

## Diverse roles of FOXO family members in gastric cancer

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**Author contributions:** Liu J and Wu HT designed the manuscript; Chen YH searched the literature; Chen YH, Li CL, and Chen WJ analyzed the literature and wrote the manuscript; Liu J revised the manuscript critically; all authors have read and approved the final manuscript.

**Supported by** National Natural Science Foundation of China, No. 81501539; Natural Science Foundation of Guangdong Province, No. 2021A1515012180 and No. 2016A030312008; Science and Technology Planning Project of Shantou, China, No. 200617105260368; "Dengfeng Project" for the Construction of High-level Hospitals in Guangdong Province – the First Affiliated Hospital of Shantou University College Supporting Funding, No. 202003-10; and Guangdong Provincial Undergraduate Innovation and Entrepreneurship Training Project, No. S202010560121.

**Conflict-of-interest statement:** No conflict of interest is claimed by any author.

**Open-Access:** This article is an

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### Abstract

Gastric cancer (GC) is the fifth most diagnosed cancer and the third leading cause of cancer-related death worldwide. Although progress has been made in diagnosis, surgical resection, systemic chemotherapy, and immunotherapy, patients with GC still have a poor prognosis. The overall 5-year survival rate in patients with advanced GC is less than 5%. The FOXO subfamily, of the forkhead box family of transcription factors, consists of four members, FOXO1, FOXO3, FOXO4, and FOXO6. This subfamily plays an important role in many cellular processes, such as cell cycle, cell growth, apoptosis, autophagy, stress resistance, protection from aggregate toxicity, DNA repair, tumor suppression, and metabolism, in both normal tissue and malignant tumors. Various studies support a role for FOXOs as tumor suppressors based on their ability to inhibit angiogenesis and metastasis, and promote apoptosis, yet several other studies have shown that FOXOs might also promote tumor progression in certain circumstances. To elucidate the diverse roles of FOXOs in GC, this article systematically reviews the cellular functions of FOXOs in GC to determine potential therapeutic targets and treatment strategies for patients with GC.

**Key Words:** FOXO; Gastric cancer; Regulation; Therapy; Expression

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**Manuscript source:** Invited manuscript

**Specialty type:** Oncology

**Country/Territory of origin:** China

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0  
Grade B (Very good): B  
Grade C (Good): 0  
Grade D (Fair): 0  
Grade E (Poor): 0

**Received:** April 6, 2021

**Peer-review started:** April 6, 2021

**First decision:** June 23, 2021

**Revised:** July 6, 2021

**Accepted:** August 13, 2021

**Article in press:** August 13, 2021

**Published online:** October 15, 2021

**P-Reviewer:** Mohamed SY

**S-Editor:** Gao CC

**L-Editor:** Wang TQ

**P-Editor:** Yuan YY



**Core Tip:** FOXOs perform diverse roles in the occurrence and development of gastric cancer, the fifth most diagnosed type of cancer and third leading cause of cancer-related death worldwide. This article reviews the cellular functions of FOXOs in gastric cancer and provides potential therapeutic targets for patients with gastric cancer.

**Citation:** Chen YH, Li CL, Chen WJ, Liu J, Wu HT. Diverse roles of FOXO family members in gastric cancer. *World J Gastrointest Oncol* 2021; 13(10): 1367-1382

**URL:** <https://www.wjgnet.com/1948-5204/full/v13/i10/1367.htm>

**DOI:** <https://dx.doi.org/10.4251/wjgo.v13.i10.1367>

## INTRODUCTION

Gastric cancer (GC) is the fifth most diagnosed cancer and the third leading cause of cancer-related death worldwide[1]. Upper gastrointestinal series and endoscopy, which have been demonstrated to be effective for screening, have not been widely adopted worldwide because of their invasive nature and high cost. Moreover, the lack of universal guidelines for screening has increased the difficulty of early diagnosis of GC[2-4]. It is estimated that more than 700000 cancer-related deaths are caused by GC, which is primarily because the cancer is already at an advanced stage at initial diagnosis[5,6]. Unsurprisingly, although great progress has been made in diagnosis, surgical resection, systemic chemotherapy, and immunotherapy in recent decades, patients with advanced GC still exhibit a very poor prognosis, with a median overall survival (OS) of 10-12 mo and an overall 5-year survival rate of less than 5%[7-9]. To improve the availability of accurate diagnostic tests for the early detection of GC and to identify more specific therapeutic targets for GC patients, it is important to explore the molecular mechanism of GC. This will help overcome the critical limitations in diagnostics and therapeutics in patients with GC.

FOXOs, the O subfamily of the forkhead box (FOX) family of transcription factors, comprise four members, FOXO1, FOXO3, FOXO4, and FOXO6. This subfamily has been reported to be involved in the cell cycle, cell growth, apoptosis, autophagy, stress resistance, protection from aggregate toxicity, DNA repair, tumor suppression, and metabolism[10,11]. Importantly, FOXOs are involved in the pathological processes of malignant tumors, as well as in the physiological processes of development[12]. However, the functions of FOXOs in malignant tumors vary under different conditions. FOXOs function as tumor suppressors based on their ability to inhibit angiogenesis[13] and metastasis[14], and their ability to promote apoptosis[15]. However, other studies have indicated that FOXOs can also promote tumor progression under certain circumstances[10]. As transcription factors, FOXOs may affect different aspects of the occurrence and development of GC by regulating the expression of downstream target genes. This article focuses on the diverse cellular functions of FOXOs, in GCs, to identify potential early diagnostic biomarkers and therapeutic targets for patients with GC.

