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Review

Mechanisms controlling the anti-neoplastic functions of FoxO proteins

Tianyun Hou[a,b], Zhiming Li[a,b], Ying Zhao[b], Wei-Guo Zhu[a,b,*]

[a] Guangdong Key Laboratory of Genome Stability and Human Disease Prevention, Department of Biochemistry and Molecular Biology, School of Medicine, Shenzhen University, Shenzhen 518060, China

[b] Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Beijing Key Laboratory of Protein Posttranslational Modifications and Cell Function, Department of Biochemistry and Molecular Biology, School of Basic Medical Sciences, Peking University Health Science Center, Beijing 100191, China

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ABSTRACT

The Forkhead box O (FoxO) proteins comprise a family of evolutionarily conserved transcription factors that predominantly function as tumor suppressors. These proteins assume diverse roles in the cellular anti-neoplastic response, including regulation of apoptosis and autophagy, cancer metabolism, cell-cycle arrest, oxidative stress and the DNA damage response. More recently, FoxO proteins have been implicated in cancer immunity and cancer stem-cell (CSC) homeostasis. Interestingly, in some sporadic sub-populations, FoxO protein function may also be manipulated by factors such as β-catenin whereby they instead can facilitate cancer progression via maintenance of CSC properties or promoting drug resistance or metastasis and invasion. This review highlights the essential biological functions of FoxOs and explores the areas that may be exploited in FoxO protein signaling pathways in the development of novel cancer therapeutic agents.

1. Introduction

The Forkhead box O (FoxO) family is one of the 19 FOX transcriptional factor subgroups that share an evolutionary conserved 'forkhead' or 'winged-helix' DNA-binding domain [1]. The FoxO family contains four members: FoxO1 (FKHR), FoxO3 (FKHRL1), FoxO4 (AFX1) and FoxO6. These proteins recognize and bind the same consensus sequence (5′-TTGTTTAC-3′) and are ubiquitously expressed in mammalian cells except for FoxO6, which is largely restricted to adult brain tissues [2].

FoxO proteins are *bona fide* tumor suppressors. The FoxOs were originally found to be involved in carcinogenesis when chromosomal translocations identified in certain cancers precipitated the generation of PAX-FOXO, MLL-FOXO and CIC-FOXO fusion proteins [3–7], and resulted in loss of FoxO function [8,9]. Broad somatic ablation of *FoxO1, FoxO3 and FoxO4* gives rise to thymic lymphomas and hemangiomas in mice [10]. Expression of the FoxO1 protein is lost in a mouse lymphoma model [11], and disruption of FoxO function dramatically accelerates Myc-driven lymphomagenesis in mice [12]. Conversely, activation of FoxO1 suppresses tumor growth in an animal model of MYC-driven medulloblastoma [13]. FoxOs are frequently downregulated or inactivated in a variety of human cancers, including prostate cancer, breast tumors, endometrial carcinoma, classical Hodgkin lymphoma (cHL) and natural killer (NK)–cell neoplasms [14–18]. In addition, FoxOs are key downstream effectors of several oncogenic pathways, such as the PI3K/AKT, IκB Kinase (IKK) and the extracellular signal-regulated kinase (ERK) pathways, which promote the inactivation of FoxO proteins [19–21]. FoxOs also function as tumor suppressors by promoting the expression of other tumor suppressors or inhibiting the transcriptional function of certain oncogenic proteins [1,22]. Furthermore, FoxO proteins inhibit tumorigenesis through the induction of cellular senescence. As aging is a key risk factor for cancer, FoxOs are widely considered as longevity proteins [23].

FoxO proteins control a wide spectrum of cellular functions in cancer cells (Fig. 1), mainly through the regulation of gene expression. FoxOs promote apoptosis and autophagy in cancer cells [24,25]. Moreover, FoxOs are critical regulators of metabolism and ensure energy balance homeostasis. In response to oxidative stress or DNA

