Biomedicine & Pharmacotherapy 169 (2023) 115900

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Review

FOXO1, a tiny protein with intricate interactions: Promising therapeutic candidate in lung cancer

Mohammad Ebrahimnezhad [a,b], Mohammad Natami [f], Ghazaleh Hafezi Bakhtiari [g], Peyman Tabnak [b], Niloufar Ebrahimnezhad [c], Bahman Yousefi [b,e,*], Maryam Majidinia [d,**]

[a] Student Research Committee, Tabriz University of Medical Sciences, Tabriz, Iran
[b] Department of Biochemistry, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran
[c] Department of Microbiology, Faculty of Basic Science, Urmia Branch, Islamic Azad University, Urmia, Iran
[d] Solid Tumor Research Center, Cellular and Molecular Medicine Institute, Urmia University of Medical Sciences, Urmia, Iran
[e] Drug Applied Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[f] Department of Urology,Shahid Mohammadi Hospital, Hormozgan University of Medical Sciences, Bandar Abbas, Iran
[g] Faculty of Biology, University of Isfahan, Isfahan, Iran

ARTICLE INFO

Keywords:
Lung cancer
FOXO1
Transcription factors
NcRNAs
Signaling pathways

ABSTRACT

Nowadays, lung cancer is the most common cause of cancer-related deaths in both men and women globally. Despite the development of extremely efficient targeted agents, lung cancer progression and drug resistance remain serious clinical issues. Increasing knowledge of the molecular mechanisms underlying progression and drug resistance will enable the development of novel therapeutic methods. It has been revealed that transcription factors (TF) dysregulation, which results in considerable expression modifications of genes, is a generally prevalent phenomenon regarding human malignancies. The forkhead box O1 (FOXO1), a member of the forkhead transcription factor family with crucial roles in cell fate decisions, is suggested to play a pivotal role as a tumor suppressor in a variety of malignancies, especially in lung cancer. FOXO1 is involved in diverse cellular processes and also has clinical significance consisting of cell cycle arrest, apoptosis, DNA repair, oxidative stress, cancer prevention, treatment, and chemo/radioresistance. Based on the critical role of FOXO1, this transcription factor appears to be an appropriate target for future drug discovery in lung cancers. This review focused on the signaling pathways, and molecular mechanisms involved in FOXO1 regulation in lung cancer. We also discuss pharmacological compounds that are currently being administered for lung cancer treatment by affecting FOXO1 and also point out the essential role of FOXO1 in drug resistance. Future preclinical research should assess combination drug strategies to stimulate FOXO1 and its upstream regulators as potential strategies to treat resistant or advanced lung cancers.

1. Introduction

Lung cancer is the second most frequently diagnosed cancer, and its mortality and prevalence have risen significantly in the last few years. According to the recent reports, 2.1 million new lung cancer cases are identified each year and 1.8 million patients die from lung cancer globally [1]. Despite significant improvements in diagnostic and treatment procedures, the 5-year survival rate of lung cancer patients is approximately 23% [2]. Lung cancer is histologically classified into small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC), in which NSCLC accounts for more than 80% of all cases [3]. Currently, the conventional therapy of NSCLC, chemotherapy, and surgical resection have shown to be helpful against earlier stages of lung cancer, and the co-administration of radiotherapy with chemotherapy has been regarded as the preferred approach for therapy of locally advanced, incurable NSCLC patients [4]. Additionally, despite the latest advancements in novel treatments including molecular targeted therapy, immunotherapy, genomic corrections, and gene therapy, the overall survival rate of patients has not risen considerably in clinical settings, due to the high rate of regional recurrence, metastasis, and acquired or innate drug resistance [5,6]. Therefore, to improve the effectiveness of currently available therapies, subtle knowledge of the molecular

* Corresponding author at: Department of Biochemistry, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran.
** Corresponding author.
E-mail addresses: bahmanusefi@gmail.com (B. Yousefi), majidinia.m@umsu.ac.ir (M. Majidinia).

https://doi.org/10.1016/j.biopha.2023.115900
Received 24 July 2023; Received in revised form 8 November 2023; Accepted 14 November 2023
Available online 18 November 2023

Table 1
PI3K/AKT and FOXO1 in lung cancer.

Upstream regulator	Cancer type	Axis	Model	Description	
purified plum polyphenols (PPP)	NSCLC	↓PI3K/↓AKT ↑FOXO1/↑ Bcl-2 and cleaved caspase-3	In vitro	. "PPP had a considerable ability to limit A549 cell proliferation by causing apoptosis, as seen by an elevation in the Bax/Bcl-2 ratio." . "PPP causing the apoptosis of the A549 NSCLC cells via inhibition of the PI3K/AKT pathway, and upregulation the FOXO1 and its downstream targets Bcl-2 and cleaved caspase-3 level"	[12]
Cellular retinol-binding protein-1 (CRBP-1)	NSCLC	↓AKT/↑FOXO1	In vitro	"Reduced proliferation and cell viability caused by the restoration of CRBP-1 expression in H460 NSCLC cell line was correlated with down-regulation of AKT-related gene"	[43]
WTIP	NSCLC	↓AKT/↑FOXO1	In vitro and in vivo	"WTIP impairs AKT phosphorylation and enhances the transcriptional activity of FOXO1 and further increases p27Kip1 and p21Cip1 which leads to cell cycle arrest"	[40]
SEMA4B	NSCLC	↓ PI3K/AKT ↑FOXO1	In vitro and in vivo	"SEMA4B inhibits PI3K/AKT which not only increases the nuclear accumulation of FOXO1 to induce apoptosis, but also regulates MMP9 to control metastasis"	[42]

mechanisms underlying lung cancer development, progression, drug resistance, and invasion still needs to be elaborated in detail.

Transcription factors (TFs) are critical for a number of essential physiological functions that regulate the DNA transcription into mRNA by adhering to specific DNA sequences and they are either suppressed or activated to control gene expression. TF dysregulation is frequently observed in lung cancer and can result in the emergence of tumor-related features [7]. Different expressed TFs and their downstream target genes could be employed for therapeutic purposes [8]. Forkhead box (FOX) proteins are an important family of transcription factors with a specific winged-helix DNA binding domain [9]. The FOXO, a subgroup of FOX proteins, is composed of four members including FOXO1, FOXO3, FOXO4, and FOXO6, which control particular genes to govern cell-cycle arrest, apoptosis, DNA damage repair, and cell growth [10]. FOXO proteins regulate gene transcription in quiescent or growth factor-deficient cells where they typically are located in the nucleus. In the presence of growth factors' cellular survival drive, FOXO proteins transmit to the cytosol and are eventually degraded by the ubiquitin-proteasome signaling pathway. On the contrary, in the absence of cell growth factors, FOXO proteins translocate to the nucleus and modulate a number of target genes that are involved in cell cycle arrest, apoptosis, and malignancy [11]. FOXO1, the most widely studied subtype, has attracted much more attention due to its important role in lung cancer. Except for growth factors, various signaling pathways and upstream protein regulators such as PI3K/AKT, SIRTs, reactive oxygen species (ROS), and non-coding RNAs (ncRNAs) may positively or negatively modulate FOXO1 function [12–15]. Although most of the recent studies support the hypothesis that FOXO1 is a genuine anti-cancer agent the underlying mechanisms, signaling pathways and upstream regulators may reverse its tumor suppressor function. Moreover, it has been established that FOXO1 has a controversial role in the development of tumors. For instance, high FOXO1 expression in breast cancer has been associated with the upregulation of matrix metalloproteinase (MMP), facilitated cancer cell metastasis [16] and its inhibition potentiates cancer cell death [17]. Conversely, FOXO1 is downregulated in NSCLC and FOXO1 silencing is correlated with the invasive stage of cancer progression [18]. These conflicting findings reflect that the role of FOXO1 may alter based on the type of cancer cells and specific circumstances in malignancies.

In this review, we focus on the surprising role of FOXO1 in the development of lung cancer and summarize the molecular mechanisms, pathways, and non-coding RNAs (ncRNAs), which underlie the anti-neoplastic role of FOXO1. Finally, we will discuss the therapeutic approach of FOXO1 and its emerging role in the chemo/radio-resistance of lung cancer.

1.1. Structure and regulation FOXO1

The term "forkhead" was given to the two spiked-head structures found in the fetuses of the Drosophila melanogaster forkhead variant, which were linked to the development of the Drosophila fetus intestine [19]. 50 mammalian FOX proteins and 19 subfamilies (FOX stands for 'Forkhead Box' A to S) have been discovered so far and they are categorized based on their winged-helix sequence homology and other functional domains [20]. The FOX winged-helix structure resembles *butterfly* wings and comprises three N-terminal α-helices, two loops, and three β-strands [21,22]. Considering this distinctive structural characteristic, the FOX proteins control gene expression by detecting the cis-regulatory region in their target genes to directly influence gene expression [20].

FOXO1, a subtype of highly conserved FOXO proteins, contains approximately 110 amino acids in its domain and integrates different signals to positively or negatively modulate cellular activities such as anti-oxidative enzymes, apoptosis, development, autophagy, and immune regulators [23,24]. Gene expression and the nucleocytoplasmic cycling of FOXO1 are regulated by a nuclear localization signal, a forkhead DNA-binding domain, a transactivation domain, and a nuclear export sequence [25]. Furthermore, A variety of posttranscriptional modifications, including ubiquitination, acetylation, deacetylation, arginine methylation, and phosphorylation, are involved in FOXO1 regulation [23].

Some protein kinases target the phosphorylation of FOXO1 and modify various sites on FOXO1 to change their cellular location, transcriptional activity, and DNA binding affinity [26]. PI3K pathway, insulin signaling substrates 1 and 2, and AKT/SGK protein kinases are important regulators of FOXO1 which facilitates FOXO1 binding to 14–3–3 proteins, phosphorylate FOXO1 and enhance the translocation of FOXO1 from the nucleus to cytoplasm resulting in its transcriptional inactivation [27]. Conversely, some Other protein kinases such as JNK, AMPK, p38, macrophage stimulating 1, and cyclin-dependent kinase 1 disrupt FOXO1 binding to 14–3–3 proteins, decrease FOXO1 phosphorylation, and promote its nuclear localization [28].

Similar to phosphorylation, acetylation has been demonstrated to mediate multiple biological functions of FOXO1 and may both boost and reduce FOXO1 transcriptional activity. The enzymes histone deacetylases and histone acetyltransferase regulate the impact of acetylation on FOXO1. It has also been noted that FOXO1's acetylation at K222, K245, K248, K265, K274, and K294 controls both its sensitivity to AKT phosphorylation and DNA-binding affinity. In more detail, acetylation of FOXO1 reduces its DNA binding affinity and thereby promotes its transcriptional activity, furthermore, this mechanism could be reversed by its deacetylation [29,30].

Ubiquitination has a dual role in FOXO1 regulation. Similar to other proteins, FOXO1 could be targeted for proteasome degradation via polyubiquitination. Some ubiquitin E3 ligases are required for the FOXO1 ubiquitination, which causes FOXO1 degradation. Mono-ubiquitination of FOXO1 exerts the opposite effect and enhances FOXO1 nuclear localization [27,30]. Even though mostly FOXO1 serves as a

tumor suppressor in most malignancies, there are shreds of evidence that it can also exhibit oncogenic effects via maintaining cancer stem cells [31], reactivation of the PI3K-AKT pathway via negative feedback [32] and mediating drug resistance [33]. Therefore, more investigation into its structure and controlling its posttranscriptional modifications could help to determine the specific role of FOXO1 in tumorigenesis.