## CHARACTERISTICS OF FOXO FAMILY MEMBERS

It is well known that transcription factors regulate the expression of target genes by identifying and binding to specific DNA sequences, after which they participate in the formation of a complex signaling network to maintain cell homeostasis[16]. Dysregulation of transcription factors leads to a variety of pathological changes in cells, results in the occurrence of various diseases, and determines the various behaviors of malignant tumors[17,18]. Among various transcription factors, FOX transcription factors are widely distributed in organisms from yeasts to humans. They are characterized by a forkhead domain (FHD) and a highly conserved DNA binding domain (DBD) that is composed of 100 amino acid residues folded into a helix-turn-helix motif with two characteristic large loops and three  $\alpha$  helices[19].

Among the different types of FOX transcription factors, the four FOXO isoforms, FOXO1, FOXO3, FOXO4, and FOXO6, in mammals belong to the O subfamily of the FOX family of transcription factors[20]. FOXOs have four common domains, including

a FHD, a nuclear export sequence (NES) domain, a nuclear localization signal (NLS), and a C-terminal transactivation domain (TAD), although FOXO6 lacks the NES domain (Figure 1). All FOXOs can recognize and bind to two sequences: the Daf-16 family member-binding element (DEB), 5'-GTAAA(T/C)AA-3', and the insulin-responsive sequence (IRE), 5'-(C/A)(A/C)AAA(C/T)AA-3'[21,22].

### Expression pattern of FOXOs

FOXO1, FOXO3, and FOXO4 are widely expressed in almost all tissues, and their transcriptional activity changes as they shuttle between different subcellular localizations[22,23]. FOXO6, a novel member of the FOXO class reported by Jacobs *et al*[24], was originally only observed in the central nervous system, but subsequent investigations have confirmed that FOXO6 is also expressed in peripheral tissues, including the lungs, liver, kidneys, intestine, muscle, and adipose tissue[25]. Interestingly, the expression pattern of FOXO6 is different from that of other FOXO isoforms in its evolution, and it is the least characterized member of the FOXO family. Due to the lack of an NES sequence, FOXO6 does not shuttle between the nucleus and cytoplasm and is located only in the nucleus[26].

### Regulatory mechanism of FOXOs

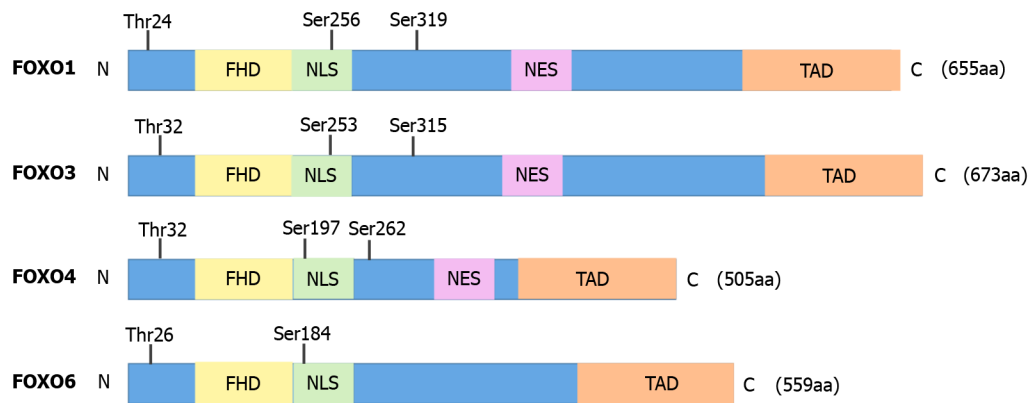
FOXOs function as central transcription factors that regulate many cellular processes through transcriptional activity. Unsurprisingly, FOXOs are also regulated by multiple signaling pathways involving synthesis, phosphorylation, acetylation, and ubiquitination, which mainly determine subcellular localization, transcriptional activity, and protein stability[11,22,27]. As transcription factors, FOXOs usually exist in the nuclei of quiescent or growth factor (GF)-deficient cells. When GFs are absent, FOXOs shuttle into and accumulate in the nucleus to promote cell cycle arrest, stress resistance, and apoptosis, by upregulating the transcription of a series of target genes. However, in the presence of cell GFs, FOXOs relocate to the cytoplasm for degradation by the ubiquitin-proteasome pathway[23].

