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Review Article

FOXO transcription factors in non-alcoholic fatty liver disease☆

X. Charlie Dong

Department of Biochemistry and Molecular Biology, Center for Diabetes and Metabolic Diseases, Indiana University School of Medicine, Indianapolis, IN, USA

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ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) is a chronic progressive liver disorder that begins with simple hepatic steatosis and progresses to non-alcoholic steatohepatitis, fibrosis, cirrhosis, and even liver cancer. As the global prevalence of NAFLD rises, it is increasingly important that we understand its pathogenesis and develop effective therapies for this chronic disease. Forkhead box O (FOXO) transcription factors are key downstream regulators in the insulin/insulin-like growth factor 1 (IGF1) signaling pathway, and have been implicated in a range of cellular functions including the regulation of glucose, triglyceride, and cholesterol homeostasis. The role of FOXOs in the modulation of immune response and inflammation is complex, with reports of both pro- and anti-inflammatory effects. FOXOs are reported to protect against hepatic fibrosis by inhibiting proliferation and transdifferentiation of hepatic stellate cells. Mice that are deficient in hepatic FOXOs are more susceptible to non-alcoholic steatohepatitis than wild-type controls. In summary, FOXOs play a critical role in maintaining metabolic and cellular homeostasis in the liver, and dysregulation of FOXOs may be involved in the NAFLD development.

1. Introduction

Forkhead box O (FOXO) transcription factors belong to the O subfamily of the forkhead box protein family.[1] There is a single *FOXO* gene in *Caenorhabditis elegans* (*DAF-16*) and *Drosophila* (*dFOXO*), and four *FOXO* genes (*FOXO1/3/4/6*) in mammals. FOXO proteins are highly conserved, especially the forkhead box and transactivation domains and the AKT serine/threonine protein kinase phosphorylation sites (Fig. S1). Mammals and other animals, such as *Caenorhabditis elegans* and *Drosophila,* share similar insulin/insulin-like growth factor (IGF) 1 signaling cascades (Fig. 1). Insulin/IGF1 activate insulin receptor/IGF1 receptor, which subsequently activate insulin receptor substrates through tyrosine phosphorylation. The activated insulin receptor substrates stimulate phosphoinositide 3-kinase, which converts phosphatidylinositol-4,5-bisphosphate [PI(4,5)P_2] to phosphatidylinositol-3,4,5-trisphosphate [PI(3,4,5)P_3]. This stimulates 3-phosphoinositide-dependent protein kinase 1 and mechanistic target of rapamycin complex 2, which activate AKT at Thr308 and Ser473, respectively.[2–4] FOXOs are the immediate downstream effectors of AKT (Fig. 2).

FOXO transcriptional activity can be regulated by various post-translational modifications, though is predominantly regulated by phosphorylation and acetylation.[5] AKT kinases play a critical role in FOXO inactivation by phosphorylating a few conserved serine/threonine sites of each FOXO (FOXO1-Thr24/Ser256/Ser319, FOXO3-Thr32/Ser253/Ser315, FOXO4-Thr32/Ser197/Ser262, FOXO6-Thr26/Ser184).[6] In addition to AKT, there are a number of other kinases that can phosphorylate FOXOs, including adenosine monophosphate (AMP)-activated protein kinase (AMPK), c-Jun N-terminal kinase (JNK), extracellular signal-regulated kinase (ERK), p38 mitogen-activated protein kinase, mammalian sterile 20-like kinase 1, and protein kinase R-like endoplasmic reticulum kinase.[7] In addition to phosphorylation, FOXOs can be acetylated by p300/cyclic AMP response element-binding (CREB) binding protein (CBP) acetyltransferases and deacetylated by sirtuin (SIRT) 1 and histone deacetylase 3.[8–17]

FOXOs have pleiotropic functions in animal systems, with effects on cell survival, anti-oxidative stress, autophagy, and metabolism (Fig. 3). In this short review, I will summarize our current understanding of liver FOXOs and their role in NAFLD development.

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E-mail address: xcdong@iu.edu.

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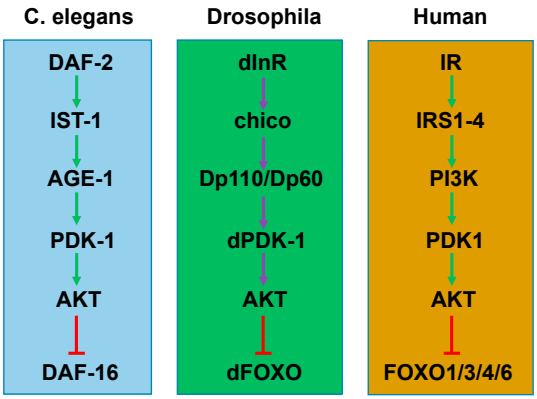

Fig. 1. The insulin/insulin-like signaling pathways are evolutionally conserved. The FOXO transcription factors are regulated by the insulin/insulin-like signaling pathways that are well conserved in *C. elegans*, *Drosophila*, and mammals. Stimulation by insulin or insulin-like growth factors (IGFs), activates the insulin/IGFs receptors, and subsequently the signaling cascade of IRS→PI3K→PDK1→AKT. As a result, FOXOs are phosphorylated and inhibited by AKT. Abbreviations: FOXO, forkhead box O ; IR, insulin receptor; IRS, insulin receptor substrate; PI3K, phosphoinositide 3-kinase; PDK1, 3-phosphoinositide-dependent protein kinase 1; AKT, RAC-alpha serine/threonine-protein kinase.

