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Review

FoxO transcription factors in cancer metabolism

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ABSTRACT

FoxO transcription factors serve as the central regulator of cellular homeostasis and are tumor suppressors in human cancers. Recent studies have revealed that, besides their classic functions in promoting cell death and inducing cell cycle arrest, FoxOs also regulate cancer metabolism, an emerging hallmark of cancer. In this review, we summarize the regulatory mechanisms employed to control FoxO activities in the context of cancer biology, and discuss FoxO function in metabolism reprogramming in cancer and interaction with other key cancer metabolism pathways. A deeper understanding of FoxOs in cancer metabolism may reveal novel therapeutic opportunities in cancer treatment.

1. Introduction

In order to maintain cellular homeostasis, metazoans have evolved an intricate signaling network which senses and adapts to the changes in the extracellular or intracellular environment. Successful adaptation and long-term survival under altered physiological conditions are dependent on the precise regulation of gene expression, which is mainly controlled by the specific recruitment of transcription factors (TFs) to the target gene promoters or enhancer regions. Therefore, TFs serve as the ultimate effector molecules and even define the fate of a cell [1]. The human genome encodes around 2000 TFs, which regulate a diverse array of cellular processes ranging from cell division to cell death [2]. Dysregulation of TFs results in various pathological conditions including cancer. Indeed, TFs have often been found to be mutated, deleted, or amplified in many cancers, and therefore have been considered as attractive therapeutic targets for cancer treatment [3].

The forkhead box O (FoxO) family of TFs are the central regulator to the metazoan physiology and have diverse cellular functions including cell cycle, cell growth, apoptosis, autophagy, stress resistance, protection from aggregate toxicity, DNA repair, tumor suppression, and metabolism [4–8]. They have also been implicated in the regulation of organ development, stem cell maintenance, and cell differentiation, suggesting their crucial roles in development [9–11]. FoxOs belong to the superfamily of TFs known as forkhead box TFs and are characterized by the presence of an evolutionarily conserved winged-helix DNA binding motif and the forkhead domain [8]. The expression of FoxO target genes is regulated by selective recruitment of FoxOs to the consensus DNA sequence TTGTTAC and their interactions with other TFs [8]. FoxOs are evolutionarily conserved and have a single orthologue in invertebrates, such as DAF-16 in *Caenorhabditis elegans* and dFOXO in *Drosophila melanogaster*. In contrast, mammalian FoxOs consist of at least four members: FoxO1, FoxO3, FoxO4, and FoxO6. The expression of specific FoxO members in mammals varies among different tissues and is regulated in a spatiotemporal manner during various developmental stages [12,13]. In addition, FoxO TFs sense the changes in the extracellular or intracellular environment and their activities are also regulated by different types of signaling stimuli, including growth factors that activate the phosphatidyl-inositol-3-kinases (PI3K)-AKT (also known as PKB) pathway and different stress signaling, such as oxidative stress [6]. Tight regulation of FoxO transcriptional activity by complex signaling networks ensures that specific gene expression switch coordinates with environmental cues. FoxOs have been implicated in various diseases, including cancer. FoxOs generally exert tumor suppression functions by promoting cell cycle arrest, apoptosis, stress resistance, and DNA repair in cancer cells, and are inactivated in various human cancers [4,14]. In addition, FoxOs act as a central regulator of cellular metabolism and longevity [5,15], thereby placing FoxOs at the crossroad of cancer and metabolism.