**Phosphorylation via the classical PI3K-AKT pathway:** Except for FOXO6, the regulation of FOXO-dependent transcription primarily depends on shuttling between the nucleus and cytoplasm. More specifically, negative regulation by the PI3K-AKT pathway is dependent on activation by GF receptor tyrosine kinases (RTKs)[28]. Under normal physiological conditions, RTKs are activated by autophosphorylation after binding GFs or insulin, which is followed by recruitment and activation of PI3K. Then, activated PI3K catalyzes phosphatidylinositol-4,5-bisphosphate (PIP<sub>2</sub>) to phosphatidylinositol-3,4,5-trisphosphate (PIP<sub>3</sub>), which serves as the docking site for AKT and PDK1. PIP<sub>3</sub> facilitates the translocation of PDK1 and AKT to the cell membrane, where AKT is activated by phosphorylation on threonine 308 by PDK1. Activated AKT phosphorylates FOXOs at three sites to promote the binding of nuclear 14-3-3 protein to FOXO, which results in masking of the FOXO NLS; this causes the export of FOXO from the nucleus and prevents nuclear entry, thus preventing FOXO from binding to corresponding sites on DNA and inhibiting its transcriptional activity[11]. When the GF-PI3K-AKT pathway is constitutively activated, such as in cancer cells, the nuclear localization of FOXOs is negatively regulated, which results in the transfer of FOXOs to the cytoplasm and loss of their activity[22]. However, in the absence of GF signals, PIP<sub>3</sub> will be dephosphorylated by PTEN (phosphatase and tensin homolog), thereby reducing PKB/AKT activity and concomitantly resulting in the loss of FOXO phosphorylation and nuclear accumulation.

According to a previously defined mechanism, FOXOs enter the nucleus, bind to a variety of transcription cofactors, and regulate the transcription of target genes related to the cell cycle, apoptosis, the antioxidant state, metabolism, and angiogenesis[28]. For FOXO6, phosphorylation of two residues (threonine 26 and serine 184) by AKT results in inactivation. Unlike other FOXOs, the PI3K-AKT pathway cannot affect the subcellular localization of FOXO6 due to the lack of carboxy-terminal AKT-dependent phosphorylation sites in FOXO6[11,25,29].

**AKT-independent phosphorylation:** Inhibition of FOXOs by the PI3K-AKT pathway is believed to enhance tumor development, while stress-activated kinases, such as c-Jun N-terminal kinase (JNK), mammalian sterile 20like kinase 1 (MST1), and protein kinase RNA-like endoplasmic reticulum kinase (PERK), play a tumor inhibitory role by promoting FOXO function in an AKT-independent manner[11].

Essers *et al*[30] illustrated that in contrast to insulin-mediated regulation, under oxidative stress, FOXO4 is phosphorylated by JNK on threonine 447 and threonine 451 in a GTPase-dependent manner, which leads to the nuclear translocation of p-FOXO4.



**Figure 1 Domains and AKT phosphorylation sites in FOXOs.** FHD: Forkhead domain; NES: Nuclear export sequence; NLS: Nuclear localization signal.

Specifically, the regulatory effect of JNK on FOXO activity involves phosphorylation of 14-3-3 on serine 184 to block 14-3-3 proteins from binding to FOXOs[11,31].

Lehtinen *et al*[32] extended the molecular mechanism by which oxidative stress influences cell survival and homeostasis, by demonstrating the role of the protein kinase MST1 in oxidative stress-induced cell death. In the case of increased cellular oxidative stress, MST1 phosphorylates FOXO proteins at a conserved site to disrupt their interaction with 14-3-3 proteins, which results in FOXO nuclear translocation, and induces neuronal cell death[32]. Soon after, Yuan *et al*[33] also found that MST1-induced phosphorylation of FOXO1 at serine 212, which corresponds to serine 207 in FOXO3, disrupts the association between FOXO1 and 14-3-3 proteins. The above findings indicate that MST1-FOXO1 signaling is an important link to serum-deprivation-induced neuronal cell death.

Recently, PERK was found to be involved in endoplasmic reticulum (ER) stress related to the onset of type 2 diabetes[34]. Imbalances between protein synthesis and folding lead to ER stress, which partially enhances FOXO activity through the PERK pathway. Interestingly, although three target sites serine 298, serine 301, and serine 303 on FOXO1 can be phosphorylated by PERK, PERK-mediated phosphorylation preferentially occurs on serine 298, which is not a target site for AKT[34]. Phosphorylation by PERK enhances the transcriptional activity of FOXOs and counteracts the effect of Akt phosphorylation[34,35].

In addition, extracellular signal-regulated kinase (ERK), p38, cyclin-dependent kinases (CDKs), adenosine monophosphate-activated protein kinase (AMPK), and I $\kappa$ B kinase (I $\kappa$ K) regulate FOXOs in an AKT-independent manner. For example, mitogen-activated protein kinases (MAPKs), ERK, and p38 jointly phosphorylate FOXO1, which results in p-FOXO1 serving as a coactivator for Ets-1[36]. Additionally, ERK mediates the phosphorylation of FOXO3 at serine 294, serine 344, and serine 425, which permits the association of p-FOXO3 with the E3 ubiquitin ligase MDM2 (murine double minute 2). This in turn results in the ubiquitination and degradation of p-FOXO3 to promote cell proliferation and tumorigenesis[37]. CDK2 binds to and phosphorylates FOXO1 at serine 249 in a glucose-dependent manner, and loss of CDK2 may mediate persistent insulin secretion defects through this pathway[38,39]. Lu *et al*[40] proposed FO1-6nls, a FOXO1-derived peptide inhibitor of CDK1/2-mediated phosphorylation of FOXO1 at serine 249, as a potential therapeutic for the treatment of prostate cancers. AMPK phosphorylates FOXO1 and forms the AMPK/FOXO1 axis, which is involved in multiple pathological processes, such as liver fibrosis[41], cardiac hypertrophy[42], and epithelial-mesenchymal transition (EMT) [43]. The phosphorylation of FOXO3 at serine 644 by I $\kappa$ K normally leads to ubiquitin-dependent proteasomal degradation[44], but causes cytoplasmic retention in acute myeloid leukemia[45].