2. Molecular mechanisms of FOXO1 regulation in lung cancer

2.1. PI3K/AKT

Phosphoinositide 3-kinases (PI3Ks), a large group of signaling lipid enzymes are involved in various biological processes, including differentiation, cell growth, and cell cycle progression. Protein kinase B or Akt, a serine/threonine kinase, is a typical downstream target of the PI3K signaling pathway [34]. It's well established that FOXO1 tadminister its function through interaction and regulating various kind of signaling pathways and axis; FOXO1 is an outstanding target for P13K/AKT signaling that has been stimulated (Table 1) [35,36]. Activation of PI3K leads to translocation of AKT to the cytoplasm and nucleus, causing phosphorylation of a variety of genes; Phosphorylation of target proteins by Akt could be inhibitory or stimulatory, reducing or boosting their function. Phosphorylation induced by Akt results in the suppression of FOXO1, which reverses the tumor suppressor role of FOXO1; thus, stimulating the P13K/AKT axis may result in a tumorigenesis condition [37,38]. Furthermore, considering AKT/FOXO1 function, activation or inhibition of other signaling pathways or upstream regulators should be taken into account to influence this pathway in therapeutic approaches. WT1–interacting protein (WTIP), a coregulator of the Wilms tumor gene (WT1), acts as a tumor suppressor via increasing the expression of p21Cip1 and p27Kip1, the cyclin-dependent kinase (CDK) inhibitors, and downregulating cyclin D1 and p-Rb levels in NSCLC without any inhibitory effects on WT1 [39]. A recent study has reported that the AKT/FOXO1 pathway has an interplay role in WTIP-induced cell cycle arrest. WTIP significantly augments nuclear FOXO1 retention by decreasing phosphorylated AKT. In more detail, Activated FOXO1 promotes the expression of CDK inhibitors p21Cip1 and p27Kip1 resulting in G1/S arrest of NSCLC [40]. The PI3K/AKT/-FOXO1 signaling pathway has received more attention in recent years due to its importance in lung cancer, and recent studies have uncovered various upstream regulators that modulate this axis; Sema domain of semaphorin 4B (SEMA4B), a subtype of semaphorins protein, is new one that has a crucial role in the tumorigenesis of NSCLC [41] and also enhances nuclear vs. cytoplasmic FOXO1 levels via suppression of the PI3K/AKT signaling pathway. This action leads to the inhibition of tumor cell development through the binding of FOXO1 to the promoter of cell-cycle-inhibitor p21, which inhibits tumor cell proliferation [42]. Similarly, another study has revealed that the anti-proliferative features of natural polyphenolic compound purified from plum on A549 lung cancer cells are exerted through inhibition of the PI3K/AKT and translocation of FOXO1 to the nucleus which executes its transcriptional functions and consequently stimulates pro-apoptotic Bcl2-like protein 11 downstream apoptosis pathway [12].

The interplay between FOXO1 and AKT pathway could be a probable factor in the induction of pro or anti-apoptotic effects and considering that influencing direct phosphorylation of AKT is a difficult process, thus, targeting AKT/FOXO1 alone is not enough to control FOXO1 expression. Other upstream regulators such as WTIP [40] and SEMA4B [42] are needed to be detected to exert the instinctive anticancer ability of FOXO1 on lung cancer cells.

2.2. SIRTs

Sirtuins (SIRTs), a subgroup of NAD+ -dependent deacetylases, are highly preserved from primitive organisms to human beings and are thought to be important in lung cancer development. SIRTs regulate a variety of considerable physiologic mechanisms including cell division, embryonic differentiation, aging, and metabolism [44,45]. An overview of the literature revealed that there is a correlation between SIRT and FOXO1; SIRT1 may have a role in cellular survival and apoptotic processes through deacetylating FOXO transcription factors (Table 2) [46]. Zhang et al. have found that *S*-nitrosoglutathione (GSNO), a nitric oxide-derived molecule, induces lung cancer cells apoptosis through nitrosylating peroxiredoxin-2 (Prdx2); nitrosylated Prdx2 disturbs the Prdx2s formation and suppresses the antioxidant activity of Prdx2 which leads to AMP-activated protein kinase (*AMPK*) activation. They further noticed that activated AMPK induces SIRT1 phosphorylation, increases the acetylation of FOXO1, and promotes nuclear translocation of FOXO1 which finally causes apoptosis in NCI-H1299 cells of lung cancer [13]. There are other shreds of evidence that repressing SIRT, induces FOXO1-mediated apoptosis. Quinone oxidoreductase 1 (NQO1), a eukaryotic flavin protease enzyme, is overexpressed in cancer cell tumors compared to normal tissues [47]. In line with this, a well-known study by Liu et al. turned out that activation of NQO1 triggered by oxidative stress suppresses SIRT1, and this leads to the nuclear accumulation of acetylated FOXO1, which facilitates apoptotic signaling [48].

Table 2
SIRT1 and FOXO1 in lung cancer.

Upstream regulator	Cancer type	Axis	Model	Description	
GSNO	Lung cancer	↑AMPK /↓ SIRT1/ ↑FOXO1	In vitro and in vivo	"GSNO causes accumulation of endogenous H_2O_2 via suppression of Prdx2. Endogenous H_2O_2 provokes AMPK activity which leads to inhibition of SIRT1 and stimulation of FOXO1 "	[13]
NQO1	NSCLC	↓SIRT1/ ↑FOXO1	In vitro and in vivo	"NQO1 triggered oxidative stress induces proapoptotic condition through phosphorylation of SIRT1 and enhancement of the nuclear accumulation of FOXO1 "	[48]

2.3. DNA damage

DNA damage is a well-recognized factor in the initiation and development of malignancies. Exogenous threats, consisting of chemical agents, irradiation, and endogenous mechanisms increase reactive oxygen species (ROS), create nucleotide fragments or aberrant nucleotides causing diverse damage in chains of the DNA strand [49]. DNA damage raises the possibility of mutations and genomic instability is one of the most significant variables contributing to tumorigenesis. By occurring DNA damage there is a requirement for a process to maintain genome stability. The induction of several repair mechanisms with the main goal of restoring DNA integrity refers to DNA damage response (DDR) [50]. DDR motivate checkpoints to identify DNA damage site and trigger repair pathways to induce DDR-mediated apoptosis [51].

Recent studies have focused on the interplay role of FOXO1 in DDR. A study by Ju et al. on H1299 lung cancer cells has shown that FOXO1 expression upon DNA damage caused by alkylating agents can vary depending on the severity of cell injury. While mild DNA damage can overexpress FOXO1, severe cell stress can exert a positive effect. Upon DDR activation, FOXO1 promotes apoptotic genes such as p27Kip1, GADD45, and Bim in H1299 lung cancer cells, causing cell cycle arrest.

Table 3
Oxidative stress and FOXO1 in lung cancer.

Upstream regulator	Cancer type	Axis	Model	Description	
JNK	NSCLC	↑FOXO1/↑p27 (Kip1)-Bim-GADD45	In vitro	"JNK facilitates nuclear translocation of FOXO1 and enhances FOXO1-depend repair response during DNA damage."	[52]
UBE2T	NSCLC	↓FOXO1	In vitro and in vivo	"UBE2T enhances epithelial-mesenchymal transition (EMT) dependent radioresistance through FOXO1 degradation and activation of Wnt/β-catenin signaling pathway."	[53]
Isovalerylspiramycin I (ISP-I)	NSCLC	↓PI3K/AKT/↑FOXO1	In vitro and in vivo	"Excessive ROS accumulation caused by ISP-I enhances FOXO1 expression via inhibition of PI3K/AKT pathway and stimulates consequent apoptosis and G2/M arrest"	[14]
A-485	NSCLC	↑FOXO1	In vitro	"ROS production enhances FOXO1 expression and induces autophagy leading to growth arrest commitment"	[55]
NQO1	NSCLC	↓SIRT1/↑FOXO1	In vitro and in vivo	"NQO1 triggered oxidative stress induces proapoptotic condition through phosphorylation of SIRT1 and enhancement of the nuclear accumulation of FOXO1 "	[48]

C-Jun N-terminal kinases (JNK) is another protein kinase involves in DNA damage and positively regulates FOXO1 transcriptional activity and its target genes. Therefore, reinforcing JNK expression can be considered a strategy to induce FOXO1 nuclear translocation effectively [52].

Another regulator of FOXO1 during DNA damage which acts upside down of JNK is the ubiquitin-conjugating enzyme E2T (UBE2T). UBE2T is an overexpressed oncogene in lung cancer cells that protects tumors from ionizing radiation by inducing proteasomal degradation of FOXO1 and subsequent activation of the Wnt/β-catenin pathway, a strong regulator of Epithelial-to-mesenchymal transition (EMT) [53]. More investigation has implicated the impressive role of SIRT1/FOXO1 and PI3K/AKT/FOXO1 cascades in oxidative stress-induced DDR [48]. During NQO1 activation-triggered oxidative stress, the cellular level of NAD^+, as a co-substrate for SIRT1, was reduced and led to consequent inhibition of SIRT1 enzyme activity [54]. Under high levels of oxidative stress and inhibited SIRT1, inappropriately prolonged FOXO1 activation stimulates apoptosis downstream target gene of FOXO1 and causes

Table 4
Reciprocal interplay between FOXO1 and ncRNAs in lung cancer.

ncRNA	Cell line	Downstream	Role of FOXO1	Upstream (this can be a drug even!)	Function	Ref
miR-1269a (Oncogene)	A549 and H1975/NSCLC	↓FOXO1	TS		Increased proliferation, migration, and invasiveness	[88]
miR-421 (Oncogenic)	A549/NSCLC	↓FOXO1	TS		Promoted the viability of A549 lung cancer	[76]
miR-629 (Oncogenic)	BEAS-2B H1299, and H460/ NSCLC	↓FOXO1	TS		Enhanced proliferation, migration, and invasion	[77]
Circ_0000353 (Tumor suppressor)	A549 cells, H226 cells, H23 93 cells, H838 cells, and H226/ NSCLC	↓miR-411–5p/ ↑FOXO1	TS		Impeded the proliferation, migration, and invasion	[87]
Circ_0002483 (Tumor suppressor)	A549, H1299, H358, and PC9/ NSCLC	↓miR-182–5p/ ↑FOXO1	TS		Inhibited NSCLC progression, increased the sensitivity of NSCLC cells to Taxol	[86]
miR-122–3p (Tumor suppressor)	A549/NSCLC	↑FOXO	TS		Abrogated cell proliferation and promoted cell apoptosis	[69]
miR-486 (Tumor suppressor)	H1299 and H1792/	↑FOXO1	TS	Propofol induced the expression of miR-486	Induced cell apoptosis and suppressed lung cancer cell viability	[70]
miR-9 (Oncogenic)	A549, Calu-1, H157, H460 and HCC827/NSCLC	↑FOXO1	TS	Erlotinib	Erlotinib downregulated miR-9 expression to induce FOXO1 expression and inhibit tumor cell growth	[75]
miR-411 (Oncogenic)	H1299, and H1792/NSCLC	↓FOXO1	TS		Promoted cell proliferation	[89]
miR-183 (Oncogenic)	A549/NSCLC	↓FOXO1	TS		Increased NSCLC growth	[74]
ANCR lncRNA (Oncogenic)	A549/NSCLC	↓FOXO1	TS		Induced the proliferative ability of A549 cells	[80]
lncRNA SOX2-OT (Oncogenic)	A549/NSCLC	↓ miR-122–3p/ ↓FOXO1	TS		Reduced apoptosis, cell cycle arrest, and potentiated migration	[81]
LncRNA LINC00261 (Tumor suppressor)	A549 and SPC-A1	↓miR-1269a/ ↑FOXO1	TS		Inhibited lung cancer progression, growth, metastasis, and promoted apoptosis	[82]
miR-96 (Oncogenic)	A549 and PC-9/NSCLC	↓FOXO1 and DUSP1	TS		Improved migration, invasion, and proliferation	[78]
miR-3188 (Tumor suppressor)	A549 and H1299/NSCLC		TS	FOXO1	Negatively regulated tumor growth	[71]
miR-155 (Oncogenic)	(H1299, H1650, H460, A549/ NSCLC	↓FOXO1/ROS	TS		Promoted NSCLC cell proliferation	[90]
miR-183–5p (Oncogenic)	A549, SPCA-1, PC-9, and 95-D/ NSCLC	↓FOXO1	TS		Facilitated the migration, proliferation, EMT, and invasion	[91]

programmed cell death in A549 lung cancer cells [48]. Additionally, a recent study on NSCLC cell lines showed that ROS accumulation could significantly suppress the PI3K/AKT signaling pathway, which in turn upregulates FOXO1 expression to induce its apoptosis and cell cycle arrest-related downstream genes [14]. Except for ROS-mediated apoptosis, some other research has authenticated that ROS accumulation could also regulate autophagy in cancerous cells by affecting FOXO1 function. The spiro oxazolidinedione compound indicated as A-485 is a histone acetyltransferase inhibitor that exhibits antitumor effects in tumorigenesis, especially through modulating autophagy. Ansari et al. have realized that in response to A-485 treatment of A549 and H1299 lung cancer cells, intracellular ROS accumulation was increased dose-dependently. They further showed that ROS production could enhance the transcriptional activity of FOXO1 which may facilitate ROS-induced autophagy [55]. A large body of evidence showed that FOXO1 has a tumor suppressor role in response to DDR. Therefore, finding a mechanism to affect upstream regulators of FOXO1 during DDR may elucidate FOXO1′s future therapeutic aspect in malignancies (Table 3).

