (Artzt and Wu, 2010; Biedermann *et al.*, 2010; Feng and Bankston, 2010). Galarneau and Richard (2005) defined a consensus sequence (NACUAAY-$N_{1\text{-}20}$-UAAY) for the QKI response element (QRE) and identified >1400 putative mRNA targets of QKI in the mouse using bioinformatics analysis, including *FOXO1*.

Yu *et al.* (2014) demonstrated interaction of QKI with three QREs located within the *FOXO1* 3′-UTR. QKI was shown to decrease *FOXO1* mRNA stability and to impair *FOXO1* expression in breast cancer cells: siRNA-mediated knockdown of QKI led to an up-regulation of FOXO1 mRNA and protein, whereas QKI overexpression resulted in FOXO1 down-regulation. Importantly, inhibition of proliferation by all-*trans*-retinoic acid or treatment with 5-FU led to down-regulation of QKI, up-regulation of *FOXO1* expression and up-regulation of luciferase activity in the *FOXO1* 3′-UTR assay.

Two recent studies demonstrate that the QKI↑/FOXO1↓ regulatory axis may play an important role in susceptibility to ischemic heart injury (Guo *et al.*, 2011; Guo *et al.*, 2014). QKI is highly expressed in rat cardiomyocytes; however, following ischaemia *in vivo* or simulated ischaemia *in vitro*, its predominant isoform QKI-5 was strongly down-regulated – even more so after reperfusion (ischaemia/reperfusion, I/R) (Guo *et al.*, 2011). In line with the aforementioned QKI/FOXO1 antagonism, FOXO1 levels were strongly up-regulated by ischaemia and I/R and further enhanced when siRNA-mediated QKI knockdown preceded I/R. Elevated FOXO1 levels resulted in up-regulation of Bim and FasL (known FOXO target gene products) and increased apoptosis (Guo *et al.*, 2011). Interestingly, QKI knockdown alone, that is, without I/R, was not sufficient to induce FOXO1 in H9C2 cardiac myoblasts. *FOXO1* is a target gene of transcription factor E2F-1 (Nowak *et al.*, 2007), and E2F-1 itself has been shown to be up-regulated by I/R and at the same time was

necessary and sufficient to up-regulate FOXO1 after I/R, both *in vivo* and *in vitro* (Angelis *et al.*, 2011). In view of these data, we propose that *FOXO1* is doubly regulated during I/R in the heart: I/R induces its transcription and abolishes its post-transcriptional repression by QKI.

In a follow-up report, Guo *et al.* (2014) extended their studies to the hearts of leptin-deficient (*ob*/*ob*) mice; these mice exhibit type 2 diabetes-like symptoms. They observed that QKI-5 was down-regulated in murine *ob*/*ob* hearts as compared with the wild-type controls. Accordingly, FOXO1 was up-regulated and strongly activated in the mutant in comparison with the wild-type mice, as shown by its predominant localization in cellular nuclei. Interestingly, FOXO1 activation was linked to myocardial nitrosative stress and endoplasmic reticulum stress, further promoting myocardial I/R injury and apoptosis. Both siRNA-mediated down-regulation of FOXO1 and overexpression of ectopic QKI-5 in *ob*/*ob* hearts *in vivo* attenuated stress and I/R injury. In agreement with the results obtained in breast cancer cells (Yu *et al.*, 2014), QKI overexpression lowered *FOXO1* mRNA stability in primary neonatal cardiomyocytes (Guo *et al.*, 2014).

The molecular mechanism by which QKI destabilizes *FOXO1* mRNA remains unknown. Could QKI cooperate with miRNAs/miRISCs that are bound to the *FOXO1* 3′-UTR? Wang *et al.* (2010) showed that the QKI isoform QKI-6 can interact with argonaute 2 (Ago2), the catalytic component of RISC, in a human glioblastoma cell line. Furthermore, as a result of an oxidative stress-inducing treatment with arsenic oxide, QKI-6 co-localized with Ago2 and myelin basic protein mRNA in the cytoplasmic stress granules. Additionally, Chen *et al.*, (2012) reported that QKI binds and stabilizes mature miR-20a in doxorubicin-treated astrocytes. It therefore seems likely that crosstalk between QKI and particular miRNA/miRISC may exist under certain conditions.