**Acetylation:** Histone acetylation is an epigenetic modification that regulates numerous genes essential for various biological processes, including development and stress responses[46]. It has been reported that calcium response element-binding protein (CBP)/p300 acetylates FOXOs to promote their phosphorylation by AKT and allows FOXOs to be retained in the cytoplasm[47]. However, stress-induced FOXO1 acetylation also arrests FOXO1 ubiquitination and prevents FOXO1 degradation through the ubiquitin-proteasome pathway[48]. Importantly, acetylation of FOXOs is a reversible process and can be eliminated by histone acetyltransferases and histone



deacetylases (HDACs)[49,50]. For example, Sirt1, a class III HDAC, can deacetylate FOXOs and increase their transcription[47]. However, this increased effect is eliminated quickly because of the facilitated degradation of deacetylated FOXOs through the ubiquitin-proteasome pathway[51].

**Other posttranslational modifications:** In addition to phosphorylation, acetylation, and polyubiquitination, the activity of FOXOs is regulated by other posttranslational modifications, including mono-ubiquitination, methylation, and glycosylation.

In contrast to degradation induced by polyubiquitination, mono-ubiquitination enhances FOXO activity. Interestingly, under oxidative stress, MDM2, which promotes the degradation of p-FOXO3, can induce mono-ubiquitination of FOXO4 to increase FOXO4 nuclear entry and transcriptional activity[52]. Methylation of FOXO1 by protein arginine methyltransferase 1 (PRMT1) inhibits AKT-induced phosphorylation, and thus, promotes FOXO1 retention in the nucleus and increases the expression of downstream target genes[53]. However, methylation of FOXO3 by the Set9 methyltransferase reduces the DNA-binding and transcriptional activities of FOXO3[54]. O-glycosylation improves the transcriptional activity of FOXO1 without influencing its subcellular localization[55]. Recently, N6-methyladenosine modifications of *FOXO1* mRNA, reported by Jian *et al*[56], were demonstrated to mediate METTL14-induced endothelial inflammation and atherosclerosis. Shin *et al*[57] identified a novel posttranslational modification of the FOXO family, O-GlcNAcylation of FOXO3 at serine 284, that impairs the ability of FOXO3 to induce subsequent cancer cell growth *via* abrogation of the p53 regulatory circuit.

Of course, other posttranslational modifications may exist and remain to be discovered. The transcriptional activities of FOXOs are involved in regulating the cell cycle, oxidative stress, apoptosis, and autophagy, as well as metabolic and immunoregulatory factors. Moreover, FOXO3 is closely related to longevity in humans[58-60]. The biological function of FOXO6 has not been well studied, and most research has indicated its participation in glucose and lipid metabolism[26]. Unsurprisingly, FOXOs are involved in many aspects of malignant tumors.

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## ROLES OF FOXOS IN CANCERS

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It is well known that FOXOs are tumor suppressors in many types of malignant tumors[29]. Usually, in cancers, the PI3K-PKB/AKT signaling pathway is enhanced, and FOXOs are negatively regulated downstream molecules in the pathway. Specifically, activation of FOXOs leads to cell cycle arrest and apoptosis[28]. Therefore, reduction of PI3K/AKT phosphorylation *via* knockdown techniques or suppression with specific inhibitors enhances the transcriptional activity of FOXOs and induces cell cycle arrest and cell apoptosis in colorectal cancer (CRC) and pancreatic cancer cells [61,62].

In terms of cell cycle control, Baugh and Sternberg[63] found that the induced expression of cell cycle kinase inhibitors (CKIs) by FOXOs leads to the inhibition of cyclin/CDK complexes, which are responsible for cell cycle progression at different phases. This causes cell cycle arrest in G0/G1 and G2 phases and even senescence and promotes developmental arrest *via* transcriptional regulation of numerous target genes that control various aspects of development[63].

Moreover, in both normal and cancer cells, FOXOs are reported to induce the expression of proapoptotic genes, resulting in apoptosis. Wang *et al*[64] showed that activation of AMPK-FOXO is upstream of the KLF2 pathway and contributes to the induction of apoptosis and differentiation by DT-13 (Liriope muscari baily saponins C) in acute myelocytic leukemia. Laporte *et al*[65] revealed that HDAC inhibition-induced apoptosis and decreased tumor burden in synovial sarcoma are related to reactive oxygen species (ROS)-mediated FOXO activation and the subsequent increase in the expression of the proapoptotic factors BIK, BIM, and BMF. Interestingly, in the case of detachment from the extracellular matrix, FOXOs induce anoikis and prevent metastasis by promoting BMF expression, whereas under anchorage-independent conditions, cyclin D1 induces an antagonistic effect on FOXO-regulated anoikis[66].