2.4. STYK1

EMT, a mechanism in which epithelial cells become spindle-like mesenchymal cells, plays a key role in cancer progression and augments migratory and invasive properties [56]. In this respect, FOXO1 has become the center of a debate regarding whether suppresses the EMT process or, conversely, exhibits pro-metastatic functions via facilitating EMT. Lai and colleagues have conducted a study to clarify the role of FOXO1 in human lung cancer cell lines and found that serine threonine tyrosine kinase 1 (STYK1)/FOXO1 pathway has a crucial role in this process [57]. STYK1, a novel oncogene member of the receptor protein tyrosine kinases (*RPTK*) family, is overexpressed in NSCLC. Elevated expression of STYK1 is associated with cancer cell invasion through downregulating the E-cadherin expression and consequent induction of EMT [58,59]. Lai et al. have highlighted the interplay role of FOXO1 in STYK1-mediated EMT activation. The phosphorylation of FOXO1 and subsequent suppression of FOXO1 occurred concurrently with the stimulatory effects of STYK1 on migratory characteristics. In more detail, the amount of FOXO1 phosphorylation, which is negatively associated with the FOXO1 activity, was assessed by measuring the ratio of phosphorylated-FOXO1 (p-FOXO1) to FOXO1; and expression of STYK1 positively correlated with p-FOXO1. As a result, STYK1 has an appositive effect on cell migration, invasion, and promotes EMT by blocking the tumor suppressor effect of FOXO1 [57].

3. The reciprocal interplay between FOXO1 and ncRNAs

3.1. ncRNAs

It has been well established that our body's proteins are transcripted by a small portion of the human genome, and a considerable part of other genes are encoded into ncRNAs [60]. NcRNAs could be categorized according to the length of nucleotides into short ncRNAs and long ncRNAs (lncRNAs). Essential short ncRNAs typically consist of microRNAs (miRNAs), and circular RNAs (circRNAs) [61]. Emerging studies indicate that non-coding ncRNAs are tightly correlated to tumor onset, development, progression, and drug resistance or may reverse these actions in lung cancer [62,63].

3.2. miRNAs

MiRNAs belong to short ncRNAs with sizes ranging from 18 to 25 nucleotides long, and they play a role in a variety of metabolic and physiological pathways, particularly those that control cell growth, maturation, and survival. However, they have complicated expression patterns, which lead to improper expression of them in approximately all types of cancers and challenge their classification as tumor suppressors or oncogenes [64,65]. Under specific conditions, miRNA can restrict or stimulate mRNA translation, promote mRNA degradation, and modulate mRNA transcription [66]. As seen in the Table 4 most of the ncRNAs which have a role in the pathogenesis or alleviation of tumor cells in lung cancer are miRNAs. And the majority of mentioned miRNAs that interact with FOXO1 in lung cancer have an oncogenic role, except miR-486, and miR-122–3p which both of them upregulates the expression of FOXO1 and miR-3188 as probable downstream target of FOXO1.

MiR-486 and miR-122–3p exhibit their antitumor ability through similar molecular mechanisms. It has been identified that the expression level of miR-486 was reduced in lung tumors compared with uninvolved lung tissues [67]. In addition, miR-122–3p is downregulated in some types of malignancies [68]. The elevated level of miR-486 and miR-122–3p increases apoptosis-related proteins such as bim and activated caspase-3 by directly targeting and upregulating FOXO1 [69,70]. In contrast to the mentioned miRNAs, which both them directly target FOXO1; miR-3188 coordinates with FOXO1 via PI3K/AKT/c-JUN axis to exert antitumor effects. In more detail, miR-3188 organizes a negative feedback loop by regulation of the mTOR-p-PI3K/AKT-c-JUN signaling pathway [71]. The transcription factor c-JUN has been reputed as a key player in tumorigenesis and the mammalian target of rapamycin (mTOR) is an oncogene protein kinase that constitutively stimulates PI3K/AKT [72,73]. MiR-3188 inactivates the PI3K/AKT pathway by direct suppression of mTOR, which results in consequent c-JUN and p-mTOR downregulation. Similar to miR-3188, FOXO1 also suppresses PI3K/AKT/c-JUN to inhibit NSCLC cell proliferation. Surprisingly, miR-3188 failed to increase the FOXO1 expression, indicating that miR-3188 could be a possible downstream molecule of FOXO1 [71].

Recently, it has been acknowledged that the 3′ UTR region of FOXO1 is targeted by oncogenic microRNAs, such as miR-183 [74] and miR-9 [75] that their expression is enhanced in NSCLC cell lines (Table 4). More importantly, in terms of cell migration, some oncogenic miRNAs can increase cancer cell viability and invasion by inhibition of FOXO1. For example, transwell and MTT assays on NSCLC cell lines revealed that miR-421 and miR-629 have been found to promote lung cancer cell viability and metastasis by direct downregulation of FOXO1 [76,77]. Alongside with direct effect of these two mentioned miRNAs on FOXO1 some other signaling pathways and downstream target genes are involved in exerting the oncogenic role of miR-421 and miR-629. Upon FOXO1 inhibition mediated by miR-421, activated AKT/ Glycogen synthase kinase-3 β (GSK-3β) pathway upregulates the protein expression of p-AKT, p-GSK-3β, cyclin D1, and p-Rb which is strongly associated with diminished apoptosis and cell cycle progression in A549 cells [76]. Concomitant with the direct effect of miR-629 on FOXO1, surprisingly miR-629 activates the PI3K/AKT pathway which may potentiate its negative effect on FOXO1 [77]. MiR-96 is another one that exhibits its metastatic role by targeting FOXO1 and Dual-specificity phosphatase 1 (DUSP1), a key negative regulator gene in cell invasion. Ding et al. showed that Overexpressed MiR-96 in NSCLC cell lines downregulates DUSP1 expression by sponging FOXO1 [78].

3.3. lncRNAs

LncRNAs are RNA molecules that have more than 200 nucleotides and lower stability compared to short ncRNAs [61]. LncRNAs have previously been suggested to be malfunctioning or dysregulated in malignancies, with pro- or antitumor capability, especially in lung cancer [79]. For example, lncRNA anti-differentiation noncoding RNA (ANCR) and SOX2 overlapping transcript (SOX2-OT) are involved in lung cancer tumorigenesis by modulating FOXO1 expression [80,81]. It was demonstrated that lncRNA ANCR can directly bind FOXO1 protein and suppress its expression. lncRNA ANCR-related inhibition of FOXO1 facilitates the expressions of Bcl-2 and cyclin D1 but inhibits those of P27 and Bax, therefore alleviating the apoptosis and cell cycle arrest in lung cancer cells [80]. SOX2-OT is another oncogenic lncRNA that

Table 5
FOXO1 and treatment opportunities in lung cancer.

Treatment	Cancer type	Drug type	axis genes	Model	Description	Ref.
CNB	NSCLC	Natural compound	↓G9a/↑FOXO1/ ↓ CK8 ↓PCNA, ↓Ki67 ↑cleaved caspase3/8 ↓Bcl-2 ↑Bax ↑PUMA ↑ PARP	In vitro/ in vivo	"CNB can significantly increase FOXO1 expression in A549 cell apoptosis causing induction of Bax, PUMA, PARP, and cleaved caspase3/8 and suppression Bcl-2 " " CNB enhances FOXO1 expression by inhibiting the expression of *G9a and consequently suppresses* the invasion-related protein, CK8, and proliferative related protein PCNA "	[95]
Cisplatin	NSCLC	Alkylating agent	↑FOXO1 ↑FOXO3a	In vitro/ in vivo	"Cisplatin promotes the expression of FOXO1 and FOXO3a and induces apoptosis in NCSLC. In addition, LY294002, an inhibitor of the PI3K/AKT axis, increases the cytotoxicity of cisplatin via upregulation of FOXO1 and FOXO3a "	[92]
Hyperoside	NSCLC	Natural compound	↑FOXO1 ↓CCAT1	In vitro/ in vivo	"Hyperoside decreased NSCLC cell growth and promoted apoptosis by upregulating FOXO1 expression and downregulating the amount of colon cancer-associated transcript 1 (CCAT1) in EGFR-TKI resistance NSCLC cells."	[105]
Glucosamine	Lung adenocarcinoma	Natural compound	↓PI3K/AKT ↓MAPK/ERK ↑FOXO1 ↑FOXO3	In vitro	"Glucosamine modulated A549 cell proliferation, via O-GlcNAc modification-induced downregulation of the MAPK/ERK and PI3K/AKT and inhibited the phosphorylation of ERK and AKT which respectively may result in activation of FOXO3 and FOXO1″	[94]
Erlotinib	NSCLC	Kinase inhibitor	↑FOXO1	In vitro	"Oncogenic miR-9 targets FOXO1 and reduces its expression to promote proliferation and erlotinib operates its inhibitory effect through downregulation of miR-9/FOXO1 axis."	[75]
Depsipeptide	Human lung cancer	HDAC inhibitor	↑FOXO1/↑Bim	In vitro	"Depsipeptide, a novel HDAC inhibitor, induces apoptosis and cell cycle arrest in cancer cells via activation of Bim which is directly associated with increased acetylation of FOXO1."	[93]
IL7	Mice lung cancer	*Cytokine*	↑PI3K-AKT-mTOR/ ↑p300/↑FOXO1/ IL-9↑	In vitro/ in vivo	"IL7 stimulates the PI3K-AKT-mTOR pathway to enhance the histone acetyltransferase p300. Activated p300 dephosphorylates FOXO1 to trigger the production of IL-9 protein and provide the antitumor ability of TH9 cells."	[101]
IFN-γ	Mice lung cancer	*Cytokine*	↑FOXO1/↑IL-27	In vitro/ in vivo	"IFN-γ inhibits mice lung cancer metastasis through FOXO1-mediated induction of IL-27 and NK cell expansion."	[103]

influences FOXO1 activity by regulation of another miRNA. lncRNA SOX2-OT transfection of lung cancerous A549 cell line inhibits FOXO1 by downregulation of miR-122–3p leading to enhanced migration, reduced apoptosis, and cell cycle arrest compared to untreated cells [81].

In contrast to the mentioned oncogene lncRNA, LINC00261 is a tumor suppressor that positively affects FOXO1 expression. lncRNA LINC00261 upregulates FOXO1 by sponging miR-1269a which is associated with promoted proliferation and metastasis of lung cancer cells [82]. As seen in Table 4 FOXO1 acts as a tumor suppressor in investigated lncRNAs.