Abbreviations: ATM, ataxia telangiectasia mutated; cHL, classical hodgkin lymphoma; CML, chronic myelogenous leukemia; CSC, cancer stem cell; ERK, the extracellular signal-regulated kinase; ERα, the nuclear receptor estrogen receptor α; FoxO, forkhead box O; G6PC, glucose-6-phosphatase; GLUT1, glucose transporter 1; HDAC, histone deacetylase; HDACIs, HDAC inhibitors; HIF1α, hypoxia-inducible factor 1 α; HSC, hematopoietic stem cell; IKK, the IκB Kinase; JNK, C-jun NH2-terminal kinase; LIC, leukemia-initiating cell; mTORC, mammalian target of rapamycin complex; NK, natural killer cell; NTC, non-tumorigenic cell; PEPCK1, phosphoenolpyruvate carboxykinase; PGC1α, peroxisome proliferative activated receptor-gamma co-activator 1α; PTEN, phosphatase and tension homolog; ROS, reactive oxygen species; SIRT, the NAD+-dependent histone deacetylase sirtuin; TGFβ, transforming growth factor-β; TKI, tyrosine kinase inhibitor; T_{REG} cell, regulatory T cell; XBP-1u, unspliced X-box-binding protein-1

* Corresponding author at: Guangdong Key Laboratory of Genome Stability and Human Disease Prevention, Department of Biochemistry and Molecular Biology, School of Medicine, Shenzhen University, Shenzhen 518060, China.

E-mail addresses: zhuweiguo@szu.edu.cn, zhuweiguo@bjmu.edu.cn (W.-G. Zhu).

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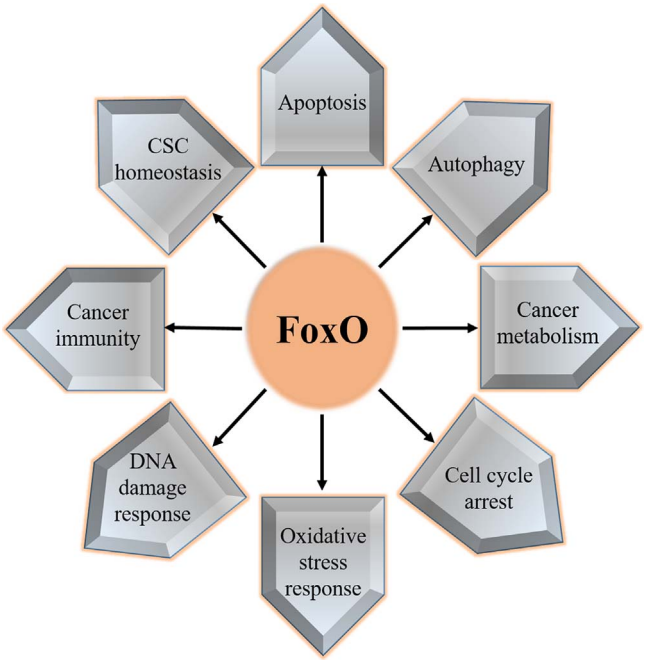

Fig. 1. Biological functions of FoxO proteins. FoxO proteins mainly function as tumor suppressors but also regulate numerous, diverse biological functions, including: apoptosis, autophagy, cancer metabolism, cell cycle arrest, oxidative stress, the DNA damage response, cancer immunity and cancer stem cell homeostasis.

damage, FoxO proteins become activated through various mechanisms and mediate the proper response to these stimuli, such as inducing cell cycle arrest. It is noteworthy that when cells are challenged by constant stress, FoxOs can induce apoptotis or autophagic cell death. In addition, FoxO proteins have critical roles in cancer immunity and cancer stem cell (CSC) homeostasis [26,27]. The CSC homeostasis model is one of two classic models used to understand the process of tumor progression, heterogeneity and therapeutic resistance. By this model, malignant tumor-propagating cells are denoted as CSCs, and these cells represent a distinct population that can be prospectively isolated from the remainder of the tumor and have the capacity to repopulate and self-renew [28].

Although FoxO proteins function as potent transcription factors, they can also regulate tumorigenesis in a transcription-independent manner. For example, FoxO1 inhibits prostate cancer (PCa) proliferation by forming a co-repressor complex with histone deacetylase 3 (HDAC3) to inhibit androgenic and androgen-independent activation of the androgen receptor [29]. In parallel, FoxO1 binds and inhibits PCa-associated ERG-mediated gene expression as well as PCa cells invasion independent of FoxO1 transcriptional activity, interestingly, concomitant FoxO1 deficiency and aberrant activation of ERG promotes prostate tumorigenesis and cell invasion [30]. Cytosolic FoxO1 regulates autophagy through binding Atg7 in colon cancer cells, leading to autophagic cell death and tumor suppression [25]. In addition, FoxO3 forms a complex with ataxia telangiectasia mutated (ATM) and the histone acetyltransferase Tip60 to mediate ATM activation upon DNA damage [31,32]. Conversely, the oncogenic fusion protein PAX3-FoxO1, a primary driver of alveolar rhabdomyosarcoma (RMS), induces de novo super enhancers and recruits the BET bromodomain protein BRD4 to drive expression of its target oncogenes, resulting in a significant susceptibility to BRD inhibition [33].