It is widely accepted that ROS abnormally accumulate in cancer cells due to the reprogramming of redox metabolism, which plays opposite roles in various aspects of occurrence and development of malignant tumors[67]. Upon AKT activation, FOXOs become phosphorylated and translocate from the nucleus, which results in reduced expression of superoxide dismutase 2 (SOD2) and an increase in ROS and mitochondrial dysfunction[68]. Therefore, FOXOs promote detoxification of cells by

inducing SOD2 and catalase expression, thus protecting cells from damage due to excessive accumulation of ROS and preventing cancer development.

Based on a previous mechanism, a series of investigations reported a significant relationship between FOXO expression and the clinical parameters of malignant tumors. Xu *et al*[69] found that a low level of FOXO4 expression in non-small cell lung cancer patients is significantly correlated with TNM stage and lymph node metastasis, which suggests an inhibition of FOXO4 function during the process of EMT. In CRC tissues, the expression of FOXO3 is also significantly lower than that in normal tissues, and interestingly, the progressive downregulation of FOXO3 is correlated with the progression of pathological stage in patients with CRC. Moreover, the mean disease-free survival (DFS) of CRC patients with low FOXO3 expression is significantly shorter compared with that of CRC patients with high FOXO3 expression[70]. Wu *et al*[71] conducted multivariate analyses and revealed that FOXO1 expression is an independent biomarker for predicting DFS in patients with breast cancer, with lower levels of FOXO2 predicting poorer OS. Not surprisingly, reduced FOXO1 levels were observed in prostate cancer and are responsible for promoting the migration and invasiveness of prostate cancer cells *via* Runx2 regulation[72]. Therefore, it is known that reduced FOXO levels play an important role in tumor metastasis.

For further study, knockout techniques have provided additional methods by which the function and molecular mechanism of FOXO in tumors can be investigated. Renault *et al*[73] revealed that FOXO3 is a direct target of the *p53* tumor suppressor gene. However, no association was observed between FOXO3 loss and *p53* loss in tumor development. Paik *et al*[74] established a FOXO1/FOXO3/FOXO4 triple knockout mouse model and observed common and severe vascular lesions and premature death, while the tumor spectrum following triple FOXO deletion was much more limited than that after PTEN/AKT misregulation.

However, every coin has two sides. The expression of FOXO3 has been found to be increased in glioblastoma (GBM), and a high level of FOXO3 is associated with a poor prognosis in GBM patients. In addition, FOXO3 knockout significantly reduces, whereas FOXO3 overexpression enhances, the proliferation and invasiveness of GBM cells[75]. Yu *et al*[76] demonstrated that the expression of FOXO3 can be upregulated by SP1, which promotes CRC cell progression *in vitro* and *in vivo*. FOXO3 was found to promote tumor growth, under hypoxic conditions, and angiogenesis in aggressive neuroblastoma, which predicts adverse clinical outcomes[77]. In addition, FOXO3 acts as a conditional chemoprotection factor in late-stage neuroblastoma, enhancing tumor cell survival under chemotherapy[78]. The above reports reveal the complicated roles of FOXOs in cancer. As Hornsveld *et al*[28] suggested, FOXOs may function to support resilience in both healthy and cancer cells, rather than as typical tumor suppressors.

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## EXPRESSION PATTERNS OF FOXOS IN GCS

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Unsurprisingly, the expression level of FOXOs is often altered in GC. Decreased levels of FOXO1/FOXO3/FOXO4 and increased expression of FOXO6 in GC have been reported. By examining 50 pairs of samples, Zang *et al*[79] found that the mRNA level of *FOXO1* is downregulated in GC tissues compared with corresponding noncancerous tissues. Lower levels of FOXO3 mRNA and protein have also been found in GC tissues compared with peritumoral tissues[80]. Similarly, FOXO4 expression is consistently lower in GC tissues than in adjacent normal tissues[81]. However, FOXO6 has been reported to be overexpressed in GC. Elevated FOXO6 expression was demonstrated to promote the proliferation, invasiveness, and migration of GC cells, and is associated with a poor prognosis in GC patients[82,83]. Although FOXO1/FOXO3/FOXO4 are often downregulated in GC, and mainly play a tumor inhibitory role, FOXOs possess tumor-promoting functions in certain conditions, and these functions are associated with different underlying molecular mechanisms.

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## MOLECULAR MECHANISMS OF FOXOS IN GC

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### ***Tumor-suppressive roles of FOXOs***

**Tumorigenesis and proliferation:** Tumorigenesis begins with one or more genetic or epigenetic changes in a single cell, followed by subsequent changes that promote tumor development and progression of the tumor to a more aggressive phenotype. Following the accumulation of multiple genetic and epigenetic changes, when a cell

has adapted enough to escape cellular homeostasis, cancer processes are initiated[84]. The expression level of FOXO4 is controlled by methylation of its promoter, and Zhou *et al*[85] showed that hypermethylation of FOXO4, which is induced by ubiquitin-like containing PHD ring finger 1, is involved in GC carcinogenesis.

