

mTOR in radiotherapy of lung cancer: Mechanisms of radiation resistance and therapeutic implications (Review)

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Received June 3, 2025; Accepted November 11, 2025

DOI: 10.3892/ijo.2025.5834

Abstract. Radiotherapy is an important treatment for tumors; however, some patients exhibit poor sensitivity to radiation, leading to unsatisfactory outcomes. mTOR regulates critical processes such as cell proliferation, autophagy and DNA repair, serving a central role in tumor biology. Moreover, mTOR inhibitors have shown potential to enhance radiotherapy effectiveness and address radiation resistance. Although drug resistance and side effects limit their clinical use, combining therapies and optimizing treatment plans could improve results. The present review summarizes how mTOR signaling contributes to radiation resistance in lung cancer, as well as the underlying molecular mechanisms. Understanding these pathways may aid the development of new combination therapies to improve treatment options for patients with lung cancer.

Contents

1. Introduction
2. mTOR protein
3. mTOR in lung cancer pathogenesis
4. mTOR and radioresistance in lung cancer
5. Clinical applications and future prospects of mTOR inhibitors
6. Conclusion

1. Introduction

Lung cancer is a prevalent malignancy worldwide; according to the latest GLOBOCAN report, ~2.48 million new lung cancer cases are diagnosed each year and it accounts for 12.4% of global cancer incidence, thus ranking as the most common cancer globally. In addition, lung cancer is the leading cause of cancer-related deaths, with an estimated 1.8 million fatalities representing 18.7% of total cancer mortality. Notably, China bears the highest lung cancer incidence and mortality rates worldwide (1).

Radiotherapy serves as a primary treatment for lung cancer across different stages and pathological types, markedly improving local control rates and survival (2,3). However, intrinsic or acquired radioresistance remains a clinical challenge to treatment outcomes and patient prognosis (4,5).

mTOR serves pivotal roles in cell proliferation, metabolism and survival (6). In lung cancer, abnormal activation of mTOR is closely associated with tumor development (7). In addition, accumulating evidence (8,9) has demonstrated that mTOR not only promotes tumor cell proliferation but also mediates radioresistance. Furthermore, mTOR signaling exhibits crosstalk with other key pathways, particularly PI3K/AKT. This crosstalk further complicates the mechanisms of radiotherapy resistance in lung cancer (10). These findings position mTOR inhibitors as promising agents to overcome radioresistance. Notably, rapamycin and its derivatives have demonstrated therapeutic potential across various types of cancer, including lung, breast, liver and colorectal cancer (11-14).

The present review focuses on the role of mTOR in lung cancer radioresistance, explores associated molecular

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Abbreviations: DFS, disease-free survival; G6PD, glucose-6-phosphate dehydrogenase; HIF-1 α , hypoxia-inducible factor-1 α ; IR, irradiation; KD, knockdown; OE, overexpression; PDCD4, programmed cell death 4; SBRT, stereotactic body radiotherapy; STMN1, stathmin 1

Key words: mTOR, mTOR inhibitor, lung cancer, radioresistance, resistance mechanisms

mechanisms and evaluates the clinical prospects of mTOR inhibitors for enhancing radiotherapy efficacy. To achieve this, a systematic literature search was conducted. PubMed (<https://pubmed.ncbi.nlm.nih.gov/>), Web of Science (<https://www.webofscience.com/>) and Scopus (<https://www.scopus.com/>) were searched up to May 2024 using key words such as ‘mTOR’, ‘lung cancer’, ‘radiotherapy resistance’, ‘mTOR inhibitors’, ‘PI3K/AKT’, ‘SCLC’ and ‘immunotherapy’. Findings from original research, including *in vitro* cellular experiments and *in vivo* animal models, were subsequently assessed, as well as relevant clinical trials, meta-analyses and other review articles. Notably, non-peer-reviewed materials were excluded unless critical original data were required. By synthesizing these findings, the present review aims to elucidate how mTOR signaling mediates radioresistance and to propose optimized therapeutic strategies to improve outcomes for patients with lung cancer.

2. mTOR protein

mTOR is a highly conserved serine/threonine kinase belonging to the phosphatidylinositol kinase-related kinase family. The soil bacterium *Streptomyces hygroscopicus*, which produces rapamycin, was initially identified in 1931. Vézina *et al* (15) then discovered the molecular target of rapamycin, mTOR, in 1975 on Easter Island (Rapa Nui, Chile). The mature mTOR protein comprises 2,549 amino acid residues (molecular weight: ~289 kDa) and is encoded by the mTOR gene situated on chromosome 1p36.2. Following transcription, splicing, translation and post-translational modifications, the functional mTOR protein localizes to multiple intracellular compartments, including the endoplasmic reticulum, Golgi apparatus, mitochondrial outer membrane, lysosomes, cytoplasm and nucleus (16-18). Structurally, mTOR has two clusters of repeats at its N-terminus. Each cluster has 20 tandem HEAT repeats; HEAT stands for Huntingtin, EF3, the A subunit of PP2A, and TOR1, and these repeats form hydrophobic surfaces, which are critical for protein-protein interactions, membrane anchoring and cytoplasmic trafficking. Adjacent to these, the focal adhesion targeting (FAT) domain stabilizes protein complexes through scaffold-like interactions, while the FKBP12-rapamycin binding domain serves as the binding site for the FKBP12-rapamycin complex. The kinase domain, functioning as the catalytic core, phosphorylates serine/threonine residues in substrate proteins to regulate downstream signaling. Finally, the C-terminal FATC domain interacts spatially with the FAT domain to expose the catalytic site, a configuration essential for the enzymatic activity of mTOR (19) (Fig. 1A).