3.4. *circRNAs*

In contrast to lncRNAs and miRNAs, circRNAs have a continuous closed loop. Because of circRNAs' covalently closed formations, they are more persistent than lncRNAs and miRNAs [83]. CircRNAs have received much attention as an independent biomarker in the prognosis, diagnosis, and therapeutic targeting of lung cancer and their dysregulation influences various aspects of cancer progression, consisting of invasion, occurrence, and recurrence [84]. CircRNAs regulate the expression of genes involved in migration, tumorigenesis, and apoptosis by affecting signaling pathways, transcription factors, or other ncRNAs that specify their oncogenic or tumor suppressor role [85]. Similar to other ncRNAs, circRNAs have a key role in lung cancer tumorigenesis through post-transcriptional regulation of FOXO1. Circ-0000353 and circ-0002483 are two of circRNAs with tumor suppressor roles that affect FOXO1 expression [86,87]. Li et al. have shown that circ_0002483 is downregulated in NSCLC cell lines and patients with a lower level of circ_0002483 expression represent a worse prognosis compared to the control group. Overexpression of circ_0002483 in A549 and H1299 cells led to remarkable upregulation of FOXO1 by sponging miR-182–5p. More importantly, circ_0002483-related activation of FOXO1 enhances the sensitivity of NSCLC to Taxol, a diterpenoid alkaloid with anti-tumor properties [86]. Consisting with the mentioned study, circ_0000353 is another circRNA which positively regulates FOXO1 by suppressing miR-411–5p. Furthermore, upregulated FOXO1 caused by circ_0000353 attenuates proliferation and migration in NSCLC cell lines [87].

3.5. *FOXO1 as a therapeutic target*

Given that most of the research conducted until now supports the tumor suppressor property of FOXO1, it seems that restoring its expression may reverse lung tumorigenesis in the early stages. An increasing number of studies have shown that restoration of FOXO1 could enhance the therapeutic efficacy of anticancer drugs such as cisplatin [92] and depsipeptide, a novel HDAC inhibitor [93]. Depsipeptide-mediated acetylation of FOXO1 is a specific modification that triggers the Bim expression and elicits cancer cell death [93]. Conversely, FOXO1-related apoptosis of NSCLC cell lines induced by cisplatin was independent of Bim expression [92]. This revealed that despite the similar anticancer mechanism induced by FOXO1 activation, the downstream target gene of FOXO1 could be different depending on the administered pharmacological compound. In addition, some of these anticancer drugs target upstream agents of FOXO1 to stimulate its function. Glucosamine, a natural compound found in cartilage, abrogates FOXO1 phosphorylation and facilitates its nuclear translocation by inhibiting PI3K/AKT pathway. Nuclear accumulation of FOXO1 upregulates the protein expression of Fas ligand (FasL) and Bim, which are involved in apoptosis, and p21cip1 and p27kip1, which have a key role in cell cycle arrest [94]. Cinobufagin (CNB) is another anticancer natural compound extracted from *Chansu*, an herbal traditional Chinese medicine, which indirectly affects FOXO1 expression and suppresses A549 cells proliferation, invasion, and migration in a time- and dose-dependent manner [95]. *G9a* is a *histone methyltransferase with oncogenic features and its overexpression is associated with poor prognosis in*

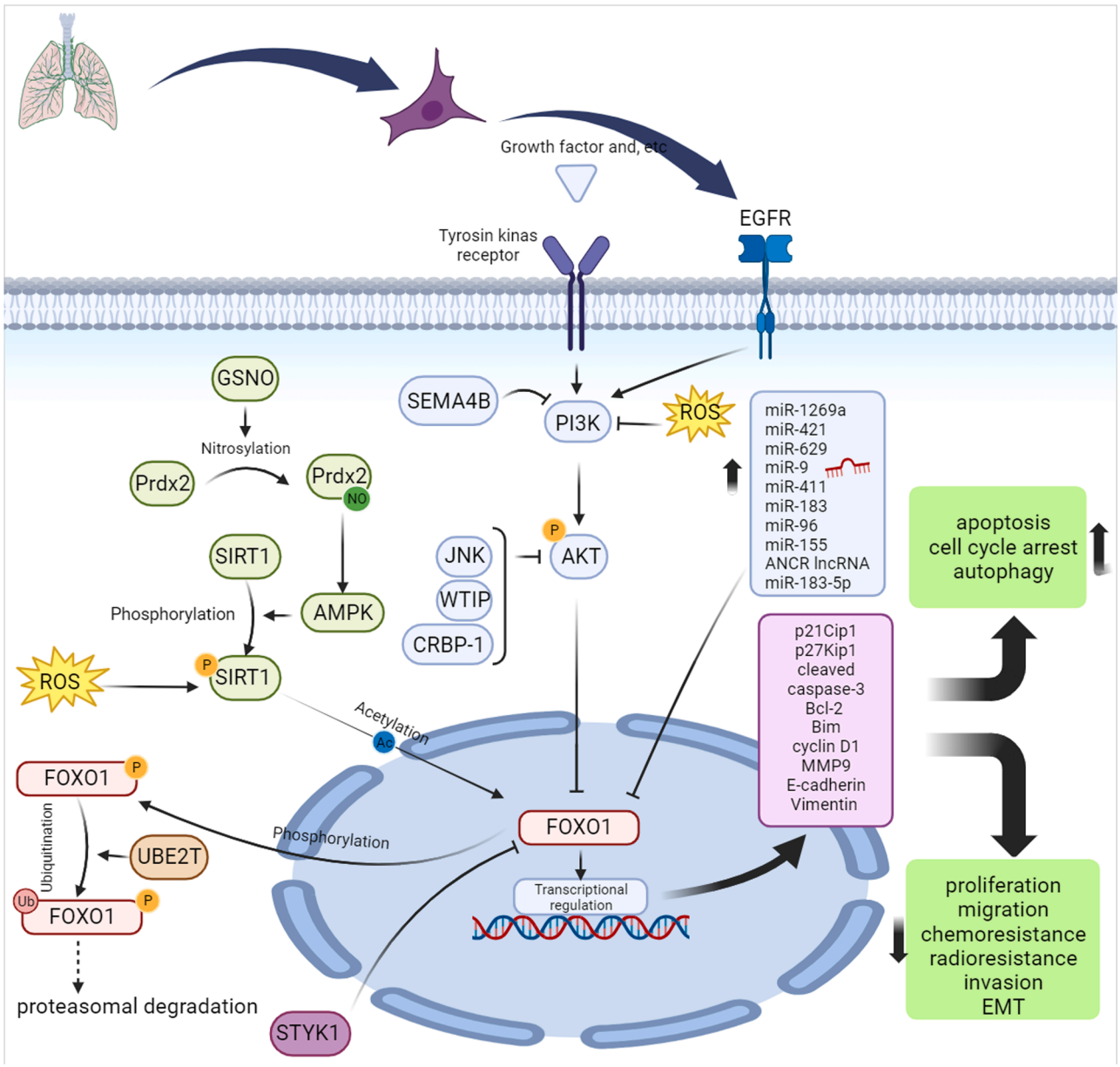

Fig. 1. A summary of FOXO1 regulation in lung cancer. Tyrosine kinases like AKT and STYK1 phosphorylate FOXO1 and decrease its nuclear accumulation. Respectively activation of some tyrosine kinases such as AMPK and JNK stimulates FOXO1 by inhibiting SIRT1 and AKT. More importantly, oxidative stress could inactivate PI3K and SIRT1 and facilitates the nuclear translocation of FOXO1. Several oncogenic miRNAs which are overexpressed in lung cancer cell lines downregulate FOXO1 expression. In the nucleus, FOXO1 can transcriptionally regulate the expression of target genes via binding to their promoter. Altogether, the mechanisms leading to transcriptional activation of FOXO1 increase apoptosis, cell cycle arrest, and palliate proliferation, invasion, and drug resistance in lung cancer cells.

most malignancies [96]. In vivo and in vitro *experiments of Zhang et al. showed that* CNB potentiates FOXO1 expression by inhibiting the expression of *G9a leading to the suppression of* proliferating cell nuclear antigen (PCNA), CK8, a migration-related protein, and increasing the expression of pro-apoptotic protein such as Bim, PUMA, Bcl-2, PARP, Caspase3/8 [95].

It also has been recognized that FOXO1 is associated with the anti-cancer mechanism of well-known chemo drugs such as EGFR-TKIs, which are mostly considered as first-line therapy in NSCLC patients [75,97]. EGFR-TKIs such as erlotinib function through the inactivation of two significant signaling pathways in cancer; Ras/MAPK and PI3K/Akt pathway which FOXO1 could be upregulated mostly through inhibited PI3K/Akt pathway [98]. The latest research finding has noticed that except for the PI3K/Akt pathway, some other regulators like miRNA could be responsible for EGFR-TKI-related FOXO1 expression. In this regard, miR-9 is an overexpressed oncogenic ncRNA in lung cancer tissues, which directly binds to its 3′-UTR region of FOXO1 and negatively regulates FOXO1 translation. It has been implicated that erlotinib may downregulate miR-9 expression through DNA methylation which further facilitates the FOXO1 expression [75].

Except for chemotherapy, radiotherapy and surgical resection as conventional therapeutic methods, immunotherapy has revolutionized lung cancer treatment efficacy and considerably increased overall patient survival, particularly for advanced patients [99,100]. Fascinatingly, novel approaches have ascertained that FOXO1 can regulate the immune system components and may provide a possible target in lung cancer immunotherapy. A well-known study on mice lung cancer hypothesized that the enhanced tumor suppressor ability of tumor-specific

Table 6
FOXO1 and radio/chemoresistance in lung cancer.

Upstream regulator	Cancer type	Axis	Model	Description	
FUT4	NSCLC	EGFR/PI3K/AKT/↓FOXO1	In vitro	"FUT4 silencing sensitizes tumor cells to cisplatin through suppressing EGFR/PI3K/AKT signaling and decrease in phosphorylation of FOXO1."	[110]
Prx1	NSCLC	AKT/↓FOXO1	In vitro/ in vivo	"Prx1 knockdown activates the caspase cascade and induces FOXO1 apoptosis via inhibition of docetaxel-induced phosphorylation of Akt and FOXO1. "	[111]
mTORC2	NSCLC	AKT/↓FOXO1	In vitro/ in vivo	"mTORC2 negatively regulates AKT and enhances the phosphorylation of FOXO1. "	[109]
Fenofibrate	NSCLC	↑PPARα ↑LXRα ↑ABCA1 ↑AMPK ↓AKT ↑FOXO1	In vitro/ in vivo	"lipid-lowering drug fenofibrate alleviates acquired resistance to gefitinib in NSCLC By inducing apoptosis via the PPAR/AMPK/AKT/FoxO1 pathway". "Enhance the expression of PPARα, ABCA1, and LXRα leading to increase the ant proliferative effects of gefitinib via reduction of the intracellular cholesterol levels."	[119]
YC-1	NSCLC	↑FOXO1	In vitro	YC-1 abrogates autophagy induced by gefitinib via inhibition of HIF-1α. "YC-1 enhances the pro-apoptotic effect of gefitinib via overexpression of FOXO1."	[121]
AKBA	Radioresistance lung cancer cells	↑maspin/↓AKT/↑FOXO1/↑p21	In vitro/ in vivo	AKBA decreases methylation of maspin and enhances its inhibitory effect on AKT leading to nuclear translocation of FOXO1	[125]

$CD4^+$ T helper 9 (T_H9) cells might be FOXO1-dependent [101]. T_H9, a highly potent effector T cell subset used in cancer immunotherapy, is differentiated from naïve $CD4^+$ T cells upon antigen stimulation in the presence of specific cytokines to mediate numerous immune responses [102]. Among these cytokines, interleukin-7 (IL-7) has been found to facilitate the differentiation of naïve $CD4^+$ T cells into T_H9 cells and augment their anticancer property. To be more specific, activated STAT5 and PI3K-AKT-mTOR pathways mediated by IL7 enhance the histone acetyltransferase p300 abundance which serves as a co-activator for FOXO1, induces its nuclear translocation, to bind to the Il9 promoter and as a consequence upregulates the protein expression of IL-9 to eventually promote differentiation and antitumor function of IL-7–T_H9 cells in mice lung tumor tissues [101]. Even more, FOXO1 has been reported to attenuate the lung metastatic burden of mice by recruiting IL-27 in the intermediate monocytes (IMo) [103]. Based on surface markers, circulating monocytes can be classified as a functionally diversified and heterogeneous cell population composed of classical monocytes (CMo), IMo, and non-CMo/patrolling monocyte (PMo) subsets. Although some debate persists, it is generally accepted that under physiological settings, IMo is a transitory stage in the differentiation of CMo to PMo [104]. IFN-γ, an inflammatory cytokine in the regulation of IMo/PMo differentiation, induced IMo expansion and hampered the metastasis of lung cancer by triggering natural killer (NK) cell expansion. In fact, it has been observed that IFN-γ provokes the transcriptional activity of FOXO1 in IMO to induce IL-27 expression and substantial NK cell expansion [103]. Altogether, most of the pharmacological compounds and immunologic responses, which influence FOXO1 were shown to enhance its expression in lung cancer (Table 5). Therefore, finding a novel mechanism to affect FOXO1 or its regulators could open up new horizons in chemotherapy, immunotherapy, and other therapeutic strategies to fight against lung malignancies. .

