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Review

Re-evaluating the role of FOXOs in cancer

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ABSTRACT

FOXO transcription factors are negatively regulated by the PI3K-PKB/AKT signaling pathway and have been mainly considered to be tumor suppressors due to their inhibitory effect on cancer cell growth and survival. However, FOXOs can also support tumor development and progression by maintaining cellular homeostasis, facilitating metastasis and inducing therapy resistance. In agreement with these opposing views on the role of FOXOs in cancer, studies using FOXO levels or activity as prognostic markers for cancer patient disease progression and survival came to contradicting results. While it is clear that FOXOs are involved in various aspects of cancer, it is debatable whether FOXOs function as tumor suppressors or supporters, or may be both depending on the context. In this review, we describe the role of FOXOs in signaling pathways and processes relevant to cancer and evaluate recent advances in understanding the role of FOXOs in cancer. Based on recent insights it becomes clear that FOXOs may not be classical tumor suppressors and that targeting FOXO activity might hold promise in cancer therapy.

1. Introduction

For a normal cell to become a cancer cell it has to obtain various traits, summarized as the hallmarks of cancer [1]. Two of the Hallmarks a potential tumor cell needs to acquire are “sustained proliferative signaling” and “evading growth suppression”. Acquisition of sustained proliferative signaling commonly arises from alteration in components of growth factor receptor (GFR) signaling pathways. Mutations that are commonly found in PI3K-PKB/AKT pathway members commonly underpin oncogenic cell proliferation and survival [2]. Key transcription factors negatively regulated downstream of PI3K-PKB/AKT signaling are members of the Forkhead Box O family (FOXO). FOXOs have been put forth as putative tumor suppressors that need to be inactivated in order to evade growth suppression based on tissue culture experiments showing their cytostatic and apoptotic potential. They are involved in a plethora of cellular functions that control many different aspects of life including lifespan, diabetes and cancer [3]. In this review we describe the role of FOXOs in cancer and evaluate recent advances in this field. By doing so we unveil that FOXO is not merely a classic tumor suppressor and illustrate a more complex supportive role for FOXOs in cancer.

Abbreviations: RTK, receptor tyrosine kinase; GF, growth factor; PI3K, Phosphatidylinositol-4,5-bisphosphate 3-kinase; PKB, protein kinase B; AKT, RAC-alpha serine/threonine-protein kinase; FOXO, forkhead box O; GFR, growth factor receptor; PDPK1, Phosphoinositide-dependent kinase-1; PTEN, Phosphatase and tensin homolog; SMAD, Mothers against decapentaplegic homolog 4; STAT, Signal transducer and activator of transcription; CBP, CREB-binding protein; HDAC, Histone deacetylase; SIRT, NAD-dependent deacetylase sirtuin; MDM, Mouse double minute; SESN, sestrin; SOD, super oxide dismutase; GPX, glutathione peroxidase; PRMT, Protein arginine methyltransferase; RUNX, Runt-related transcription factor; ERK, extracellular signal-regulated kinase; MST1, mammalian sterile 20–like kinase; NFKB, nuclear factor kappa-light-chain-enhancer of activated B cells; IKKα/β, I-kappaB kinase; CDK, cyclin dependent kinase; SGK, serum and glucocorticoid-regulated kinase; DYRK1, Dual specificity tyrosine-phosphorylation-regulated kinase; CK1, casein kinase; CKI, cell cycle kinase inhibitor; mTORC, mammalian target of rapamicin complex; PIP3, Phosphatidylinositol (3,4,5)-trisphosphate; IPO, Importin; TNPO, transportin; ASK, Apoptosis signal-regulating kinase; JNK, c-jun terminal kinase; ATM, ataxia-telangiectasia mutated kinase; ROS, reactive oxygen species; CAT, catalase; IRS, insulin receptor substrate; IGFBP, insulin-like growth factor receptor binding protein; AMPK, AMP-activated protein kinase; TNF, tumor necrosis factor; TRAIL, TNF-related apoptosis-inducing ligand; FAS, Fas cell surface death receptor; DR, death receptor; BAK, Bcl-2 homologous antagonist/killer; BAX, BCL2-associated X; BCL2, B-cell lymphoma 2; BCL-XL, B-cell lymphoma-extra large; MCL, induced myeloid leukemia cell differentiation protein; BH3, BCL2 homology domain 3; BIM, Bcl-2-like protein 11; BAD, Bcl-2-associated death promoter; BMF, Bcl-2-modifying factor; BID, BH3 interacting-domain death agonist; PUMA, p53 upregulated modulator of apoptosis; NOXA, Phorbol-12-myristate-13-acetate-induced protein; BOK, Bcl-2 related ovarian killer; ER, estrogen receptor; PAX, paired box; MLL, myeloid/lymphoid or mixed-lineage leukemia; AML, acute myeloid leukemia; CML, chronic myeloid leukemia; MMP, matrix metalloproteinase; BCR-ABL, B-cell receptor - abelson murine leukemia viral oncogene homolog; LIC, leukemia inistiating cell; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; ERBB, erb-b2 receptor tyrosine kinase; RET, rearranged during transfection; RAS, rat sarcoma viral oncogene homolog; MEK, Mitogen-activated protein kinase; IQGAP, IQ motif containing GTPase activating protein; MYC, myelocytomatosis viral oncogene homolog