mTOR exerts its biological functions through two distinct complexes: mTOR complex (mTORC)1 and mTORC2 (Fig. 1B). mTORC1 primarily regulates cell proliferation and metabolism, with its core components including mTOR, the scaffold protein regulatory-associated protein of mTOR (Raptor), and mLST8/GβL (homologous to yeast TOR1, Kog1 and Lst8). Additional regulatory proteins such as proline-rich AKT substrate of 40 kDa and DEP domain-containing mTOR-interacting protein modulate mTORC1 activity, while Tel2 and Tti1 are involved in its assembly and stability. By sensing nutrient, energy and oxygen availability, mTORC1

controls protein synthesis, autophagy and metabolic pathways (20-22), and is potentially inhibited by rapamycin, from which its name originates. By contrast, mTORC2 governs cell survival and cytoskeletal reorganization by regulating the AKT/PKB signaling pathway (23). Its core structure comprises mTOR, the scaffold protein rapamycin-insensitive companion of mTOR, and specific subunits including mammalian stress-activated protein kinase-interacting protein 1 and Protor1/2 (homologous to yeast TOR2, Avo3, Avo1 and Bit61/2). Unlike mTORC1, mTORC2 is not directly sensitive to rapamycin inhibition. However, prolonged or high-dose rapamycin treatment may indirectly suppress mTORC2 activity. The suppression of mTORC2 activity happens in hepatocytes, adipocytes, T cells and certain cancer cells, and impairs full AKT activation, subsequently reducing cell survival and proliferation (24-26).

The mTOR signaling pathway forms a complex regulatory network essential for eukaryotic cell proliferation, metabolism and survival, integrating multiple upstream and downstream effectors, as illustrated in Fig. 1A. mTORC1 activity is regulated by upstream signals including the PI3K/AKT pathway (27,28), AMP-activated protein kinase (AMPK) (29,30) and Rag GTPases (31). By sensing cellular nutrients, energy and oxygen levels, mTORC1 coordinates protein synthesis, autophagy, and metabolic processes. Its key downstream targets, S6 kinase 1 and 4EBP1, drive protein production and cell proliferation while suppressing autophagy (20). By contrast, mTORC2 acts as a PI3K signaling effector, enhancing cell survival and cytoskeletal organization through insulin, insulin-like growth factor-1 and leptin-mediated PI3K activation (32,33). It regulates the AKT/PKB pathway to influence cell proliferation and survival (34) and mediates PKC phosphorylation to support cytoskeletal remodeling and cell migration (35,36) (Fig. 1A). Collectively, mTOR critically impacts physiological and pathological processes such as apoptosis, metabolic regulation, immune responses and carcinogenesis (37), with its aberrant activation strongly associated with cancer progression (38), thus making it a prime therapeutic target.

3. mTOR in lung cancer pathogenesis

mTOR serves a critical role in the pathogenesis of lung cancer. As a key effector of the PI3K/AKT signaling pathway, mTOR regulates tumor growth and survival by modulating cellular processes including proliferation, metabolism, apoptosis and autophagy (7,39). Recent investigations have shown that mTOR is ubiquitously activated in lung cancer, with aberrant mTOR signaling observed in both non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) (40), closely associated with tumor aggressiveness and therapy resistance (41). Table I systematically outlines PI3K/AKT/mTOR-mediated resistance mechanisms in lung cancer radiotherapy, encompassing target mechanisms, interventions (such as pharmacological inhibitors, genetic modifications and radiotherapy combinations), their functions and corresponding references.

In NSCLC, mTOR overexpression (OE) drives tumor initiation, progression and metastasis, serving as a potential therapeutic target, and multiple mechanisms contribute to this dysregulation. Granville *et al* (42) revealed that tobacco-mediated carcinogenesis is dependent on mTOR activation. This