Regulating the tumorigenic ability of GC cells by FOXOs involves their ability to inhibit GC cell self-renewal. Negative crosstalk between FOXO1 and leucine-rich repeat-containing G-protein-coupled receptor 5 (LGR5) was found in GC, and down-regulation of FOXO1 increases the self-renewal capacity of GC cells by increasing LGR5 levels[86]. The newly discovered oncogene lncRNA AK023391 was reported to promote the occurrence and progression of GC through activation of the PI3K/Akt pathway, which further regulates downstream signaling, including inactivation of FOXO3[87]. An *in vitro* analysis showed that the JNK inhibitor SP600125 decreases the expression of cyclin D1, enhances FOXO1 activity, and inhibits colony formation in GC [88]. As expected, silencing FOXO1 expression leads to the partial recovery of the colony forming ability of GC cells, which indicates that JNK activation is involved in GC initiation partly through FOXO1 inhibition[88].

After tumor formation, cancer cell proliferation controlled by FOXOs is related to cell cycle arrest and induction of autophagy. FOXO1 inhibition by activation of the upstream c-Myc/NAMPT/SIRT1 signaling pathway or upregulation of downstream HER2, which results from FOXO1 Loss, promotes GC cell growth[89,90]. Su *et al*[81] found that FOXO4 induces cell cycle arrest in G1 phase and also reported a shortened S phase in GC cells. Activation of FOXO1 induces the expression of CDKI, p21<sup>Cip1</sup>, and p27<sup>Kip1</sup>, which can suppress GC cell proliferation by triggering cell cycle arrest[91,92]. MiR-96-5p and miR-1274a directly target the 3'-untranslated regions of FOXO3 and FOXO4 mRNA, respectively, and promote GC cell proliferation[93,94]. Moreover, in an acidic microenvironment, FOXO3 enhances autophagy by increasing the expression of autophagy proteins, such as LC3I, LC3II, and Beclin-1, to inhibit GC cell growth[95].

**Apoptosis:** The ability to escape apoptosis is a hallmark of cancer cells[96]. Identification of the mechanism of apoptosis induction provides potential therapeutic strategies for malignant tumors. In an  $\alpha$ -fetoprotein (AFP)-producing GC (AFP GC) model, miR-122-5p inhibited apoptosis and promoted tumor progression by directly targeting FOXO3[97]. The transcription factor RUNX3 binds to two RUNX binding elements (RBE1 and RBE2) in the promoter region of the *Bim* gene, which encodes a pro-apoptotic protein. FOXO3 binds upstream of RBE1, which triggers apoptosis by activating *Bim* transcription through a physical interaction with RUNX3[98,99]. The induced *Bim* protein promotes the release of cytochrome c into the cytoplasm to initiate the formation of the apoptosome, which activates caspase-3 and leads to the execution phase of apoptosis[100]. Shahbazi *et al*[101] revealed the molecular mechanism of apoptosis induction by the nitric oxide synthase inhibitor L-NMMA and showed that L-NMMA promotes the phosphorylation of FOXO3 at threonine 32 and activates signaling by the Rho-associated coiled-coil kinase (ROCK). ROCK has been widely shown to regulate apoptosis[101], and is expressed in GC cells independently of PI3K/AKT and caspase-3[102]. Fas-associated death domain (FADD) protein can be recruited by the intracellular death domain of death receptors. FADD participates in apoptosis induced by the extrinsic death receptor pathway[100], which can be promoted by FOXO3 by suppressing the expression of the FADD inhibitor miR-633 in GC cells[103]. These findings expand on previous reports of the underlying molecular mechanism of FOXOs in promoting apoptosis of GC cells.

**Angiogenesis:** Angiogenesis-dependent tumor growth is an important characteristic of cancers[96]. Vascular endothelial GF (VEGF) and hypoxia-inducible factor-1 $\alpha$  (HIF-1 $\alpha$ ) are critical in promoting tumor angiogenesis[104]. Under hypoxic conditions, HIF-1 $\alpha$  and HIF-1 $\beta$  subunits form heterodimers that activate the transcription of many target genes to adapt to the hypoxic environment of human cancer cells[105]. However, under anoxic conditions, inhibition of FOXO1 causes upregulated expression of HIF-1 $\alpha$  and VEGF in GC cells and increases microvessel areas in GC tissue, thus promoting angiogenesis[106,107]. In GC cells, miR-135b can be delivered *via* exosomes to human umbilical vein endothelial cells (HUVECs) and can then directly bind to and down-regulate FOXO1 mRNA in HUVECs, which promotes ring formation of HUVECs and angiogenesis[108].

Drugs can also affect angiogenesis in GC through FOXO-related signaling pathways. Zhang *et al*[109] showed that arsenic trioxide reduces FOXO3 phosphorylation by inhibiting p-AKT, which results in the increased localization of FOXO3 in the nucleus where it suppresses GC migration and angiogenesis.

**Metastasis:** Metastasis is the leading cause of cancer-related death[96], and is related to EMT, which is characterized by loss of polarity of epithelial cells, decreased expression of epithelial markers, such as E-cadherin and  $\beta$ -catenin, and increased expression of mesenchymal markers, such as N-cadherin and vimentin. These characteristics endow tumor cells with metastatic properties by enhancing cell motility, invasiveness, and resistance to apoptosis. In addition, EMT-associated transcription factors, including Snail and Zeb, are involved in core EMT programs[110,111].