3.6. FOXO1 and radio/chemoresistance

Drug resistance is a significant factor in the treatment failure of NSCLC that results in cancer recurrence and its progression. Drug transporter expression alterations, pro-survival and anti-apoptotic cascade stimulation, and non-intrinsic effects of the tumor microenvironment are several instances of cell-intrinsic resistance mechanisms [106–108]. Different signaling pathways are involved in the chemo/radio-resistance of NSCLC; on top of them, there are EGFR, PI3K/AKT, and the mammalian target of rapamycin Complex 2 (mTORC2)/AKT, interestingly, most of these pathways interact with the master regulator, FOXO1 [109,110]. Therefore, it seems that targeting FOXO1 and its modification could be efficient in sensitizing resistant tumor cells during chemo/radio-resistance (Table 6)..

FOXO1 phosphorylation during lung cancer chemotherapy has attracted much more attention as one of the most important causes of tumor cell resistance. Not only FOXO1 but also its upstream regulators have a crucial role in drug resistance. Fucosyltransferase IV (FUT4) and peroxiredoxin 1 (Prx1) are two of these regulators which drive chemoresistance in lung cancer cells via influencing FOXO1 and AKT phosphorylation [110,111]. Prx1, a thiol-specific antioxidant protein, is a major member of the 2-Cys peroxiredoxin family and its level is frequently promoted in several cancers, especially lung cancer [112]. It's well established that Prx1 overexpression is associated with apoptosis inhibition during chemo or radiotherapy. Prx1 augments the phosphorylation of AKT and its substrates FOXO1 to exhibit anti-apoptotic features. More importantly docetaxel, a widely used chemo drug of NSCLC, independently inhibits FOXO1 by induction of AKT phosphorylation and resulting A549 resistance. Hwang et al. revealed that Prx1 knockdown also enhanced the sensitivity of A549 lung cancer cells to docetaxel by suppressing docetaxel-induced phosphorylation of AKT and FOXO1 leading to caspase-8 activation [111]. Similarly, fucosyltransferase IV (FUT4), a catalyzer enzyme in the biosynthesis of fucosylated polysaccharides, is another negative regulator of FOXO1 which has been overexpressed in lung cancer [110,113]. Recent reports have shown that FUT4 is involved in drug resistance of various cancers through the induction of PI3K/AKT signaling [114]. More investigations highlighted the interplay role of FOXO1 in FUT4-related chemoresistance. In A431 lung cancer cells, FUT4 inhibited FOXO1-induced apoptosis by activation of PI3K/AKT signaling via EGFR phosphorylation and more importantly attenuated the sensitivity of A431 cancer cells to cisplatin, a frequent anticancer drug applied in NSCLC [110].

Since FOXO1 is involved in cell cycle arrest and apoptosis, it plays an essential role in driving transcriptional response against chemotherapy in lung cancer. As aforementioned FOXO1 regulates NSCLC cell viability and apoptosis according to its modification; phosphorylation of FOXO1 results in cell growth, and its acetylation stimulates apoptosis [11,115]. A recent study by Xu et al. has indicated the effective role of FOXO1 in *preventing* and overcoming epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) resistance in NSCLC patients [109]. TKIs have been extensively utilized in clinical treatments with significant advantages for advanced NSCLC patients. But after receiving TKI drugs for 6–12 months, cancer cells acquire resistance to TKI [116,117]. Given that the mechanistic/mammalian target of rapamycin (mTOR)/AKT pathway is stimulated in cancers [118] and is closely associated with FOXO1 function, controlling its expression can serve as an indirect strategy for targeting FOXO1 as well. Xu and colleagues noticed that the mTORC2-AKT-FOXO1 signaling pathway was dysregulated in TKI-resistant NSCLC cells, and FOXO1 is highly phosphorylated. More

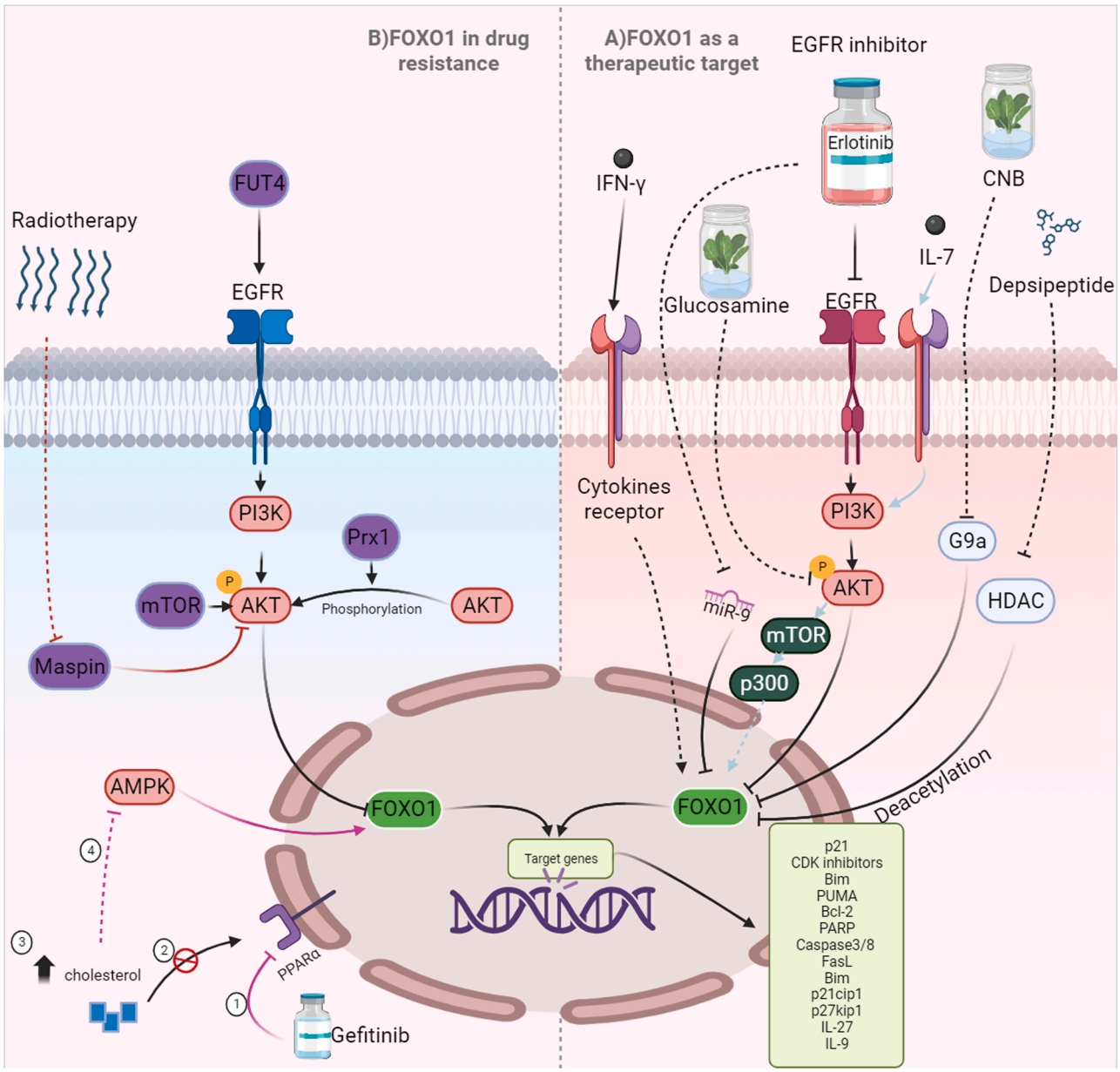

Fig. 2. A summary of FOXO1 in lung cancer treatment and its role in drug resistance. **A)** Administration of EGFR-TKIs such as erlotinib in cancerous cells could reverse the inhibitory effect of EGFR/PI3K/AKT axis on FOXO1 and augment its nuclear translocation. On the other hand, erlotinib inactivates oncogenic ncRNAs such as miR-9 to induces FOXO1 function. Other therapeutic compound such depsipeptide facilities FOXO1 acetylation by inhibition HDACs. Natural compound including CNB and glucosamine has been reputed to enhance the transcriptional activity of FOXO1. **B)** During chemotherapy of lung cancer, some upstream regulators of FOXO1 such as Prx1, FUT4, and mTOR diversely influence EGFR/PI3K/AKT cascade to inhibit FOXO1 function and increase the resistance of tumor cells. Moreover, some chemo drugs such as gefitinib increase fatty acid consumption and diminish the intracellular ATP levels by downregulation of PPARa expression. Decreased ATP level caused by fatty acid consumption inactivates AMPK and results in FOXO1 inhibition. Radiotherapy in lung cancer suppresses the inhibitory effect of maspin on AKT and decreases the nuclear translocation of FOXO1.

interestingly, they mentioned that to achieve a better antitumor effect and overcome TKI resistance, both mTORC2/AKT and PI3K/AKT should be inhibited together to acetylate FOXO1 and influence its downstream pro-apoptotic and antiproliferative genes which haven't been elucidated in this study [109].

The importance of the AKT/FOXO1 complex even gets bolder when fenofibrate, a PPARα agonist lipid-lowering drug, was confirmed to be involved in the sensitization of EGFR-TKIs resistance NSCLC cell lines by targeting this complex. Gefitinib, a widely used EGFR-TKI, dysregulates the cholesterol efflux pathway by downregulation of peroxisome proliferator-activated receptor α (PPARα) expression, which is a ligand-activated transcription factor with a key role in lipid metabolism. Downregulated PPARα enhanced intracellular cholesterol levels in gefitinib-resistant cell lines compared to gefitinib-sensitive cell lines [119]. Upon fenofibrate-related activation of PPARα, the fatty acid oxidation machinery is also likely to be transcriptionally activated, shifting energy metabolism to fatty acids consumption instead of glucose utilization [120]. As a result, PPARα activation decreased the ATP levels and enhanced the phosphorylation of AMPK. Activated AMPK suppressed AKT phosphorylation and induced FOXO1 expression to initiate the intrinsic apoptotic pathway [119]. Newer investigations have suggested that autophagy is responsible for EGFR-TKIs resistance of NSCLC cell lines with an interplay role of FOXO1 [121]. Autophagy is a conserved transport pathway that maintains cellular homeostasis by

modulating a lysosome-dependent degradative mechanism [122]. It is well established that autophagy is a crucial kinase-independent function of EGFR. EGFR signaling contributes to autophagy suppression therefore EGFR-TKI treatment of cancer cells augments autophagy which results in tumor cell survival and chemoresistance [123,124]. The study of Hu and colleagues showed that inhibition of autophagy by 3-(5-Hydroxymethyl-2-furyl)– 1-benzyl indazole (YC-1), an activator of *soluble guanylyl cyclase* with antitumor property, dramatically blocks gefitinib-induced autophagy via interrupting the junction of autophagosomes and lysosomes, hence boosting gefitinib's pro-apoptotic impact in resistant cancer cells. Intriguingly, they noticed that this phenomenon was linked to higher FOXO1 transcriptional activity, and suppressed autophagy may enhance the FOXO1 expression to exert apoptotic features in gefitinib-resistant cancer cells [121].