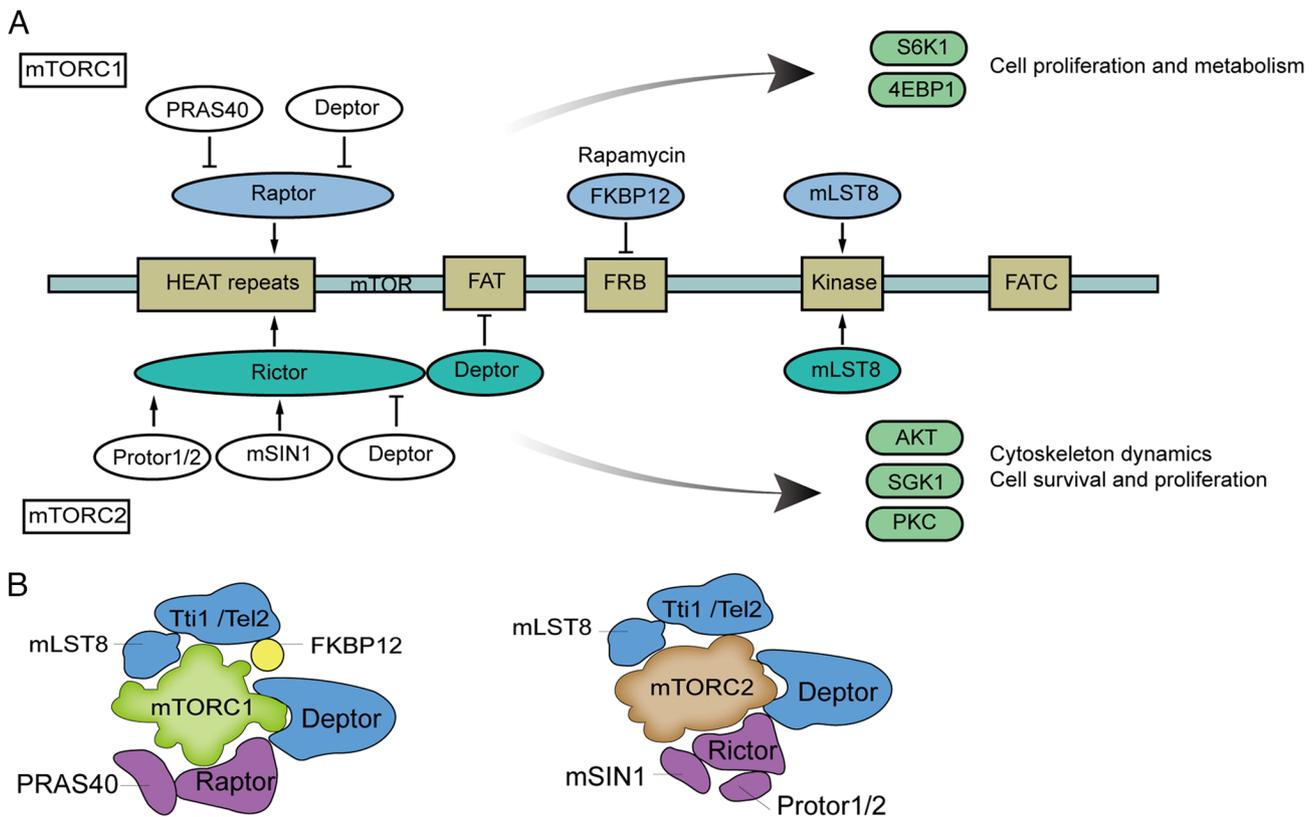


Figure 1. Structure and functional domains of mTORCs. (A) Schematic diagram illustrating the subunit compositions of mTORC1 and mTORC2, including their core components and distinct regulatory subunits. mTORC1 comprises six core subunits: mTOR, Raptor, mLST8, PRAS40, Deptor and the Tti1/Tel2 complex. This complex regulates cell proliferation via downstream effectors (4EBP1, S6K1). mTORC2 consists of seven components: mTOR, Rictor, mSIN1, Protor1/2, Deptor, mLST8 and Tti1/Tel2, and modulates cytoskeletal dynamics, cell survival and cell proliferation through AKT, SGK1 and PKC. (B) Structural schematic diagrams highlighting subunit arrangements. mTORC1 is depicted with Raptor, PRAS40, and the FRB domain, while mTORC2 shows Rictor and mSIN1. Diagrams illustrate distinct architectural features, including Raptor-mediated substrate recruitment in mTORC1 and Rictor-dependent membrane localization in mTORC2. Deptor, DEP domain-containing mTOR-interacting protein; FAT, focal adhesion targeting; FRB, FKBP12-rapamycin binding; mSIN1, mammalian stress-activated protein kinase-interacting protein 1; mTORC, mTOR complex; PRAS40, proline-rich AKT substrate of 40 kDa; Raptor, regulatory-associated protein of mTOR; Rictor, rapamycin-insensitive companion of mTOR; S6K1, S6 kinase 1.

previous study also showed that rapamycin effectively reduces the size and proliferation of tumors induced by NNK (a tobacco-specific carcinogen). This finding implicates mTOR in tobacco-related lung squamous carcinoma. Additionally, mTOR upregulation may arise from genetic mutations (such as EGFR, KRAS and ALK) disrupting PI3K/AKT signaling (43-47), epigenetic modifications (DNA methylation and histone acetylation) (48), and tumor microenvironment factors. Zhang *et al* (49) demonstrated that mTOR signaling promotes angiogenesis and metastasis in NSCLC. Inhibiting mTORC2, in turn, can suppress cell migration, metastasis and epithelial-mesenchymal transition (EMT).

Compared with NSCLC, SCLC is characterized by high aggressiveness and rapid growth, and it is often diagnosed at advanced stages. Studies have indicated that mTOR signaling is similarly hyperactivated in SCLC, and is associated with its aggressive phenotype and treatment resistance (50-52). mTOR governs SCLC growth and survival by regulating proliferation, metabolism, apoptosis and autophagy. In SCLC, MYC, a commonly amplified oncogene, activates mTOR signaling through multiple pathways, such as the PI3K/AKT and MAPK pathways, to accelerate tumor cell proliferation (53). Furthermore, eIF4E, a downstream effector of mTORC1, supports tumor growth by regulating

protein synthesis. Matsumoto *et al* (54) identified aberrant activation of the MYC-eIF4E axis as a primary driver of resistance to the mTOR inhibitor everolimus in SCLC. This finding underscores the interplay between mTOR signaling and MYC/eIF4E pathways. While both NSCLC and SCLC may benefit from mTOR pathway modulation, their therapeutic efficacy and resistance mechanisms differ. As noted, mTOR activity in NSCLC is predominantly linked to EGFR signaling, whereas resistance in SCLC involves MYC and eIF4E pathways.

4. mTOR and radioresistance in lung cancer

mTOR serves a critical role in cancer radioresistance. Radiotherapy eliminates cancer cells by inducing DNA damage; however, some tumor cells evade this effect through mTOR signaling activation, leading to radiation resistance (11,55). By regulating biological processes, such as cell proliferation, metabolism, autophagy and DNA repair, mTOR promotes cancer cell survival during radiotherapy. In lung cancer, abnormal mTOR pathway activation is strongly associated with radioresistance (56). Current evidence has demonstrated that mTOR promotes resistance to radiotherapy in lung cancer through multiple mechanisms. To provide a

Table I. PI3K/AKT/mTOR-mediated resistance mechanisms.

First author, year	Target mechanism	Intervention	Function	(Refs.)
He, 2021	AKT/mTOR pathway downregulation	Scutellarin + Iodine-125 seeds	Enhances apoptosis and inhibits proliferation	(65)
Choi, 2010	Mutant KRAS/EGFR leads to PI3K-AKT-mTOR signaling, which mediates DNA-PKcs activity	KRAS siRNA, PI3K/AKT/mTOR inhibitors	Enhances radiosensitivity via apoptosis; reduces DNA repair	(67)
Holler, 2016	Dual mTORC1 and AKT signaling mediates DNA repair (NHEJ)	Rapamycin + MK2206 (AKT inhibitor)	Impairs DNA repair; increases radiation sensitivity	(68)
Kim, 2021	Compensatory MEK/mTOR signaling	Trametinib (MEK inhibitor) + temsirolimus (mTOR inhibitor)	Reduces survival; enhances apoptosis and radiosensitivity	(64)
Zhang, 2019	AKT/mTOR signaling regulates COX-2 expression	Celecoxib + radiotherapy	Enhances apoptosis; prevents radioresistance	(69)
Xiong, 2021	SIRT6 regulates PI3K/AKT/mTOR downregulation	SIRT6 OE + radiotherapy	Enhances radiosensitivity; inhibits tumor progression	(70)
Hamid, 2021	PI3K/mTOR signaling regulates EGFR signaling	EGFR/PI3K/mTOR inhibitors	Provides selective therapeutic benefit in lung cancer models (such as A549 cells)	(71)

mTORC, mTOR complex; DNA-PKcs, DNA-dependent protein kinase catalytic subunit; NHEJ, non-homologous end joining; OE, overexpression; siRNA, small interfering RNA.