In this review, we first present a detailed discussion on the intricate regulatory mechanisms employed to fine-tune the transcriptional activities of FoxOs in cancer, followed by a discussion of the biological roles of FoxOs in tumor suppression. We then focus on the new insights in FoxO regulation of cancer metabolism. Finally, we discuss the cross talks between FoxOs and other important pathways/cellular processes

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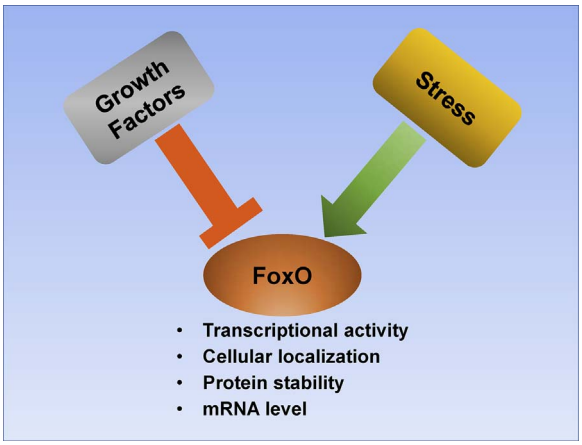

Fig. 1. FoxO regulation by growth factor and stress signaling. Growth factors inhibit FoxOs whereas stress signaling generally activates FoxOs. FoxOs are modulated at several mechanistic levels as indicated.

involved in cancer metabolism. It is important to note that FoxO regulation of metabolism also plays pivotal roles in insulin resistance, diabetes, and obesity [7,16,17]. However, this topic will be beyond the scope of this review focusing on metabolic function of FoxOs in cancer.

2. Molecular mechanisms of FoxO regulation

FoxO TFs are regulated by the coordinated actions of multiple signaling pathways at several mechanistic levels, including regulation of FoxO transcriptional activity, cellular localization, protein stability, and mRNA levels (Fig. 1). These multiple modes of regulation ensure the condition-specific activation or inhibition of FoxOs. Notably, many of the FoxO regulators also play instrumental roles in cancer biology, and the regulatory modes to control FoxOs are often dysregulated in cancer.

2.1. Regulation by growth factor-PI3K-AKT signaling

Classically, FoxO activity is regulated via an evolutionarily conserved pathway that involves the negative regulation of FoxOs by growth factor-PI3K-AKT pathway. Under normal physiological conditions, binding of insulin or other growth factors to receptor tyrosine kinases (RTKs) results in RTK activation through autophosphorylation. Activated RTK recruits PI3K via phosphotyrosine sites in the cytoplasmic tail of RTKs or adaptor proteins. This recruitment leads to activation of PI3K, which in turn catalyzes the production of lipid second messenger phosphatidylinositol-3,4,5-triphosphate (PIP3) from its substrate phosphatidylinositol-4,5-bisphosphate (PIP2) [18,19]. Generation of PIP3 marks the initiation of a signaling cascade that regulates various aspects of cellular physiology including cell cycle, cell survival, metabolism, apoptosis, and DNA repair. Specifically, PIP3 functions as a docking site for pleckstrin homology (PH) domain-containing proteins including AKT and phosphoinositide-dependent kinase-1 (PDK1) [20]. Recruitment of PDK1 and AKT to the plasma membrane facilitates partial activation of AKT via phosphorylation at Thr308 by PDK1. In addition, phosphorylation at Ser473 on AKT by mammalian target of rapamycin complex 2 (mTORC2, also known as mechanistic target of rapamycin complex 2) leads to full activation of AKT [21]. AKT activation can be reversed by the action of phosphatase and tensin homolog (PTEN), which functions as a lipid phosphatase to convert PIP3 back to PIP2 [22].