Apart from the impressive role of the AKT/FOXO1 pathway in mediating chemoresistance in cancer cells, this pathway has drawn much attention at the onset of radioresistance in lung cancer cells. Phosphorylation of AKT and FOXO1 may induce resistance in lung cancer cells during radiotherapy. A recent study suggested a key role for mammary serine protease inhibitor (maspin) as an upstream regulator of AKT/FOXO1 in the radioresistance A549 lung cancer cell line [125]. Maspin, a serpin protease inhibitor, functions as a tumor suppressor gene in various kinds of malignancies [126]. Furthermore, it has been reported that maspin is hypermethylated in radioresistant lung cancer cells, and its inhibition enhances the resistance of tumor cells to radiotherapy [127]. It seems that methylated maspin phosphorylates AKT and leads to the inhibition of FOXO1 in the radioresistance cancer cell. Upon maspin demethylation caused by Acetyl-keto-b-boswellic acid (AKBA), a well-known anti-tumor compound isolated from a Chinese natural plant inhibited AKT facilitates the nuclear translocation of FOXO1 which results in cell cycle arrests via increment of the p21 expression, a cyclin-dependent kinase inhibitor [125].

4. Conclusion and prospective

According to the evidence collected, a picture emerges in which FOXO1's action in lung cancer is more positive than previously believed. Studies demonstrating a tumor-supportive ability for FOXO1 provide an emerging approach that can be utilized for new insights into lung carcinogenesis and the role of its regulators in this mechanism. Additionally, while targeting the PI3K/AKT pathway has an important impact on restoring FOXO1 activity, other transcription factors and proteins are involved in its regulation. Protein kinases such as AMPK and JNK positively regulate FOXO1 and conversely, AKT and STYK1 exert a negative effect on FOXO1 expression in lung cancer. Notably, FOXO1 exhibits its tumor-suppressive role by developing a reciprocal interplay with regulators of the cell cycle like Cyclins and CDKs and pro-apoptotic proteins including Bim, PUMA, PARP, Bcl-2, and Caspase3/8. The accelerating growth of tumor cells mostly exposes them to hypoxic conditions which facilitate ROS production, oxidative stress, and DDR. More investigation on lung cancer highlighted the impressive role of excessive ROS production as an upstream regulator of FOXO1 which inhibits SIRT1 and PI3K/AKT and enhances the transcriptional activity of FOXO1. Intriguingly, the majority of FOXO1's upstream regulators are ncRNAs that target the 3′ UTR region of the FOXO1, and analysis of their outcomes potentiates the tumor-suppressor role of FOXO1 in lung malignancies. The mechanisms of action of conventional lung cancer chemotherapeutics such as erlotinib, depsipeptide, and cisplatin are inevitably associated with the FOXO1 transcription factor. Furthermore, restoring FOXO1 expression could be administered in the sensitization of lung cancer cells to docetaxel, gefitinib, or cisplatin.

However, a large amount of research on FOXO1 functions in lung cancer metabolism has been conducted in cancer cell lines. The creation of appropriate animal models should be considered for future research in order to better understand the regulatory function of FOXO1 in vivo. Elucidating the effect of FOXO1 transcriptional function in the metabolic characteristics of malignant and normal cells allows us to identify possible vulnerabilities that could be addressed by appropriate therapeutic strategies. Apart from the mentioned agents that influence FOXO1 activity, more investigation is required to identify other regulators and signaling pathways involved in FOXO1 modification. Even though some studies have authenticated the beneficial effects of FOXO1 in lung cancers, pharmacological tools that efficiently impact FOXO1 activity are still under development. Fundamental knowledge of mechanisms underlying FOXO1 regulations and how they provide particular transcriptional output will make it possible to develop medications that target FOXO1 and prepare the way for possible combination therapies and overcoming drug resistance in lung cancer.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Funding

Not applicable.

CRediT authorship contribution statement

ME, PT, and GHB wrote the article; NE and MN prepared the tables and figures; MM and BY designed and revised the article. All the authors studied and approved the final manuscript. The authors declare that all data were generated in-house and that no paper mill was used.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

Data will be made available on request.

Acknowledgments

The authors would like to thank Shohada Clinical Research Development Unit, Shohada Hospital, Tabriz University of Medical Science, Tabriz, Iran.

References

[1] R. Siegel, K. Miller, H. Fuchs, A. Jemal, Erratum to "Cancer statistics, 2021", CA Cancer J. Clin. 71 (1) (2021) 7–33.
[2] K.D. Miller, L. Nogueira, A.B. Mariotto, J.H. Rowland, K.R. Yabroff, C.M. Alfano, et al., Cancer treatment and survivorship statistics, 2019, CA: a Cancer J. Clin. 69 (5) (2019) 363–385.
[3] M. Zheng, Classification and pathology of lung cancer, Surg. Oncol. Clin. 25 (3) (2016) 447–468.
[4] C. Zappa, S.A. Mousa, Non-small cell lung cancer: current treatment and future advances, Transl. Lung Cancer Res. 5 (3) (2016) 288.
[5] B. Zulfiqar, A. Farooq, S. Kanwal, K. Asghar, Immunotherapy and targeted therapy for lung cancer: current status and future perspectives, Front. Pharmacol. 13 (2022).
[6] C. Swanton, R. Govindan, Clinical implications of genomic discoveries in lung cancer, N. Engl. J. Med. 374 (19) (2016) 1864–1873.
[7] J.H. Bushweller, Targeting transcription factors in cancer—from undruggable to reality, Nat. Rev. Cancer 19 (11) (2019) 611–624.
[8] A. Ahmad, S. Rashid, A.A. Chaudhary, A.S. Alawam, M.I. Alghonaim, S.S. Raza, R. Khan, Nanomedicine as potential cancer therapy via targeting dysregulated transcription factors. Seminars in Cancer Biology, Elsevier, 2023.
[9] D.-H. Bach, N.P. Long, T.-T.-T. Luu, N.H. Anh, S.W. Kwon, S.K. Lee, The dominant role of forkhead box proteins in cancer, Int. J. Mol. Sci. 19 (10) (2018) 3279.