Table II. Autophagy and apoptosis modulation in radioresistance.

First author, year	Target mechanism	Intervention	Function	(Refs.)
Kim, 2008	mTOR inhibition regulates autophagy	RAD001 (mTOR inhibitor) + caspase-3 inhibitor	Improves radiotherapy efficacy	(77)
Kim, 2009	Bcl-2/mTOR signaling regulates autophagy	Rapamycin + ABT-737 (Bcl-2 inhibitor)	Enhances radiosensitization	(80)
Kim, 2013	PTEN deficiency leads to autophagy inhibition	mTOR inhibitors + PTEN KD	Restores autophagy	(81)
Kim, 2014	PI3K/mTOR blockade regulates autophagy	NVP-BEZ-235 (dual PI3K/mTORi) + radiotherapy	Enhances radiosensitivity in cisplatin-resistant NSCLC	(82)
Liang, 2015	ATM/MAPK14 regulates mTOR inhibition, which further modulates autophagy	ATM/MAPK14 KD	Reduces autophagy and enhances radiosensitivity	(83)
Zhang, 2016	STMN1 regulates PI3K/mTOR downregulation, which further modulates autophagy upregulation	STMN1 KD + X-ray	Reduces autophagy-mediated radioresistance	(84)
Lai, 2021	Maf1 phosphorylation regulates ATF5-dependent UPRmt	Rapamycin	Inhibits UPRmt	(85)

ATF5, activating transcription factor 5; KD, knockdown; NSCLC, non-small cell lung cancer; mTORi, mTOR inhibitor; STMN1, stathmin 1; UPRmt, mitochondrial unfolded protein response.

concise overview of these complex mechanisms, Tables I-IV summarize key findings from preclinical studies.

PI3K/AKT/mTOR signaling pathway and DNA repair. The PI3K/AKT/mTOR pathway is a critical intracellular signaling

Table III. miRNA-induced regulation of the mTOR pathway.

First author, year	Target mechanism	Intervention	Function	(Refs.)
Yuan, 2020	miR-410 regulates PTEN downregulation, which further leads to PI3K/mTOR upregulation	miR-410 KD, PI3K/AKT/mTOR inhibitors	Promotes EMT and radioresistance	(91)
Chen, 2022	miR-181a regulates PTEN downregulation, which further induces AKT/mTOR upregulation	miR-181a inhibitors	Reduces radiosensitivity via PTEN suppression	(93)
Jiang, 2017	miR-21 regulates PDCD4 downregulation, which further activates PI3K/AKT/mTOR upregulation	miR-21 inhibitors	Reduces radiosensitivity by decreasing apoptosis	(94)
Huang, 2021	circPVT1 acts as a miR-1208 sponge, which further leads to PI3K/mTOR upregulation	circPVT1 silencing	Enhances radiosensitivity by disrupting the ceRNA loop	(95)
Yin, 2018	miR-99a regulates mTOR downregulation	miR-99a OE/AZD2014	Enhances radiation sensitivity by inhibiting mTOR	(96)
Li, 2020	miR-101-3p regulates mTOR downregulation	miR-101-3p OE/rapamycin	Enhances radiation sensitivity by inhibiting mTOR	(98)
Tang, 2016	miR-208a regulates p21 downregulation, which further activates AKT/mTOR upregulation	miR-208a OE/KD	Promotes cell proliferation and radioresistance	(99)

ceRNA, competing endogenous RNA; circPVT1, circular PVT1; EMT, epithelial-mesenchymal transition; KD, knockdown; miRNA/miR, microRNA; OE, overexpression; PDCD4, programmed cell death 4.

cascade that regulates physiological processes, including cell proliferation, apoptosis, angiogenesis and energy metabolism in normal cells. Its aberrant activation promotes tumor progression by suppressing apoptosis, accelerating cell cycle progression, enhancing angiogenesis and promoting metastasis (57-59). In lung cancer, the PI3K/AKT/mTOR pathway is frequently activated via genetic mutations, amplifications and receptor tyrosine kinase activation. This activation is associated with intrinsic radiosensitivity, tumor cell proliferation and hypoxia, all of which contribute to radiotherapy resistance (12,60).

Mechanistically, activation of this pathway enhances radioresistance by upregulating DNA repair proteins such as DNA-dependent protein kinase catalytic subunit (DNA-PKcs), which accelerates the repair of radiation-induced DNA double-strand breaks (61,62) (Fig. 2). This enhanced DNA repair is a primary escape mechanism for irradiated tumor cells. However, Toulany *et al* (61) further revealed limitations in radiosensitizing KRAS mutant NSCLC through PI3K inhibition alone. These limitations are attributed to compensatory MEK-ERK pathway activation. Tumor cells counteract PI3K suppression by enhancing MEK-ERK signaling, which

sustains survival via AKT-dependent upregulation of DNA repair proteins (such as DNA-PKcs and Rad51), ultimately impairing radiotherapy efficacy. Dual targeting of PI3K and MEK has emerged as a promising strategy to overcome this resistance (63). Kim *et al* (64) demonstrated that combining the MEK inhibitor trametinib with the mTOR inhibitor temsirolimus may enhance radiosensitivity in NSCLC cells by boosting radiation-induced apoptosis and inducing prolonged DNA breaks.

Preclinical studies have established robust evidence implicating PI3K/AKT/mTOR pathway activation in mediating tumor cell radioresistance (Table I). For example, scutellarin combined with iodine-125 seeds targets the AKT/mTOR pathway to enhance apoptosis and inhibit proliferation in NSCLC, offering a potential therapeutic approach (65). To validate the clinical relevance of these findings, Sebastian *et al* (66) conducted a clinical study analyzing tumor samples from 92 patients with T1-3N0 NSCLC treated with stereotactic body radiotherapy (SBRT). This previous study revealed that elevated PI3K pathway activity was significantly associated with increased local recurrence risk (HR=1.72, 95% CI=1.40-98.0, P=0.023) and shorter disease-free survival

Table IV. SCLC, hypoxia and other mTOR-mediated radioresistance mechanisms in lung cancer.