As discussed already, the 3′-UTR of *FOXO1* mRNA is bound both by miR-27a, miR-96 and miR-182 (Guttilla and White, 2009) and by the QKI protein (Yu *et al.*, 2014) in MCF-7 breast cancer cells. Targeting of these miRNAs with antisense inhibitors had the same effect on endogenous *FOXO1* expression as the knockdown of QKI, in both cases leading to up-regulation of FOXO1 mRNA and protein levels (compare Guttilla and White, 2009; Yu *et al.*, 2014). Future experiments will be required to ascertain whether the two effects are independent, that is, the simultaneous miRNA inhibition and QKI knockdown in one experiment would have an additive effect and lead to much stronger FOXO1 up-regulation. Alternatively, the effect of miRNAs and QKI may be interconnected, and then a treatment targeting only one of the factors (e.g. targeting of miRNAs) would be expected to also block binding of the other (e.g. QKI) to the 3′-UTR.

We compared the locations of AREs recognized by HuR within the 3′-UTR of *FOXO1* mRNA, as reported by Li *et al.* (2013), with the locations of QKI response elements (Galarneau and Richard, 2005; Yu *et al.*, 2014). Interestingly, the second ARE overlaps with the third QRE in the 3′-UTR (Figure 3). This binding site arrangement raises a possibility of mutually exclusive binding of the two regulatory proteins to the *FOXO1* transcript. Moreover, 5-FU treatment of MDA-MB-231 breast cancer cells led to FOXO1 up-regulation in both reports, with concurrent up-regulation of HuR (Li *et al.*, 2013) and down-regulation of QKI (Yu *et al.*, 2014). Based on these data, it seems reasonable to propose that post-transcriptional regulation of FOXO1 involves functional interplay between specific miRNAs, HuR and QKI. In such a way, FOXO1 protein formation could be up-regulated post-transcriptionally via these interactions in response to various stressful stimuli, including oxidative stress (Figure 4).

Conclusions and perspectives

Post-transcriptional regulation emerges as a new level of control of FOXO functions. As demonstrated by numerous recent publications, a wide range of miRNAs can directly regulate *FOXO* transcripts. This occurs in a variety of cell types and tissues and under diverse physiological and pathological conditions, including cancer (Table 1). A vast majority of these reports addresses an involvement of only a single miRNA, in a given cell type and process, and shows its role in *FOXO* translational inhibition or mRNA destabilization.

However, an accumulating body of evidence (unrelated to the FOXO field) points to a considerably more complex nature of post-transcriptional regulatory mechanisms and their diverse effects on mRNA translation and stability. For example, under certain physiological conditions, some miRNAs may (in addition to repressing translation of their target mRNAs) also contribute to the stimulation of target mRNA translation by recruiting activating regulatory proteins (Vasudevan and Steitz, 2007; Vasudevan *et al.*, 2007; reviewed by Steitz and Vasudevan, 2009).

Similarly, HuR – described previously as a positive regulator of mRNA stability and translation by antagonizing the repressive effect of miRNAs – can also cooperate with specific miRNAs to destabilize and repress particular mRNAs: HuR and miRNA let-7/RISC both bind the 3′-UTR of c-Myc mRNA and cooperate in its repression (Kim *et al.*, 2009; reviewed in Meisner and Filipowicz, 2010; Srikantan *et al.*, 2012). Intriguingly, by cooperating with let-7/Ago2 to destabilize a different RNA, a long intergenic noncoding RNA (*lincRNA-p21*), HuR can indirectly derepress the translation of *JunB* and *CTNNB1* (β-catenin) mRNAs. This is because under low HuR levels, *lincRNA-p21* accumulates in the cell and directly represses the translation of *JunB* and β-catenin (Yoon *et al.*, 2012). This example particularly nicely illustrates the complexity of post-transcriptional regulatory interactions.