FOXO1 silencing results in upregulation of HER2 expression, which induces a mesenchymal cell phenotype, including decreased E-cadherin levels, increased Snail levels, and the presence of many filamentous processes with abundant actin bundles in GC cells, thus promoting the migration and invasiveness of GC cells[89]. Human telomerase reverse transcriptase cooperates with MDM2 to enhance FOXO3 degradation through ubiquitination, thus attenuating the inhibition of integrin  $\beta$ 1 (ITGB1) expression induced by FOXO3. Subsequent increased ITGB1 expression promotes degradation of the extracellular matrix and enhances invasiveness of GC cells[112]. In addition to cell cycle arrest, Su *et al*[81] also found that upregulation of FOXO4 reduces the metastatic ability of GCs by decreasing vimentin expression, which inhibits EMT.

**Chemoresistance:** Studies that have focused on the role of FOXOs in GC chemoresistance are limited. Park *et al*[113] investigated resistance of GC cells to lapatinib in GC cells and showed that FOXO1 serves as an important link between the HER2 and MET signaling pathways by negatively regulating HER2 and MET expression at the transcriptional level, which could reverse resistance to lapatinib. Moreover, rosmarinic acid (RA) was found to increase FOXO4 expression by downregulating miR-6785-5p and miR-642a-3p levels and enhancing the sensitivity of drug-resistant GC cells to 5-fluorouracil[114].

### **Tumor-promoting roles of FOXOs**

Although many studies support the inhibitory effect of FOXOs in cancers, several recent studies have provided solid evidence of the opposite effect, whereby FOXOs can promote GC progression, including proliferation, invasion, migration, and chemoresistance.

Park *et al*[115] reported that treatment with cisplatin increases the mRNA level of *FOXO1* and promotes the accumulation and activation of the FOXO1 protein to confer protection against cisplatin-induced cytotoxicity in GC cells. Interestingly, in addition to their findings of the suppressive role of FOXO1 in acquired lapatinib-resistance in HER2-positive GC cells, Park *et al*[115] also investigated the role of FOXO1 in cisplatin-resistant GC cells. They showed that constitutive activation of FOXO1 increases resistance to cisplatin, whereas FOXO1 silencing enhances cisplatin-induced cytotoxicity along with apoptotic features in GC cells. Yu *et al*[116] artificially overexpressed FOXO3, and found that increased FOXO3 levels enhance the migratory and invasive abilities of GC cells by directly activating the transcription of cathepsin L, which targets and cleaves E-cadherin, leading to EMT. In contrast, FOXO3 knockdown experiments produced different results *in vitro* and *in vivo*. Li *et al*[117] reported that FOXO3 promotes cell survival in colon cancer under serum-free conditions, which suggests that the role of FOXO3 in tumorigenesis might depend on the environment. In the initial stage of GC, the AKT pathway becomes constitutively activated, resulting in phosphorylation and inactivation of FOXO3, which is beneficial to tumor proliferation. However, in advanced stages of GC, hypoxia, oxidative stress, and restricted serum access promote activation of FOXO3 to help cell adapt to a stressed state and enhance cell survival[116,117].

High FOXO6 expression promotes the proliferation of GC cells by binding to the transcription factor hepatic nuclear factor 4, which mediates histone acetylation and leads to subsequent induction of c-Myc expression after removal of HDAC3 from the *c-Myc* gene promoter[82]. Noncoding RNA activated by DNA damage, an lncRNA with potential carcinogenic effects in bladder and colon cancers, was found to be downregulated in GC cells, which could reduce the targeted inhibition of FOXO6 by miR-608 through competitive inhibition[118].

Therefore, it can be inferred that the changing microenvironment of GC at different stages of development may be one of the reasons why studies on the role of FOXOs in GC have reached opposite conclusions as to whether FOXOs participate in tumor progression.



## POTENTIAL CLINICAL SIGNIFICANCE OF FOXOS IN GCS

### Prognostic value of FOXOs

As mentioned above, phosphorylation results in the translocation of FOXO1 to the cytoplasm, which prevents FOXO-dependent transcription and loss of FOXO-dependent regulation of downstream target genes. High levels of phosphorylated FOXO1 are associated with vascular invasion, lymph node metastasis, distant metastasis, and higher pTNM stage in colon cancer and are indicative of a poor prognosis in astrocytomas[119,120]. In prostate cancer, the traditional Chinese medicines CFF-1 (alcohol extract from an anticancer compound Chinese medicine) and ISO (isorhapontigenin) inhibit cell growth and induce cell apoptosis by decreasing p-FOXO1 and regulating the expression of apoptosis-related and cycle-related genes[121, 122]. These findings are consistent with the antitumor effect of FOXO1 in GC. However, Kim *et al*[123] reported that p-FOXO1 is expressed in 84.6% of GC tissues and that its expression is higher in early stage GC and is correlated with better outcomes. These findings further confirm that the role of FOXO1 is dependent on cancer stage.

Yang *et al*[80] reported a significant correlation between low FOXO3 levels and large tumor size, poor histopathological classification, greater depth of invasion, local lymph node metastasis, distant metastasis, and high AJCC stage. Upregulation and activation of FOXO3 in GC are closely associated with a good outcome in GC patients [124], which suggests that FOXO3 is a potential prognostic marker as well as a therapeutic target in GC patients. Li *et al*[125] demonstrated that a low FOXO4 level is an independent prognostic factor for poor OS and DFS in GC patients, while a high FOXO6 level promotes tumor invasiveness and predicts a poor prognosis in GC patients[83].