First author, year	Target mechanism	Intervention	Function	(Refs.)
Chen, 2019	EMT suppression (wild-type PIK3CA/KRAS)	RAD001 (mTORC1 inhibitor) + IR	Enhances radiosensitivity by suppressing EMT-related protein expression	(90)
Deng, 2023	SCLC PI3K/mTOR signaling regulates G6PD degradation, which further induces ROS upregulation	BEZ235 and GSK2126458 (PI3K/mTOR inhibitors) + IR	Overcomes radioresistance via G6PD degradation and oxidative stress	(102)
Kim, 2009	Hypoxia/HIF-1 α stabilization (via PI3K/AKT/mTOR)	Hsp90 inhibitors (17-AAG) + radiotherapy	Blocks radiation-induced HIF-1 α stabilization, enhances antitumor effects	(105)
Subtil, 2014	Carbon ion radiotherapy regulates HIF-1 signaling and mTOR activity	Carbon ion radiotherapy	Attenuates HIF-1 signaling and mTOR induction	(106)
Jung, 2013	CXCR4 regulates STAT3/AKT/mTOR signaling	CXCR4 inhibition (AMD3100, siRNA)	Eliminates cancer stem-like cells in drug-resistant NSCLC	(107)
Dodson, 2022	NRF2-CHML-mTOR axis	CHML KD	Inhibits NSCLC progression and overcomes chemo/radioresistance	(108)
Zheng, 2016	General mTOR inhibition	Rapamycin + IR	Enhances lung cancer radiosensitivity and protects normal lung cells	(109)

EMT, epithelial-mesenchymal transition; G6PD, glucose-6-phosphate dehydrogenase; HIF-1 α , hypoxia-inducible factor-1 α ; IR, irradiation; KD, knockdown; mTORC, mTOR complex; NSCLC, non-SCLC; ROS, reactive oxygen species; SCLC, small cell lung cancer; siRNA, small interfering RNA.

(DFS) (HR=3.98, 95% CI=1.57-10.09, P=0.0035) in patients with early-stage NSCLC receiving SBRT. Mechanistically, AKT/mTOR signaling deregulation has been directly linked to chemoradiation resistance in lung squamous cell carcinoma. Proteomics analysis of chemoradiation-resistant patient-derived xenograft models and cell lines has identified upregulated phosphorylated (p)-AKT and p-mTOR, and mTOR kinase inhibitors have been shown to sensitize these resistant cells to radiation (67). For KRAS-mutated NSCLC, single targeting of PI3K often fails due to MEK/ERK-dependent Akt reactivation. Dual inhibition of PI3K and MEK, however, can block this compensatory signaling, impair DNA double-strand break repair via non-homologous end joining, and significantly enhance radiosensitivity (68).

Additionally, downstream effectors of PI3K/AKT/mTOR signaling contribute to radioresistance through multiple routes. For example, Akt/mTOR signaling-driven COX-2 overexpression fosters radioresistance, and combining celecoxib (a COX-2 inhibitor) with radiotherapy enhances apoptosis and prevents radioresistance (69). Furthermore, SIRT6, an epigenetic regulator, suppresses PI3K/Akt/mTOR signaling, and SIRT6 overexpression enhances radiosensitivity and inhibits tumor progression in lung cancer (70). Targeting these downstream nodes has shown promise. For example, dysregulated

PI3K/mTOR/EGFR crosstalk drives resistance, whereas dual inhibitors targeting EGFR and PI3K/mTOR show selective therapeutic benefit in lung cancer models, such as A549 cells (71).

However, PI3K activity showed no significant association with overall survival (P=0.49), regional recurrence (P=0.15) or distant metastasis (P=0.85) according to a study by Sebastian *et al* (66). These results position PI3K activity as a potential biomarker for predicting local recurrence and DFS in SBRT-treated NSCLC; however, validation in larger multicenter cohorts remains essential to confirm clinical applicability.

Autophagy regulation. Autophagy is a key metabolic and homeostatic mechanism that allows cells to adapt to environmental stress and damage by degrading damaged organelles, misfolded proteins and cellular debris, thereby preserving normal cellular function (72). Under physiological conditions, autophagy serves as a protective process essential for clearing dysfunctional or senescent cellular components (73). In cancer cells, however, aberrant activation of the mTOR signaling pathway suppresses autophagy, allowing tumor cells to escape radiotherapy-induced damage (74). Studies have indicated that mTOR acts as a primary negative regulator of autophagy. It