[10] J. Ma, S. Matkar, X. He, X. Hua, FOXO family in regulating cancer and metabolism. Seminars in cancer biology, Elsevier, 2018.
[11] R.K. Yadav, A.S. Chauhan, L. Zhuang, B. Gan, FoxO transcription factors in cancer metabolism. Seminars in cancer biology, Elsevier, 2018.
[12] W. Li, M. Cheng, W. Zhang, R. He, H. Yang, New insights into the mechanisms of polyphenol from plum fruit inducing apoptosis in human lung cancer A549 Cells Via PI3K/AKT/FOXO1 pathway, Plant Foods Hum. Nutr. 76 (2021) 125–132.
[13] Y. Zhang, C. Sun, G. Xiao, H. Shan, L. Tang, Y. Yi, et al., S-nitrosylation of the Peroxiredoxin-2 promotes S-nitrosoglutathione-mediated lung cancer cells apoptosis via AMPK-SIRT1 pathway, Cell Death Dis. 10 (5) (2019) 329.
[14] Z. Liu, M. Huang, Y. Hong, S. Wang, Y. Xu, C. Zhong, et al., Isovalerylspiramycin I suppresses non-small cell lung carcinoma growth through ROS-mediated inhibition of PI3K/AKT signaling pathway, Int. J. Biol. Sci. 18 (9) (2022) 3714–3730.
[15] M. Rani, R. Kumari, S.P. Singh, A. Devi, P. Bansal, A. Siddiqi, et al., MicroRNAs as master regulators of FOXO transcription factors in cancer management, Life Sci. (2023), 121535.
[16] X. Feng, Z. Wu, Y. Wu, W. Hankey, T.W. Prior, L. Li, et al., Cdc25A regulates matrix metalloprotease 1 through Foxo1 and mediates metastasis of breast cancer cells, Mol. Cell. Biol. 31 (16) (2011) 3457–3471.
[17] D. Flores, A. Lopez, S. Udawant, B. Gunn, M. Keniry, The FOXO1 inhibitor AS1842856 triggers apoptosis in glioblastoma multiforme and basal-like breast cancer cells, FEBS Open Bio (2023).
[18] Z. Gao, R. Liu, N. Ye, C. Liu, X. Li, X. Guo, et al., FOXO1 inhibits tumor cell migration via regulating cell surface morphology in non-small cell lung cancer cells, Cell. Physiol. Biochem. 48 (1) (2018) 138–148.
[19] D. Weigel, G. Jürgens, F. Küttner, E. Seifert, H. Jäckle, The homeotic gene fork head encodes a nuclear protein and is expressed in the terminal regions of the Drosophila embryo, Cell 57 (4) (1989) 645–658.
[20] B.A. Benayoun, S. Caburet, R.A. Veitia, Forkhead transcription factors: key players in health and disease, Trends Genet. 27 (6) (2011) 224–232.
[21] S.S. Myatt, E.W.-F. Lam, The emerging roles of forkhead box (Fox) proteins in cancer, Nat. Rev. Cancer 7 (11) (2007) 847–859.
[22] M. Castaneda, Pd Hollander, S.A. Mani, Forkhead box transcription factors: double-edged swords in cancer, Cancer Res. 82 (11) (2022) 2057–2065.
[23] Y.-q Xing, A. Li, Y. Yang, X.-x Li, L.-n Zhang, H.-c Guo, The regulation of FOXO1 and its role in disease progression, Life Sci. 193 (2018) 124–131.
[24] K. Psenakova, K. Kohoutova, V. Obsilova, M.J. Ausserlechner, V. Veverka, T. Obsil, Forkhead domains of FOXO transcription factors differ in both overall conformation and dynamics, Cells 8 (9) (2019) 966.
[25] F. Shi, T. Li, Z. Liu, K. Qu, C. Shi, Y. Li, et al., FOXO1: another avenue for treating digestive malignancy?. Seminars in cancer biology Elsevier, 2018.
[26] A.S. Lalmansingh, S. Karmakar, Y. Jin, A.K. Nagaich, Multiple modes of chromatin remodeling by Forkhead box proteins, Biochim. Et. Biophys. Acta (BBA)-Gene Regul. Mech. 1819 (7) (2012) 707–715.
[27] Y. Wang, Y. Zhou, D.T. Graves, FOXO transcription factors: their clinical significance and regulation, BioMed. Res. Int. 2014 (2014).
[28] I. Tikhanovich, J. Cox, S.A. Weinman, Forkhead box class O transcription factors in liver function and disease, J. Gastroenterol. Hepatol. 28 (2013) 125–131.
[29] H. Daitoku, J.-i Sakamaki, A. Fukamizu, Regulation of FoxO transcription factors by acetylation and protein–protein interactions, Biochim. Et. Biophys. Acta (BBA)-Mol. Cell Res. 1813 (11) (2011) 1954–1960.
[30] H. Huang, D.J. Tindall, Regulation of FOXO protein stability via ubiquitination and proteasome degradation, Biochim. Et. Biophys. Acta (BBA)-Mol. Cell Res. 1813 (11) (2011) 1961–1964.
[31] X. Zhang, M. Rielland, S. Yalcin, S. Ghaffari, Regulation and function of FoxO transcription factors in normal and cancer stem cells: what have we learned? Curr. Drug Targets 12 (9) (2011) 1267–1283.
[32] A. Lin, H.-l Piao, L. Zhuang, D.D. Sarbassov, L. Ma, B. Gan, FoxO transcription factors promote AKT Ser473 phosphorylation and renal tumor growth in response to pharmacologic inhibition of the PI3K–AKT PathwayFoxOs regulate renal tumor suppression by PI3K–AKT inhibition, Cancer Res. 74 (6) (2014) 1682–1693.
[33] C.-Y. Han, K.-B. Cho, H.-S. Choi, H.-K. Han, K.-W. Kang, Role of FoxO1 activation in MDR1 expression in adriamycin-resistant breast cancer cells, Carcinogenesis 29 (9) (2008) 1837–1844.
[34] N. Jiang, Q. Dai, X. Su, J. Fu, X. Feng, J. Peng, Role of PI3K/AKT pathway in cancer: the framework of malignant behavior, Mol. Biol. Rep. 47 (6) (2020) 4587–4629.
[35] M.M.L. Choudhary, S. Sisodia, A review on PI3K/AKT-an signalling pathway for the cancer treatment, Eur. J. Mol. Clin. Med. (EJMCM) 9 (09) (2022).
[36] M. Szydłowski, E. Jabłońska, P. Juszczyński, FOXO1 transcription factor: a critical effector of the PI3K-AKT axis in B-cell development, Int. Rev. Immunol. 33 (2) (2014) 146–157.
[37] S. Du, H. Zheng, Role of FoxO transcription factors in aging and age-related metabolic and neurodegenerative diseases, Cell Biosci. 11 (2021) 1–17.
[38] Z. Lei, I. Ali, M. Yang, C. Yang, Y. Li, L. Li, Non-esterified fatty acid-induced apoptosis in bovine granulosa cells via ROS-activated PI3K/AKT/FoxO1 pathway, Antioxidants 12 (2) (2023) 434.
[39] C. Xu, C. Wu, Y. Xia, Z. Zhong, X. Liu, J. Xu, et al., WT1 promotes cell proliferation in non-small cell lung cancer cell lines through up-regulating cyclin D1 and p-pRb in vitro and in vivo, PLoS One 8 (8) (2013), e68837.
[40] Z. Wu, M. Qiu, Z. Mi, M. Meng, Y. Guo, X. Jiang, et al., WT1–interacting protein inhibits cell proliferation and tumorigenicity in non-small-cell lung cancer via the AKT/FOXO1 axis, Mol. Oncol. 13 (5) (2019) 1059–1074.
[41] H. Jian, B. Liu, J. Zhang, Hypoxia and hypoxia-inducible factor 1 repress SEMA4B expression to promote non-small cell lung cancer invasion, Tumor Biol. 35 (2014) 4949–4955.
[42] H. Jian, Y. Zhao, B. Liu, S. Lu, SEMA4B inhibits growth of non-small cell lung cancer in vitro and in vivo, Cell. Signal. 27 (6) (2015) 1208–1213.
[43] A. Ferlosio, E. Doldo, S. Agostinelli, G. Costanza, F. Centofanti, A. Sidoni, A. Orlandi, Cellular retinol binding protein 1 transfection reduces proliferation and AKT-related gene expression in H460 non-small lung cancer cells, Mol. Biol. Rep. 47 (2020) 6879–6886.
[44] M. Zheng, C. Hu, M. Wu, Y.E. Chin, Emerging role of SIRT2 in non-small cell lung cancer, Oncol. Lett. 22 (4) (2021) 1–9.
[45] L. Bai, G. Lin, L. Sun, Y. Liu, X. Huang, C. Cao, et al., Upregulation of SIRT6 predicts poor prognosis and promotes metastasis of non-small cell lung cancer via the ERK1/2/MMP9 pathway, Oncotarget 7 (26) (2016) 40377.
[46] S. Dilmac, N. Kuscu, A. Caner, S. Yildirim, B. Yoldas, A.A. Farooqi, G. Tanriover, SIRT1/FOXO signaling pathway in breast cancer progression and metastasis, Int. J. Mol. Sci. 23 (18) (2022) 10227.
[47] K. Zhang, D. Chen, K. Ma, X. Wu, H. Hao, S.N.A.D. P. Jiang, H: quinone oxidoreductase 1 (NQO1) as a therapeutic and diagnostic target in cancer, J. Med. Chem. 61 (16) (2018) 6983–7003.
[48] H. Liu, R. Xing, X. Cheng, Q. Li, F. Liu, H. Ye, et al., De-novo NAD+ synthesis regulates SIRT1-FOXO1 apoptotic pathway in response to NQO1 substrates in lung cancer cells, Oncotarget 7 (38) (2016) 62503.
[49] J.F. Alhmoud, J.F. Woolley, A.-E. Al Moustafa, M.I. Malki, DNA damage/repair management in cancers, Cancers 12 (4) (2020) 1050.
[50] M. Wang, S. Chen, D. Ao, Targeting DNA repair pathway in cancer: mechanisms and clinical application, MedComm 2 (4) (2021) 654–691.
[51] J. Aengenvoort, M. Sekeres, P. Proksch, G. Fritz, Targeting mechanisms of the DNA damage response (DDR) and DNA repair by natural compounds to improve cAT-triggered tumor cell death, Molecules 27 (11) (2022) 3567.
[52] Y. Ju, T. Xu, H. Zhang, A. Yu, FOXO1-dependent DNA damage repair is regulated by JNK in lung cancer cells, Int. J. Oncol. 44 (4) (2014) 1284–1292.
[53] H. Yin, X. Wang, X. Zhang, Y. Zeng, Q. Xu, W. Wang, et al., UBE2T promotes radiation resistance in non-small cell lung cancer via inducing epithelial-mesenchymal transition and the ubiquitination-mediated FOXO1 degradation, Cancer Lett. 494 (2020) 121–131.
[54] S. Caito, S. Rajendrasozhan, S. Cook, S. Chung, H. Yao, A.E. Friedman, et al., SIRT1 is a redox-sensitive deacetylase that is post-translationally modified by oxidants and carbonyl stress, FASEB J. 24 (9) (2010) 3145–3159.
[55] M.S.Z. Ansari, V. Stagni, A. Iuzzolino, D. Rotili, A. Mai, D. Del Bufalo, et al., Pharmacological targeting of CBP/p300 drives a redox/autophagy axis leading to senescence-induced growth arrest in non-small cell lung cancer cells, Cancer Gene Ther. 30 (1) (2023) 124–136.
[56] Q. Zhang, F. Lin, J. Huang, C. Xiong, Mechanical transmission enables EMT cancer cells to drive epithelial cancer cell migration to guide tumor spheroid disaggregation, Sci. China Life Sci. 65 (10) (2022) 2031–2049.
[57] Y. Lai, F. Lin, X. Wang, J. Zhang, J. Xia, Y. Sun, et al., STYK1/NOK promotes metastasis and epithelial-mesenchymal transition in non-small cell lung cancer by suppressing FoxO1 signaling, Front. Cell Dev. Biol. 9 (2021), 621147.
[58] P. Chen, W.-M. Li, Q. Lu, J. Wang, X.-L. Yan, Z.-P. Zhang, X.-F. Li, Clinicopathologic features and prognostic implications of NOK/STYK1 protein expression in non-small cell lung cancer, BMC Cancer 14 (2014) 1–7.
[59] Z. Ma, D. Liu, W. Li, S. Di, Z. Zhang, J. Zhang, et al., STYK1 promotes tumor growth and metastasis by reducing SPINT2/HAI-2 expression in non-small cell lung cancer, Cell Death Dis. 10 (6) (2019) 435.
[60] J.K. Guo, M. Guttman, Regulatory non-coding RNAs: everything is possible, but what is important? Nat. Methods 19 (10) (2022) 1156–1159.
[61] L. Statello, C.-J. Guo, L.-L. Chen, M. Huarte, Gene regulation by long non-coding RNAs and its biological functions, Nat. Rev. Mol. Cell Biol. 22 (2) (2021) 96–118.
[62] H. Yan, P. Bu, Non-coding RNA in cancer, Essays Biochem. 65 (4) (2021) 625–639.
[63] H. Yang, C. Qi, B. Li, L. Cheng, Non-coding RNAs as novel biomarkers in cancer drug resistance, Curr. Med. Chem. 29 (5) (2022) 837–848.
[64] T. Annese, R. Tamma, M. De Giorgis, D. Ribatti, microRNAs biogenesis, functions and role in tumor angiogenesis, Front. Oncol. 10 (2020), 581007.
[65] E. Uzuner, G.T. Ulu, S.B. Gürler, Y. Baran, The role of MiRNA in cancer: pathogenesis, diagnosis, and treatment, miRNomics: Micro Biol. Comput. Anal. (2022) 375–422.
[66] S. Oliveto, M. Mancino, N. Manfrini, S. Biffo, Role of microRNAs in translation regulation and cancer, World J. Biol. Chem. 8 (1) (2017) 45.
[67] J. Wang, X. Tian, R. Han, X. Zhang, X. Wang, H. Shen, et al., Downregulation of miR-486-5p contributes to tumor progression and metastasis by targeting protumorigenic ARHGAP5 in lung cancer, Oncogene 33 (9) (2014) 1181–1189.
[68] J. Zhang, Y. Cui, X. Lin, G. Zhang, Z. Li, MiR-122-3p sensitizes breast cancer cells to ionizing radiation via controlling of cell apoptosis, migration and invasion, Int J. Clin. Exp. Pathol. 10 (1) (2017) 215–223.
[69] W. Wang, J. Yang, F. Yu, W. Li, L. Wang, H. Zou, X. Long, MicroRNA-122-3p inhibits tumor cell proliferation and induces apoptosis by targeting Forkhead box O in A549 cells, Oncol. Lett. 15 (2) (2018) 2695–2699.
[70] N. Yang, Y. Liang, P. Yang, T. Yang, L. Jiang, Propofol inhibits lung cancer cell viability and induces cell apoptosis by upregulating microRNA-486 expression, Braz. J. Med. Biol. Res. 50 (2017).
[71] C. Wang, E. Liu, W. Li, J. Cui, T. Li, MiR-3188 inhibits non-small cell lung cancer cell proliferation through FOXO1-mediated mTOR-p-PI3K/AKT-c-JUN signaling pathway, Front. Pharmacol. 9 (2018), 1362.