Key mechanisms of FoxO regulation were first identified in 1999. A series of classical experiments demonstrated that AKT phosphorylates FoxOs at three residue (Thr24, Ser256, Ser391 for FoxO1, Thr32, Ser253, Ser315 for FoxO3, and Thr28, Ser193, Ser258 for FoxO4), and this phosphorylation event negatively regulates FoxO nuclear localization, thereby preventing FoxO association with TF binding sites on DNA and inhibiting its transcriptional activity [23–27]. One current model proposes that AKT-mediated FoxO phosphorylation prevents FoxO association with DNA by facilitating their binding to nuclear 14-3-3 protein, resulting in enhanced export from nucleus and diminished re-entry into nucleus possibly by masking the nuclear localization signal (NLS) in FoxOs [28]. Aside from AKT, FoxOs is also inactivated by phosphorylation via AKT-related serum and glucocorticoid-inducible kinase (SGK), which, similar to AKT, can be activated by PDK1-mediated phosphorylation [29]. Although both AKT and SGK share similar FoxO phosphorylation sites, they show preferential activity at selective residues [29]. In contrast to other FoxO members discussed above, the PI3K-AKT pathway fails to prevent FoxO6 nuclear shuttling due to a lack of carboxyl-terminal AKT-dependent phosphorylation sites in FoxO6. However, phosphorylation at the other two residues in FoxO6 disrupts its binding affinity towards DNA, leading to its inactivation [30,31].

2.2. Regulation by AKT-independent phosphorylation

In contrast to growth factor-PI3K-AKT signaling which induces the nuclear exclusion of FoxOs, cellular oxidative stress generally promotes nuclear localization of FoxOs, which then mediates antioxidant response by regulating the expression of key antioxidant genes such as catalase, superoxide dismutases (SODs), and sestrins [5]. Nuclear translocation of FoxOs following oxidative stress is mediated by an evolutionarily conserved signaling that involves c-Jun N-terminal kinase (JNK) [32,33]. Specifically, following oxidative stress, JNK phosphorylates FoxO4 at Thr447 and Thr451, resulting in its nuclear translocation even in presence of the PI3K-AKT signaling [34]. JNK can also indirectly regulate FoxO activity by dissociating FoxO from 14-3-3 via phosphorylating 14-3-3 at Ser184 [35]. Nuclear translocation of FoxOs and expression of pro-apoptotic genes following oxidative stress can also be mediated by mammalian sterile 20-like kinase-1 (MST1). MST1 phosphorylates FoxO3 at Ser207, causing disruption of FoxO3 interaction with 14-3-3 [36]. Interestingly, the upstream signaling resulting in MST1 activation might also involve its phosphorylation at Ser82 by JNK [37].

FoxOs also serve as a key component of the nutrient sensing circuit and have been implicated in extending lifespan along with dietary restriction. AMP-activated protein kinase (AMPK) is a central regulator of energy homeostasis. High cellular AMP to ATP ratio following energy deprivation results in AMPK activation [38,39]. Activated AMPK then phosphorylates a variety of substrates promoting cellular catabolism and simultaneously inhibiting cellular anabolism [38]. AMPK activation also alters the expression of many genes to adapt to energy stress partly through FoxOs. Specifically, AMPK phosphorylates FoxO3 at six different residues (Thr179, Ser399, Ser413, Ser439, Ser555, and Ser588), causing upregulation of genes involved in antioxidant response and energy utilization pathways [40]. In contrast to the kinases described above that often affect nuclear-cytoplasmic shuttling of FoxOs, AMPK-mediated FoxO3 phosphorylation does not affect FoxO3 cellular localization, but may regulate FoxO3 binding on the target genes under energy stress [40]. Notably, AMPK-mediated FoxO phosphorylation also plays a role in FoxO regulation of organismal longevity following dietary restriction in *C. elegans*, highlighting that this is an evolutionarily conserved mechanism [41]. Regulation of hepatic gluconeogenesis following prolonged starvation was also found to be mediated by AMPK-FoxO signaling. Specifically, TGF-β/Smad3 signaling inhibits AMPK phosphorylation and promotes FoxO1 activation, resulting in upregulation of gluconeogenic genes [42].

Several other kinases, including cyclin-dependent kinase (CDK), Ataxia telangiectasia mutated (ATM), ATM and Rad3-related (ATR), dual-specificity tyrosine-phosphorylated and regulated kinase 1A (DYRK1A), IκB kinase (IKK), and MAPKs, can also target FoxOs in response to various signaling cues. Different CDKs have been shown to