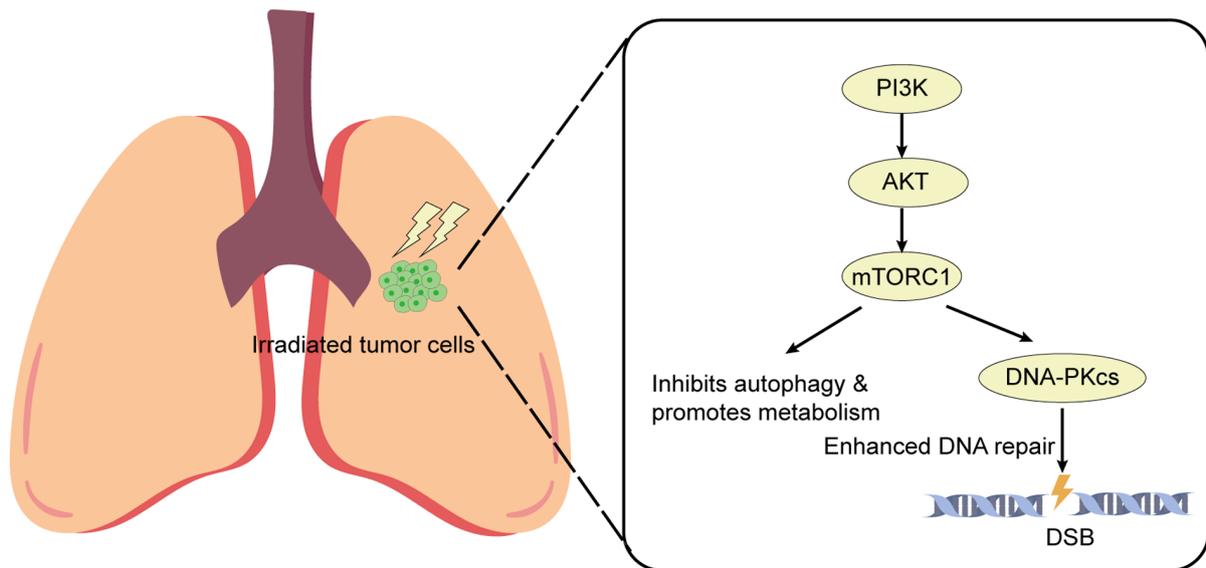


Figure 2. PI3K/AKT/mTOR pathway-mediated molecular mechanisms underlying lung cancer radioresistance. Irradiated lung tumor cells activate the PI3K/AKT/mTOR pathway, which inhibits autophagy, promotes metabolism and acts on DNA-PKcs to influence DSB repair, mediating radioresistance in lung cancer cells. DNA-PKcs, DNA-dependent protein kinase catalytic subunit; DSB, double-strand break; mTORC, mTOR complex.

not only inhibits autophagic flux but also enhances cancer cell survival by promoting growth and metabolic reprogramming, thereby fostering resistance to antitumor therapies such as radiotherapy (75,76).

In lung cancer research, the role of autophagy is complex (Table II). Kim *et al* (77) demonstrated that mTOR inhibition restores autophagic activity and enhances radiosensitivity. The findings of this previous study in cellular and murine models revealed that mTOR targeting alone fails to fully eradicate tumor cells but synergizes with radiotherapy to markedly augment apoptotic responses. This suggests that autophagy activation during radiotherapy may be modulated by apoptosis, implying that combining apoptosis inhibition with mTOR targeting may represent a novel therapeutic strategy to improve radiotherapy efficacy in patients with lung cancer.

Furthermore, Fei *et al* (78) reported that the PI3K/mTOR dual inhibitor PF-04691502 induces a senescence-like phenotype in A549 cells. This phenotype is characterized by elevated SA- β -galactosidase activity and increased LC3-II expression. This previous study also observed that co-treatment with the autophagy inhibitor chloroquine potentiates the DNA-damaging effects of the inhibitor. This observation highlights the dual role of autophagy; while its restoration by mTOR inhibitors can be sensitizing, in some contexts, inhibiting the autophagy machinery may further amplify the cytotoxic effects of PI3K/mTOR blockade. In 2020, Yan *et al* (79) investigated the interplay between autophagy and mitochondrial function by combining carbon ion irradiation (IR) with tigecycline, a glycolyline antibiotic used clinically for antimicrobial therapy and in preclinical tumor research to modulate cellular metabolism and signaling. This study demonstrated that this combination triggers severe mitochondrial dysfunction in A549 cells, marked by a notable reduction in mitochondrial ATP content and collapse of mitochondrial membrane potential. In addition, it was indicated that p-AMPK and p-AKT may antagonize mTOR signaling

through cross-talk, as demonstrated by western blot analysis of these phosphorylated proteins and downstream mTOR pathway components, modulating mitochondrial translation proteins to influence autophagy and apoptosis. Co-targeting autophagy and mTOR-associated signaling pathways may offer a more effective strategy to enhance the therapeutic efficacy of radiotherapy in lung cancer. For example, combining rapamycin with the Bcl-2 inhibitor ABT-737 enhances radiosensitization in lung cancer (80). Furthermore, restoring autophagy in PTEN-deficient contexts can be achieved with mTOR inhibitors and PTEN knockdown (81). The dual PI3K/mTOR inhibitor NVP-BEZ-235 has been shown to synergize with radiotherapy to enhance radiosensitivity in cisplatin-resistant NSCLC (82). In addition, knocking down ATM/MAPK14 reduces autophagy and boosts radiosensitivity (83), and targeting STMN1 via knockdown combined with X-ray irradiation mitigates autophagy-mediated radioresistance (84). Rapamycin also inhibits the mitochondrial unfolded protein response by modulating Maf1 phosphorylation, further impacting autophagic processes in lung cancer (85).

Collectively, these studies underline the dual role of autophagy in lung cancer therapy and highlight the central regulatory role of mTOR in autophagic processes. Co-targeting autophagy and mTOR-associated signaling pathways may offer a more effective strategy to enhance the therapeutic efficacy of radiotherapy in lung cancer.

MicroRNAs (miRNAs/miRs). miRNAs are a class of non-coding RNAs that serve pivotal roles in regulating gene expression and are frequently dysregulated in diverse types of cancer (86). Studies have revealed that miRNAs markedly contribute to tumorigenesis, progression and radioresistance by modulating cancer cell proliferation, migration, invasion and apoptosis, highlighting their potential value in early diagnosis, prognosis prediction and therapeutic intervention (87-89). In NSCLC, aberrant miRNA expression profoundly impacts

mTOR signaling pathway activity, thereby influencing radiotherapy outcomes (Table III).

miRNAs frequently promote radioresistance by suppressing tumor suppressor genes that regulate the mTOR pathway. For example, miR-410, which is commonly upregulated in cancer, promotes EMT and radioresistance by targeting PTEN to activate the PI3K/mTOR axis (90-92). OE of miR-410 has been shown to be positively associated with EMT-related markers (such as E-cadherin downregulation and vimentin upregulation) and negatively associated with PTEN expression. Genetic knockdown of miR-410 can suppress EMT and enhance radiosensitivity, suggesting it may serve as a potential biomarker or therapeutic target in NSCLC radiotherapy. Restoring PTEN expression or administering mTOR inhibitors could reverse miR-410-induced EMT and radioresistance, offering novel strategies for NSCLC-targeted therapy. Similarly, miR-181a reduces NSCLC radiosensitivity by suppressing the expression of PTEN, a negative regulator of the PI3K/AKT/mTOR pathway (93). miR-21 also reduces NSCLC radiosensitivity by targeting programmed cell death 4 to activate PI3K/AKT/mTOR signaling (94). Furthermore, Huang *et al* (95) revealed that circular PVT1 promotes radioresistance by acting as a competing endogenous RNA to sequester miR-1208, subsequently reactivating the PI3K/AKT/mTOR pathway.