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1.1. Canonical FOXO regulation

The mammalian Forkhead box O (FOXO) family of transcription factors consists of four family members; FOXO1, FOXO3, FOXO4 & FOXO6, which are evolutionary conserved and function as transcription factors through binding to the DNA consensus sequence 5′-TTGTT TAC-3′ [3–5].

The PI3K-PKB/AKT pathway negatively regulates transcriptional activity of FOXO1, FOXO3 & FOXO4. As the regulation of FOXO6 is less dependent on canonical PI3K-PKB/AKT signaling and because FOXO6 expression seems limited to the central nervous system, liver, kidney cortex and stomach, and because this is the least studied FOXO family member we mainly focus on FOXO1, FOXO3 & FOXO4 (FOXOs) in this review [6]. Upon activation of growth factor receptor tyrosine kinases, PI3K becomes activated and generates PIP3 at the plasma membrane. PIP3 functions as a docking site for PDPK1 and PKB/AKT. PDPK1 activates PKB/AKT, which subsequently phosphorylates a wide array of target proteins to stimulate glucose uptake, cell proliferation and survival [7].

Transcriptional activity of FOXOs is regulated through shuttling between the nucleus and the cytoplasm. Phosphorylation of nuclear FOXOs by PKB/AKT at three conserved RxRxxS/T residues induces the binding to 14-3-3 proteins, which facilitate nuclear export of FOXO1, FOXO3 & FOXO4 and simultaneously obstruct relocation into the nucleus [8–10]. Upon loss of GFR signaling, net dephosphorylation of PIP3 by PTEN results in reduced PKB/AKT activity, loss of FOXO phosphorylation and subsequent nuclear accumulation of FOXOs. In the nucleus, FOXOs mediate transcription of a wide array of target genes involved in cell cycle inhibition, apoptosis, redox homeostasis, metabolism and angiogenesis (Fig. 1) [3,11].

It remains a point of debate whether FOXOs regulate a specific set of target genes or are more general activators of gene expression [12]. Regardless, upon accumulation in the nucleus, FOXOs preferably bind DNA in promoters and enhancers covered with histone marks correlated with active transcription [13,14]. These observations implicate that the output of FOXOs is heavily influenced by the epigenetic status of the DNA at the moment FOXOs reside in the nucleus. Additionally, several proteins involved in transcription regulation have been reported to functionally interact with FOXOs e.g. p300/CPB, β-catenin, PPARγ, estrogen receptor, androgen receptor, SMADs, STATs and RUNX [15].

1.2. FOXO activation by cellular stresses

Upstream regulation of FOXOs is not limited to RTK signaling. Especially in cancer, localization of FOXOs can be modulated through multiple other pathways. When a cell encounters stress like elevated reactive oxygen species (ROS) levels, nutrient starvation or DNA damage, FOXOs will be activated in order to partake in re-establishing cellular homeostasis [16].

When levels of ROS are high or the reductive capacity of the cell is low, FOXOs translocate to the nucleus in two different ways. First, JNK becomes activated in response to increased levels of ROS in the cell. This can occur through the redox sensitive kinase ASK1 or the small GTPase Ral. Activated JNK antagonizes RTK signaling by phosphorylation of the insulin receptor substrate adaptor proteins IRS1/2 thereby preventing GF signaling dependent inactivation of FOXO. JNK also phosphorylates FOXOs and 14-3-3 directly, stimulating nuclear translocation of FOXOs by preventing FOXO binding to 14-3-3 [17–20].