The functions of FoxO proteins are modulated by various post-translational modifications, including phosphorylation, acetylation, ubiquitination, methylation and glycosylation [34]. Moreover, FoxOs are tightly regulated via other mechanisms in response to different stimuli, such as nuclear–cytoplasmic shuttling [2]. Numerous studies have found, however, that during cancer progression and treatment, FoxOs may be subverted by some oncogenic factors, namely aberrantly activated β-catenin and the transforming growth factor-β (TGFβ) signaling pathway, to have a negative role in enhancing cancer progression, especially in some sub-populations of CSCs [35–38]. Recently, recurrent somatic mutations of *FoxO1* were identified in B-cell non-Hodgkin lymphomas (NHLs), especially in the N-terminal region and the Forkhead box domain, associating with decreased overall survival (OS) in patients responding to the current treatment standard (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone [R-CHOP]) [3,39,40].

This review highlights the critical roles of FoxOs in tumor suppression, including the induction of apoptosis and autophagy, regulation of cancer metabolism and cell cycle arrest, response to oxidative stress and DNA damage. In particular, we emphasize the pivotal role of FoxOs in tumor immunity and CSC homeostasis. The possible mechanisms of FoxO subversion in cancer progression and how to overcome the current challenges in cancer therapy will also be discussed.

2. FoxO proteins promote apoptosis

Apoptosis-induced programmed cell death is a natural barrier to cancer development. During carcinogenesis and cancer therapy, cancer cells suffer from various physiological stresses that trigger apoptosis, but they quickly evolve various strategies to evade apoptosis and instead survive. Such strategies include the activation of oncogenic pathways and the inhibition of tumor suppressor-function [41].

FoxO-induced apoptosis is inhibited in cancers via distinct mechanisms (Fig. 2). Aberrant activation of the PI3K–AKT pathway has been widely implicated as the underlying mechanism in many cancers, whereby *AKT* gene expression is elevated, activating mutations may occur in the catalytic subunit of PI3K, and expression of the tumor suppressor phosphatase and tension homolog (PTEN) is lost [42].

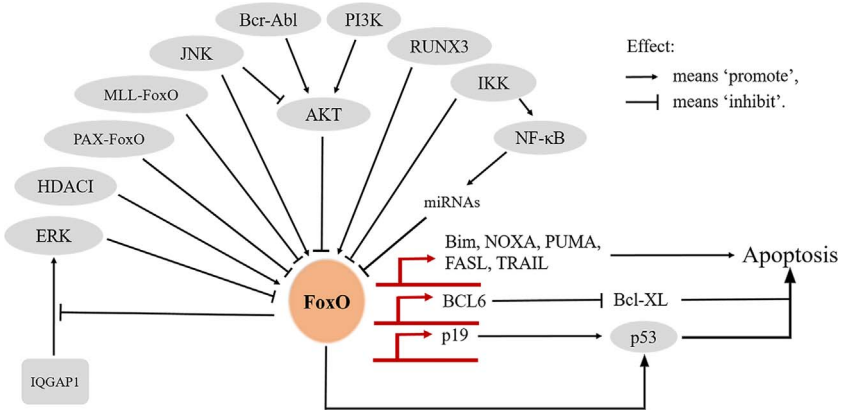

Fig. 2. FoxO proteins promote apoptosis. Upstream regulators and targets of FoxOs in regulation of apoptosis. IQGAP1, Ras GTPase-activating-like protein; ERK, the extracellular signal-regulated kinase; HDACI, histone deacetylase inhibitor; JNK, C-Jun NH2-terminal kinase; PI3 K, Phosphatidylinositol-3-kinase; IKK, the IκB Kinase; NF-κB, Nuclear factor-κB; miRNAs, microRNAs; Bim, Bcl-2-like protein 11; NOXA, phorbol-12-myristate-13-acetate-induced protein 1; PUMA, the p53 upregulated modulator of apoptosis; FASL, Fas ligand; TRAIL, tumour necrosis factor superfamily member 10; BCL6, B cell CLL lymphoma 6; Bcl-XL, B-cell lymphoma-extra large.