Conversely, miRNAs downregulated in lung cancer enhance NSCLC radiosensitivity by directly targeting mTOR. For example, miR-99a acts via mTOR as it is highly expressed in radiation-sensitive A549 cells compared with resistant counterparts. Its OE enhances radiosensitivity, whereas its inhibition induces resistance *in vitro* and *in vivo* (96). Similarly, miR-101-3p is commonly downregulated in NSCLC tissues and cell lines (97), and modulates radiosensitivity via mTOR. Li *et al* (98) showed that in radiation-resistant A549R cells, miR-101-3p upregulation can increase radiosensitivity; however, this effect is attenuated by high mTOR activity, whereas its inhibition induces resistance that can be reversed by rapamycin. This confirms that miR-101-3p downregulation drives resistance by activating mTOR, consistent with the mechanism of miR-99a. Another example is miR-208a, which promotes cell proliferation and radioresistance in NSCLC by targeting the AKT/mTOR pathway (99). Collectively, these studies highlight mTOR as a core mediator of miRNA-regulated NSCLC radiosensitivity, supporting co-targeting mTOR and these miRNAs as a promising strategy to optimize lung cancer radiotherapy.

mTOR and SCLC-specific mechanisms. Although most research on mTOR and radioresistance focuses on NSCLC, this pathway is also pivotal in highly aggressive and resistant SCLC. The mechanisms underlying radioresistance in SCLC often involve unique metabolic and epigenetic vulnerabilities, as well as oncogene-driven signaling crosstalk (Table IV).

Metabolically, the PI3K/AKT/mTOR pathway actively influences glucose metabolism to drive SCLC radioresistance (100,101). In SCLC models, dual PI3K/mTOR inhibitors (such as, BEZ235 and GSK2126458) promote autophagic degradation of glucose-6-phosphate dehydrogenase (G6PD). G6PD is the rate-limiting enzyme in the pentose phosphate pathway (PPP), which is a key survival mechanism for SCLC

cells. Disrupting the PPP via G6PD degradation increases reactive oxygen species accumulation and oxidative stress damage, ultimately enhancing IR cytotoxicity and overcoming radioresistance (102). Additionally, SCLC frequently harbors the MYC oncogene amplification, which drives aggressive proliferation and mediates resistance to mTOR inhibitors such as everolimus through the eIF4E axis (54).

Beyond metabolic and MYC-driven resistance, adaptive survival pathways are another critical mTOR-related resistance mechanism in SCLC. Therapy-induced DNA stress activates compensatory pathways, such as PARP inhibition and SCLC DNA repair strategies, which upregulate PI3K/mTOR. This feedback loop, possibly via reduced LKB1 signaling, limits PARP inhibitor efficacy alone (103,104). This highlights the use of mTOR targeting to overcome SCLC therapy resistance. Additionally, in lung cancer research, targeting hypoxia/HIF-1 α via PI3K/Akt/mTOR with Hsp90 inhibitors combined with radiotherapy blocks radiation-induced HIF-1 α stabilization and enhances antitumor effects (105). Carbon ion radiotherapy also attenuates HIF-1 signaling and mTOR induction (106). In drug-resistant NSCLC, CXCR4 inhibition eliminates cancer stem-like cells via STAT3/Akt/mTOR signaling (107). Furthermore, disrupting the NRF2-CHML-mTOR axis by CHML knockdown inhibits NSCLC progression and overcomes chemo/radioresistance (108). Moreover, rapamycin combined with irradiation enhances lung cancer radiosensitivity and protects normal lung cells (109). The activation of mTOR to counter DNA damage in SCLC supports the combination of mTOR inhibitors with DNA-damaging agents, such as radiation, highlighting the use of mTOR targeting to overcome SCLC.

mTOR and tumor immune microenvironment. The mTOR pathway acts as a key regulator of T-cell differentiation and function; therefore, its activity within tumor cells and the tumor immune microenvironment is critical for therapeutic responses.

Oncogenic activation of the PI3K/AKT/mTOR pathway is strongly associated with the transcriptional and translational regulation of programmed death-ligand 1 (PD-L1) expression on the membranes of lung cancer cells (110). This drives immune evasion, as PD-L1 binds to PD-1 on T cells to suppress antitumor immunity. Common NSCLC mutations, such as EGFR and KRAS, activate this pathway and subsequently increase PD-L1 expression, while inhibiting mTOR can downregulate PD-L1, theoretically 're-sensitizing' tumors to immune attack (111).

Although mTOR inhibitors (rapalogs) are known as immunosuppressants, they also function as immunomodulators that promote antitumor responses, notably by expanding memory CD8⁺ T cells. This dual role provides a strong rationale for combination therapy as preclinical lung cancer models confirm that pairing an mTOR inhibitor with a PD-1 antibody can markedly reduce tumor growth and increase tumor-infiltrating T cells (112). Targeting mTOR signaling alongside immune checkpoints may therefore offer a potent synergistic strategy for overcoming radioresistance and achieving systemic antitumor effects (113).

mTOR drives lung cancer radioresistance via the PI3K/AKT axis. It regulates key processes such as DNA repair, miRNA