Second, under more oxidizing conditions in the cell cysteines in FOXOs can form disulfide bridges with nuclear importers TNPO1, IPO7 and IPO8, and subsequently translocate to the nucleus [21,22]. To counteract elevated ROS production in the cell, FOXO mediates the transcription of antioxidant genes like *CAT, SESN1/2/3, SOD2, PRDX3, GPX1, GSTM1* and genes involved in the metabolic generation of the Glutathione antioxidant system and reductive entities like NADPH [23,24].

Under conditions in which glucose is limited, ATP levels in the cell drop and the ATP/AMP sensor AMP kinase (AMPK) becomes active. AMPK phosphorylates FOXOs at Ser413, Ser588 and Ser626 (numbering of human FOXO3), resulting in nuclear localization and the stimulation of target genes involved in metabolic rewiring and stress resistance [25]. Next to the well-studied regulation of FOXOs by PKB/AKT, JNK and AMPK, many other kinases attenuate FOXO activity. In response to DNA damage FOXOs bind to and become phosphorylated by ATM kinase and hereby contribute to the DNA damage response and regulation of apoptosis [26,27]. FOXOs have also been described as targets of ERK, MST1, CDKs, SGK, DYRK1A, IKKα/β and CK1 [28]. To what extent these phosphorylation events influence FOXO activity and output is however still under investigation.

FOXOs can also be modulated through other site-specific modifications including acetylation, ubiquitination, methylation, PARylation, hydroxylation and glycosylation. Best studied are acetylation by actetyl transferase p300, and deacetylating enzymes such as HDACs and SIRTs, as well as ubiquitylation by MDM2 and USP7 or methylation by PRMT and SET9 (Fig. 1) [29–34]

Taken together FOXOs are regulated by many different upstream signals and, when activated, regulate the transcription of various genes. Due to this great complexity, it is no surprise that the current understanding of how FOXOs function exactly is still incomplete. As FOXOs function at the crossroad of diabetes, cancer and aging, it is essential to understand its functions in detail. Exemplary is the fact that after two decades of research it is still not clear whether FOXOs function as tumor suppressors or supporters [35].

2. The archetype: FOXOs are tumor suppressors

2.1. Repressing the cell cycle

It was already apparent in the first seminal papers that identified that FOXOs were negatively regulated downstream of PKB/AKT signaling, that FOXOs could have tumor suppressive functions. Activation of FOXOs, either by pharmacological inhibition of PI3K-PKB/AKT or the ectopic overexpression of FOXO resulted in a robust cell cycle arrest in fibroblasts and cancer cell lines derived from colon carcinoma, glioblastoma, osteosarcoma and acute T cell leukemia [8,9,36,37].

Cell proliferation starts from a quiescent state also known as G_0 and continues by progression from G_1 to S phase. In early G_1, expression levels of Cyclin D proteins (*CCND1/2/3*) are upregulated by GFR signaling, leading to increased levels of CyclinD-CDK4/6 complexes. Cyclin D-CDK4/6 complexes inhibit the retinoblastoma family of proteins (RB, p107 and p130), resulting in the release E2F transcription factors that induce transcription of S-phase proteins including Cyclins [38]. From S-phase onward, Cyclin-E/A-Cdk2 complexes take over to ensure correct DNA replication and cellular growth before entering mitosis. Once this process is completed, Cyclin B/Cdk1 complexes become active and mitosis starts.

FOXO-induced cell cycle arrest is mediated through transcription of multiple cell cycle kinase inhibitors (CKI). The best-described CKI downstream of FOXO is $p27^{kip1}$ (CDKN1B). Besides CDKN1B, FOXOs have also been described as regulators of $p21^{cip1}$ (CDKN1A), $p57^{kip2}$ (CDKN1C) and the INK4 family of CKIs, $p15^{INK4b}$ (CDKN2B), $p16^{INK4a}$ (CDKN2A), $P18^{INK4c}$ (CDKN2C) and $p19^{INK4d}$ (CDKN2D) [36,39–41]. FOXO-mediated induction of CKI expression leads to inhibition of the Cyclin/CDK complexes responsible for progression through the different phases of the cell cycle and results in a robust cell cycle arrest in G_0/G_1, G_2, or even senescence.

2.2. Stimulating apoptosis

Next to functioning as repressors of the cell cycle, FOXOs are well described as inducers of apoptosis in many different cell types [42]. Apoptosis can be triggered through multiple cell intrinsic and extrinsic

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