Like HuR, QKI can also act in an 'opposite direction'. Larocque *et al.* (2005) showed in oligodendrocyte progenitor cells that QKI binds and stabilizes the mRNA coding for the cyclin-dependent kinase inhibitor, $p27^{Kip1}$, which in turn increases the level of $p27^{Kip1}$ protein, induces cell cycle arrest and thus ensures proper differentiation into mature oligodendrocytes. This process is disturbed, in part, in the mouse mutant harbouring a mutation in the quaking (*Qk*) locus (the so-called Quaking viable mice), leading to abnormal myelination in the central nervous system (Sidman *et al.*, 1964; Ebersole *et al.*, 1996). Of note, as the $p27^{Kip1}$-encoding gene is a target of FOXO1 (Dijkers *et al.*, 2000; Medema *et al.*, 2000; Machida *et al.*, 2003), it will be interesting to see whether and how *FOXO1* mRNA is regulated by QKI during oligodendrocyte progenitor cell differentiation.

In summary, the same regulatory molecules appear to be capable of exerting quite opposite effects, depending on target mRNA, cell type and conditions.

In addition to HuR and QKI, many other RNA-binding proteins and interacting cofactors are being identified as post-transcriptional regulators of gene expression, often acting under diverse conditions, such as during oxidative stress (Abdelmohsen *et al.*, 2008) or in development (Kedde and Agami, 2008). As an illustration, the evolutionarily conserved RNA-binding protein dead end 1 counteracts the activity of several miRNAs by precluding them from binding their target sites. This is essential for correct development of primordial germ cells in mammals and zebrafish (Kedde *et al.*, 2007; Kedde and Agami, 2008) and was hypothesized to contribute to the regulation of cell–cell communication via gap junctions (Klotz, 2012). It is therefore very likely that many more regulatory proteins will turn out to control or modulate FOXO functions post-transcriptionally, in concert with the growing battery of miRNAs (Table 1).

In view of the findings already discussed – both related and unrelated to FOXO – a number of questions arise concerning post-transcriptional regulation of *FOXO* expression. For example, do miRNAs and QKI cooperate in down-regulating FOXO1 protein? How does HuR abolish the inhibitory effect of miRNAs/QKI on *FOXO1* expression? Does HuR suppress miR-27a biogenesis? Can HuR and QKI exert an inhibitory (rather than stimulatory) and stimulatory (rather than attenuating) action, respectively, on *FOXO* expression under certain physiological conditions? Are there other RNA-binding regulatory proteins that control or modulate *FOXO* expression post-transcriptionally?

It currently appears that miRNA studies are advancing at a faster pace than research on regulatory proteins – probably due, in part, to the ease with which miRNAs can be experimentally manipulated. AntagomiRs (antimiRs, miRNA inhibitors) and miRNA mimics have become powerful standard tools. This is mirrored in recent attempts to introduce efficient and safe miRNA-targeted and miRNA-based therapeutic modalities (see Mendell and Olson, 2012; Piva *et al.*, 2013; Garofalo *et al.*, 2014). The molecular picture, however, will only be complete after we obtain a detailed knowledge of all interactions between mRNAs, miRNAs and RNA-binding proteins.

Here, we have provided an overview on post-transcriptional regulation of *FOXO* expression from the viewpoint of an emerging diversity of interactions between miRNAs and regulatory RNA-binding proteins. Accumulating evidence suggests that this post-transcriptional mode of regulation of FOXO activity is employed in reactions and adaptations to various stressful stimuli, including oxidative stress. Abnormal post-transcriptional regulation of FOXO is often linked to various disease states. Future research into the complexities of post-transcriptional regulatory interactions will bring new knowledge about the mechanisms of disease processes and open novel ways towards therapeutic intervention.

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Conflict of interest

P.U. and L.O.K. have nothing to disclose.

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