### Targeting FOXOs for GC therapeutics

Some potential GC chemotherapeutic agents antagonize tumors by targeting FOXOs and related proteins to inhibit cell growth and proliferation, and induce cell differentiation and apoptosis. Endogenous proteins, such as sphingosine kinase 1 (SPHK1) and PRMT1, microRNAs, and circular RNAs also affect FOXOs and their related signaling pathways, and change the biological characteristics of GC cells. All of these molecules are potential therapeutic targets for the treatment of GC (Table 1).

It is worth noting that the effect of some drugs is influenced by oncogene expression. Inhibition of PARP1 by olaparib can induce G2/M cell cycle arrest by activating FOXO3 in GC cells. Moreover, knockout of BRCA1 or BRCA2 increases the sensitivity of MKN28 GC cells to olaparib, which suggests that olaparib therapy may be particularly beneficial for patients with BRCA-deficient GC[126]. HER2 expression in GC tissues is reported to be higher than that in adjacent normal tissues. Luteolin, a natural flavonoid compound, can repress the growth of GC cells by increasing FOXO1 expression. Luteolin encapsulation by poly(lactic-co-glycolic acid) nanoparticles (NPs) with HER-2 antibody conjugation increases recognition and endocytosis of NPs by GC cells and significantly enhances the inhibitory effect of luteolin on GC cells[127].

Additionally, miR-633 enhances the chemoresistance of GC cells by downregulating FADD expression. Doxorubicin-induced nuclear accumulation of FOXO3 inhibits miR-633 transcription. Inhibition of miR-633 by an antagomir increases the FADD level and enhances doxorubicin/cisplatin-induced apoptosis. A miR-633 antagomir combined with doxorubicin significantly reduces GC cell growth[103].

Overall, FOXOs are promising prognostic markers and therapeutic targets in GC. However, recent studies have primarily focused on the molecular mechanism and are limited to the cell level, which indicates a huge gap between recent research findings and clinical applications. Therefore, the clinical implications of FOXOs still require clarification by additional studies.

## CONCLUSION

FOXOs have historically been regarded as tumor suppressors, but recent studies have suggested that FOXOs support resiliency in healthy and cancer cells. In GC, the antitumor effect of FOXO4 and the tumor-promoting effect of FOXO6 are relatively clear. FOXO1 and FOXO3 play dual roles in many types of cancers, including GC. Whether they promote or inhibit GC may be related to changes in the tumor microenvironment caused by tumor progression and drug treatment. In advanced GC, the effect of changes in the expression level or activity of FOXOs on GC treatment has not

**Table 1 Molecules targeting FOXOs and related proteins for potential gastric cancer therapy**

Molecule	Targets	Mechanism	Effects	Ref.
Luteolin	FOXO1	Increases FOXO1 expression	Represses GC cell growth	Ding <i>et al</i> [127]
Celecoxib	Akt, GSK3b, FOXO1, and caspase-9	Downregulates Akt, GSK3b, and FOXO1 and upregulates caspase-9 in the mitochondrial apoptotic pathway	Represses GC cell growth	Kim <i>et al</i> [128]
4-Amino-2-trifluoromethyl-phenyl retinate	14-3-3ε	Downregulates expression of 14-3-3ε, resulting in increased expression of FOXO1 and P27kip1, decreased expression of CDK2 and cyclin E, and decreased activity of AKP and LDH. Blocks the cell cycle at G0/G1 phase	Inhibits cell proliferation and induces cell differentiation	Xia <i>et al</i> [129]
Gramicidin	FOXO1	Decreases phosphorylation of FOXO1 and down-regulates the expression of cyclinD1 and Bcl-2, leading to G2/M cell cycle arrest	Inhibits cell proliferation	Chen <i>et al</i> [130]
Olaparib	PARP1	Inhibits PARP1 and thus induces G2/M cell cycle arrest by activating FOXO3	Inhibits cell proliferation	Park <i>et al</i> [126]
Bacillomycin-C16	Akt and FOXO3	Inhibits phosphorylation of Akt and increases the level of FOXO3 protein	Induces apoptosis	Lin <i>et al</i> [131]
Protein arginine methyltransferase 1	FOXO1 and BAD	Activates FOXO1 and BAD	Induces chemosensitivity	Altan <i>et al</i> [132]
Sphingosine kinase 1	FOXO1 and FOXO3	Attenuates the transcriptional activity of FOXO1 and FOXO3 via promoting PI3K/Akt-mediated phosphorylation	Enhances proliferation (targeting FOXO1) and resistance to apoptosis (targeting FOXO3)	Xia <i>et al</i> [91] and Xiong <i>et al</i> [133]
Hsa_circ_0001368	miR-6506-5p	Acts as a competing endogenous RNA for miR-6506-5p and inhibits the downregulation by miR-6506-5p on FOXO3	Inhibits tumor growth	Lu <i>et al</i> [134]
miR-1274a	FOXO4	Inhibits FOXO4 expression	Promotes tumor growth and migration	Wang <i>et al</i> [94]

been investigated. Therefore, caution should be exercised when FOXO1 and FOXO3 are used as targets for cancer treatment.

## ACKNOWLEDGEMENTS

We are thankful to Professor Lin S for his English editing and Shen L for his valuable advice and English editing.

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