2. FOXOs in glucose and lipid metabolism

The interplay between FOXO transcription factors and insulin and nutrient signaling pathways indicates that FOXOs play an important role in both glucose and lipid metabolism (Fig. 2).[18–40] The role of FOXOs in the regulation of genes that are critically involved in glucose, triglyceride, and cholesterol metabolism is summarized below.

2.1. FOXOs in hepatic glucose metabolism

FOXOs have been shown to play a critical role in hepatic glucose homeostasis. Knockout of either *FoxO1* alone or *FoxO1/3/4* altogether specifically in mouse liver leads to lower blood glucose levels under both fasting and non-fasting conditions.[21,25,26,35,36,40] *FoxO6* whole body knockout mice also exhibit lower levels of fasting and non-fasting blood glucose.[18] In response to starvation, FOXOs transcriptionally activate the hepatic gluconeogenic program by inducing a number of genes including phosphoenolpyruvate carboxykinase 1, glucose-6-phosphatase catalytic subunit, and pyruvate dehydrogenase kinase 4.[24,26,35,36,38,40,41] Meanwhile, FOXOs also inhibit glycolysis, likely through suppression of glucokinase and pyruvate kinase gene expression (Fig. 3).[24,26,35,36,38,41]

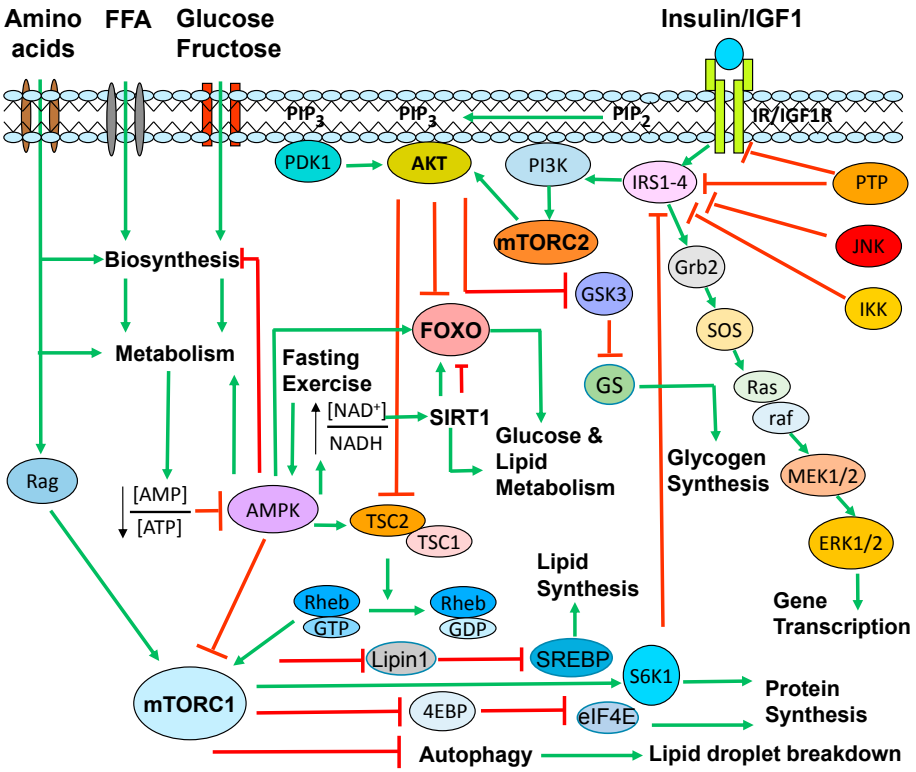

Fig. 2. Insulin signaling and nutrient sensing pathways in hepatocytes. Major signaling cascades in the insulin and amino acid signaling pathways are outlined in this simplified diagram. Insulin and nutrient signaling is normally integrated to maintain metabolic homeostasis. Insulin plays a critical role in glucose, lipid, and protein metabolism. Upon insulin stimulation, the insulin signaling cascade (IR→IRS→PI3K→PDK1/mTORC2→AKT) is activated. As a major kinase in the downstream of the insulin signaling, AKT controls hepatic glucose and lipid homeostasis. AKT activates glycogen synthesis by inhibiting GSK3 through phosphorylation. Meanwhile, AKT inhibits the FOXO transcriptional activity for hepatic gluconeogenesis through phosphorylation and nuclear exclusion of FOXO. AKT also promotes lipid and protein synthesis through activation of mTORC1. In addition to insulin, amino acids also activate mTORC1 to promote protein synthesis and inhibit autophagy. mTORC1 stimulates lipogenesis through activation of SREBPs. FOXO is also modulated via deacetylation by SIRT1, an NAD^+-dependent deacetylase. The energy sensor AMPK regulates metabolic homeostasis through activation of FOXO and inhibition of mTORC1. Abbreviations: IR, insulin receptor ; IRS, insulin receptor substrate; PI3K, phosphoinositide 3-kinase; PDK1, 3-phosphoinositide-dependent protein kinase 1; AKT, RAC-alpha serine/threonine-protein kinase; mTORC2, mammalian target of rapamycin complex 2; FOXO, forkhead box O; SIRT1, sirtuin 1; AMPK, AMP-activated protein kinase.

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