[72] Y. Peng, P. Zhang, X. Huang, Q. Yan, M. Wu, R. Xie, et al., Direct regulation of FOXK1 by C-jun promotes proliferation, invasion and metastasis in gastric cancer cells, Cell Death Dis. 7 (11) (2016) e2480-e.
[73] Y. Peng, Y. Wang, C. Zhou, W. Mei, C. Zeng, PI3K/Akt/mTOR pathway and its role in cancer therapeutics: are we making headway? Front. Oncol. 12 (2022), 819128.
[74] L. Zhang, H. Quan, S. Wang, X. Li, X. Che, MiR-183 promotes growth of non-small cell lung cancer cells through FoxO1 inhibition, Tumor Biol. 36 (2015) 8121–8126.
[75] X. Chen, L. Zhu, Z. Ma, G. Sun, X. Luo, M. Li, et al., Oncogenic miR-9 is a target of erlotinib in NSCLCs, Sci. Rep. 5 (1) (2015), 17031.
[76] X.-M. Mo, P.-F. Qin, B. Wang, F.-H. Liu, H.-H. Li, miR-421 promotes the viability of A549 lung cancer cells by targeting forkhead box O1, Oncol. Lett. 20 (6) (2020), 1-.
[77] L. Zhu, Y. Chen, J. Liu, K. Nie, Y. Xiao, H. Yu, MicroRNA-629 promotes the tumorigenesis of non-small-cell lung cancer by targeting FOXO1 and activating PI3K/AKT pathway, Cancer Biomark. 29 (3) (2020) 347–357.
[78] H. Ding, M. Chu, J. Yue, H. Huang, J. Wang, L. Zhu, MiR-96 induced non-small-cell lung cancer progression through competing endogenous RNA network and affecting EGFR signaling pathway, Iran. J. Basic Med. Sci. 22 (8) (2019) 908.
[79] S. Rajakumar, S. Jamespaulraj, Y. Shah, P. Kejamurthy, M. Jaganathan, G. Mahalingam, K. Ramya Devi, Long non-coding RNAs: an overview on miRNA sponging and its co-regulation in lung cancer, Mol. Biol. Rep. 50 (2) (2023) 1727–1741.
[80] C. Ni, P. Teng, P. Hu, Effects of ANCR lncRNA on the biological behaviors of lung cancer cells A549 and the mechanism, Transl. Cancer Res. 9 (8) (2020) 4693.
[81] Dodangeh F., Sadeghi Z., Maleki P., Raheb J. Long non-coding RNA SOX2OT enhances cancer biological traits via sponging to tumor suppressor miR-122–3p and miR-194–5p in non-small cell lung carcinoma. 2022.
[82] C. Guo, H. Shi, Y. Shang, Y. Zhang, J. Cui, H. Yu, LncRNA LINC00261 overexpression suppresses the growth and metastasis of lung cancer via regulating miR-1269a/FOXO1 axis, Cancer Cell Int. 20 (2020) 1–15.
[83] H.-H. Chen, T.-N. Zhang, Q.-J. Wu, X.-M. Huang, Y.-H. Zhao, Circular RNAs in lung cancer: recent advances and future perspectives, Front. Oncol. 11 (2021), 664290.
[84] F. Wang, C. Yu, L. Chen, S. Xu, Landscape of circular RNAs in different types of lung cancer and an emerging role in therapeutic resistance, Int. J. Oncol. 62 (2) (2023) 1–23.
[85] S. Ghafouri-Fard, M.E. Dinger, P. Maleki, M. Taheri, M. Hajiesmaeili, Emerging role of circular RNAs in the pathobiology of lung cancer, Biomed. Pharmacother. 141 (2021), 111805.
[86] X. Li, B. Yang, H. Ren, T. Xiao, L. Zhang, L. Li, et al., Hsa_circ_0002483 inhibited the progression and enhanced the Taxol sensitivity of non-small cell lung cancer by targeting miR-182-5p, Cell Death Dis. 10 (12) (2019) 953.
[87] W.-X. Zhao, Y.-L. Tang, W.-H. Wang, M.-W. Bao, Up-regulation of circ_0000353 impedes the proliferation and metastasis of non-small cell lung cancer cells via adsorbing miR-411-5p and increasing forkhead box O1, Cancer Biomark. 29 (1) (2020) 25–37.
[88] X. Wang, X. Jiang, J. Li, J. Wang, H. Binang, S. Shi, et al., Serum exosomal miR-1269a serves as a diagnostic marker and plays an oncogenic role in non-small cell lung cancer, Thorac. Cancer 11 (12) (2020) 3436–3447.
[89] Z. Zhao, L. Qin, S. Li, miR-411 contributes the cell proliferation of lung cancer by targeting FOXO1, Tumor Biol. 37 (2016) 5551–5560.
[90] L. Hou, J. Chen, Y. Zheng, C. Wu, Critical role of miR-155/FoxO1/ROS axis in the regulation of non-small cell lung carcinomas, Tumor Biol. 37 (2016) 5185–5192.
[91] Y. Deng, Z. He, X. Luo, R. Qiu, Y. Zhao, W. Luo, MiR-183-5p promotes the progression of non-small cell lung cancer through targeted regulation of FOXO1, Oncol. Transl. Med. 9 (3) (2023) 121–132.
[92] T. Sun, J. Zhang, B. Deng, X. Fan, T. Long, H. Jin, et al., FOXO1 and FOXO3a sensitize non-small-cell lung cancer cells to cisplatin-induced apoptosis independent of Bim, Acta Biochim. Et. Biophys. Sin. 52 (12) (2020) 1348–1359.
[93] Y. Yang, Y. Zhao, W. Liao, J. Yang, L. Wu, Z. Zheng, et al., Acetylation of FoxO1 activates Bim expression to induce apoptosis in response to histone deacetylase inhibitor depsipeptide treatment, Neoplasia 11 (4) (2009) 313–IN1.
[94] Z. Yu, Y. Ju, H. Liu, Anti-lung cancer effect of glucosamine by suppressing the phosphorylation of FOXO, Mol. Med. Rep. 16 (3) (2017) 3395–3400.
[95] L. Zhang, B. Liang, H. Xu, Y. Gong, W. Hu, Z. Jin, et al., Cinobufagin induces FOXO1-regulated apoptosis, proliferation, migration, and invasion by inhibiting G9a in non-small-cell lung cancer A549 cells, J. Ethnopharmacol. 291 (2022), 115095.
[96] F. Casciello, K. Windloch, F. Gannon, J.S. Lee, Functional role of G9a histone methyltransferase in cancer, Front. Immunol. 6 (2015) 487.
[97] L. Wu, L. Ke, Z. Zhang, J. Yu, X. Meng, Development of EGFR TKIs and options to manage resistance of third-generation EGFR TKI osimertinib: conventional ways and immune checkpoint inhibitors, Front. Oncol. 10 (2020), 602762.
[98] J. Sangodkar, N.S. Dhawan, H. Melville, V.J. Singh, E. Yuan, H. Rana, et al., Targeting the FOXO1/KLF6 axis regulates EGFR signaling and treatment response, J. Clin. Investig. 122 (7) (2012) 2637–2651.
[99] A. Lahiri, A. Maji, P.D. Potdar, N. Singh, P. Parikh, B. Bisht, et al., Lung cancer immunotherapy: progress, pitfalls, and promises, Mol. Cancer 22 (1) (2023), 40.
[100] F. Alemi, R. Zarezadeh, A.R. Sadigh, H. Hamishehkar, M. Rahimi, M. Majidinia, et al., Graphene oxide and reduced graphene oxide: efficient cargo platforms for cancer theranostics, J. Drug Deliv. Sci. Technol. 60 (2020), 101974.
[101] E. Bi, X. Ma, Y. Lu, M. Yang, Q. Wang, G. Xue, et al., Foxo1 and Foxp1 play opposing roles in regulating the differentiation and antitumor activity of T(H)9 cells programmed by IL-7, Sci. Signal 10 (500) (2017).
[102] Y. Lu, Q. Wang, G. Xue, E. Bi, X. Ma, A. Wang, et al., Th9 cells represent a unique subset of CD4(+) T cells endowed with the ability to eradicate advanced tumors, Cancer Cell 33 (6) (2018) 1048–1060, e7.
[103] R. Wang, W. Bao, M. Pal, Y. Liu, K. Yazdanbakhsh, H. Zhong, Intermediate monocytes induced by IFN-γ inhibit cancer metastasis by promoting NK cell activation through FOXO1 and interleukin-27, J. Immunother. Cancer 10 (1) (2022).
[104] P.B. Narasimhan, P. Marcovecchio, A.A.J. Hamers, C.C. Hedrick, Nonclassical monocytes in health and disease, Annu Rev. Immunol. 37 (2019) 439–456.
[105] Z. Hu, P. Zhao, H. Xu, Hyperoside exhibits anticancer activity in non-small cell lung cancer cells with T790M mutations by upregulating FoxO1 via CCAT1, Oncol. Rep. 43 (2) (2020) 617–624.
[106] V. Sosa Iglesias, L. Giuranno, L.J. Dubois, J. Theys, M. Vooijs, Drug resistance in non-small cell lung cancer: a potential for NOTCH targeting? Front. Oncol. 8 (2018), 267.
[107] M. Vaghari-Tabari, M. Majidinia, S. Moein, D. Qujeq, Z. Asemi, F. Alemi, et al., MicroRNAs and colorectal cancer chemoresistance: New solution for old problem, Life Sci. 259 (2020), 118255.
[108] B. Yousefi, N. Zarghami, N. Samadi, M. Majidinia, Peroxisome proliferator-activated receptors and their ligands in cancer drug-resistance: opportunity or challenge, Anti-Cancer Agents Med. Chem. (Former. Curr. Med. Chem. -Anti-Cancer Agents) 16 (12) (2016) 1541–1548.
[109] Z.-h Xu, W.-w Shun, J.-b Hang, B.-l Gao, J.-a Hu, Posttranslational modifications of FOXO1 regulate epidermal growth factor receptor tyrosine kinase inhibitor resistance for non-small cell lung cancer cells, Tumor Biol. 36 (2015) 5485–5495.
[110] W. Gao, J. Liang, Y. Ye, J. Lu, T. Lin, N. Wang, et al., FUT4siRNA augments the chemosensitivity of non-small cell lung cancer to cisplatin through activation of FOXO1-induced apoptosis, BMC Cancer 20 (1) (2020) 1–10.
[111] K.-E. Hwang, D.-S. Park, Y.-S. Kim, B.-R. Kim, S.-N. Park, M.-K. Lee, et al., Prx1 modulates the chemosensitivity of lung cancer to docetaxel through suppression of FOXO1-induced apoptosis, Int. J. Oncol. 43 (1) (2013) 72–78.
[112] H. Jiang, L. Wu, M. Mishra, H.A. Chawsheen, Q. Wei, Expression of peroxiredoxin 1 and 4 promotes human lung cancer malignancy, Am. J. Cancer Res. 4 (5) (2014) 445.
[113] L. Tian, D. Shen, X. Li, X. Shan, X. Wang, Q. Yan, J. Liu, Ginsenoside Rg3 inhibits epithelial-mesenchymal transition (EMT) and invasion of lung cancer by down-regulating FUT4, Oncotarget 7 (2) (2016) 1619.
[114] X.S. Yang, S. Liu, Y.J. Liu, J.W. Liu, T.J. Liu, X.Q. Wang, Q. Yan, Overexpression of fucosyltransferase IV promotes A431 cell proliferation through activating MAPK and PI3K/Akt signaling pathways, J. Cell. Physiol. 225 (2) (2010) 612–619.
[115] M. Farhan, M. Silva, X. Xingan, Y. Huang, W. Zheng, Role of FOXO transcription factors in cancer metabolism and angiogenesis, Cells 9 (7) (2020) 1586.
[116] D.B. Costa, S. Kobayashi, D.G. Tenen, M.S. Huberman, Pooled analysis of the prospective trials of gefitinib monotherapy for EGFR-mutant non-small cell lung cancers, Lung Cancer 58 (1) (2007) 95–103.
[117] R. Shah, J.F. Lester, Tyrosine kinase inhibitors for the treatment of EGFR mutation-positive non–small-cell lung cancer: A clash of the generations, Clin. Lung Cancer 21 (3) (2020) e216–e228.
[118] Z. Zou, T. Tao, H. Li, X. Zhu, mTOR signaling pathway and mTOR inhibitors in cancer: Progress and challenges, Cell Biosci. 10 (1) (2020) 1–11.
[119] M.-s Wang, Q.-s Han, Z.-r Jia, C.-s Chen, C. Qiao, Q.-q Liu, et al., PPARα agonist fenofibrate relieves acquired resistance to gefitinib in non-small cell lung cancer by promoting apoptosis via PPARα/AMPK/AKT/FoxO1 pathway, Acta Pharmacol. Sin. 43 (1) (2022) 167–176.
[120] J. Zou, L. Hong, C. Luo, Z. Li, Y. Zhu, T. Huang, et al., Metformin inhibits estrogen-dependent endometrial cancer cell growth by activating the AMPK–FOXO 1 signal pathway, Cancer Sci. 107 (12) (2016) 1806–1817.
[121] H. Hu, X.-W. Zhang, L. Li, M.-N. Hu, W.-Q. Hu, J.-Y. Zhang, et al., Inhibition of autophagy by YC-1 promotes gefitinib induced apoptosis by targeting FOXO1 in gefitinib-resistant NSCLC cells, Eur. J. Pharmacol. 908 (2021), 174346.
[122] W. Cao, J. Li, K. Yang, D. Cao, An overview of autophagy: mechanism, regulation and research progress, Bull. Cancer 108 (3) (2021) 304–322.
[123] B. Jutten, K. Rouschop, EGFR signaling and autophagy dependence for growth, survival, and therapy resistance, Cell Cycle 13 (1) (2014) 42–51.
[124] S. Sugita, K. Ito, Y. Yamashiro, S. Moriya, X.-F. Che, T. Yokoyama, et al., EGFR-independent autophagy induction with gefitinib and enhancement of its cytotoxic effect by targeting autophagy with clarithromycin in non-small cell lung cancer cells, Biochem. Biophys. Res. Commun. 461 (1) (2015) 28–34.
[125] C. Gong, W. Li, J. Wu, Y.-Y. Li, Y. Ma, L.-W. Tang, AKBA inhibits radiotherapy resistance in lung cancer by inhibiting maspin methylation and regulating the AKT/FOXO1/p21 axis, J. Radiat. Res. 64 (1) (2023) 33–43.
[126] T.M. Bodenstine, R.E. Seftor, Z. Khalkhali-Ellis, E.A. Seftor, P.A. Pemberton, M. J. Hendrix, Maspin: molecular mechanisms and therapeutic implications, Cancer Metastas-.-. Rev. 31 (2012) 529–551.
[127] E. Kim, A. Park, S. Dong, J. Ahn, W. Park, Global analysis of CpG methylation reveals epigenetic control of the radiosensitivity in lung cancer cell lines, Oncogene 29 (33) (2010) 4725–4731.