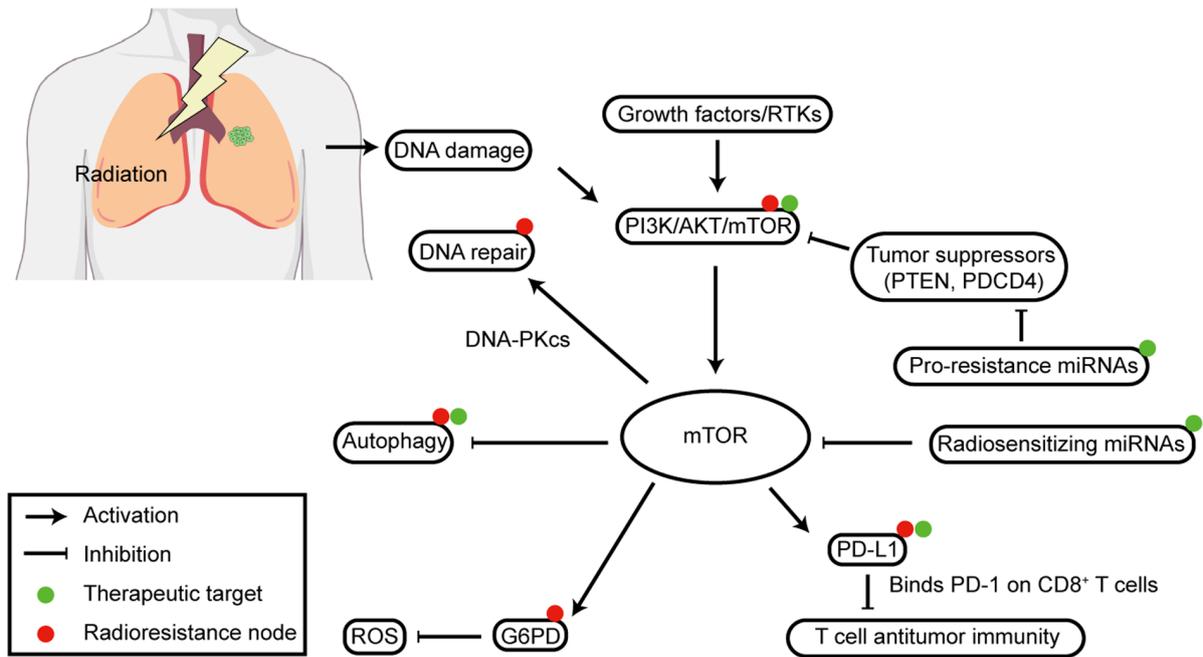


Figure 3. Mechanisms of mTOR in lung cancer radioresistance and therapeutic targets. In lung cancer, mTOR acts as a central hub driving radioresistance; it enhances DNA repair via regulating DNA-PKcs, modulates autophagy to support cellular survival, influences miRNA expression, mediates metabolic resilience in small cell lung cancer through G6PD degradation, and upregulates PD-L1 to facilitate immune evasion. Radioresistance nodes, marked by red in the figure, refer to a key molecular component or pathway where mTOR signaling promotes radioresistance, such as DNA repair, autophagy and PD-L1-mediated immune evasion. Therapeutic targets focus on disrupting these mTOR-driven pathways, including direct inhibition of mTOR, targeting its upstream PI3K/AKT axis, regulating autophagy, or combining mTOR inhibitors with anti-PD-1/PD-L1. DNA-PKcs, DNA-dependent protein kinase catalytic subunit; G6PD, glucose-6-phosphate dehydrogenase; miRNA, microRNA; PDCD4, programmed cell death 4; PD-L1, programmed death-ligand 1; ROS, reactive oxygen species; RTK, receptor tyrosine kinase.

activity, autophagy and PD-L1-mediated immune evasion. Clear radiosensitizing targets have been identified to counter these resistance mechanisms (Fig. 3). Notably, single mTOR inhibition shows limited clinical efficacy and requires combination with other therapies (such as anti-PD-1/PD-L1 and autophagy modulators) (79,110). Future efforts should focus on validating biomarkers, which may aid the development of personalized regimens and improve radiotherapy benefits for patients with lung cancer.

5. Clinical applications and future prospects of mTOR inhibitors

mTOR inhibitors target the mTOR pathway, which is critical for regulating cell proliferation, metabolism and survival. These inhibitors hold broad therapeutic potential across multiple diseases, including autoimmune disorders, endocrine conditions and cancer (114,115). Aberrant activation of the mTOR signaling pathway serves a notable role in radioresistance in NSCLC. By targeting this pathway, mTOR inhibitors demonstrate marked antitumor potential. Specifically, they enhance tumor cell radiosensitivity and counteract resistance caused by dysregulated mTOR signaling. Furthermore, combining mTOR inhibitors with radiotherapy generates synergistic antitumor effects, amplifying therapeutic efficacy.

Preclinical evidence and clinical status. Preclinical studies have consistently demonstrated the radiosensitizing potential of mTOR inhibitors. For example, Ushijima *et al* (116)

assessed the impact of the mTOR inhibitor temsirolimus on radioresistance under hypoxic conditions, using the A549 human lung adenocarcinoma cell line. This previous study revealed that while the D (10) value (dose required to kill 90% of cells) for A549 cells was 14.2 Gy under hypoxia, the combination with temsirolimus reduced this to 5.4 Gy (oxygen enhancement ratio=1.1), demonstrating its ability to suppress hypoxia-inducible factor-1 α expression and overcome hypoxia-induced radioresistance. These findings position temsirolimus as a radiosensitizer for hypoxic tumors. Another study (117) reported that the mTOR inhibitor everolimus exerts radiosensitizing effects by inducing G₂/M phase arrest in A549 cells. However, rapamycin pretreatment was shown to abolish this arrest 8 h post-radiotherapy. Early clinical trials also support this strategy. In a phase I clinical trial (118) assessing temsirolimus combined with thoracic radiotherapy (35 Gy/14f) in patients with NSCLC, among the eight evaluable patients, three achieved partial responses and two exhibited stable disease. These results underscore the preclinical and clinical synergy between mTOR inhibitors and radiotherapy, highlighting their potential to improve treatment outcomes.

mTOR inhibitor generations and therapeutic strategies. mTOR inhibitors are classified into three generations based on their mechanisms of action. First-generation inhibitors consist of antibiotic-derived allosteric inhibitors, including rapamycin and its derivatives such as temsirolimus, everolimus and ridaforolimus. Second-generation inhibitors are ATP-competitive inhibitors that selectively target the active kinase site of mTOR.

Table V. Clinical trials of mTOR inhibitors in lung cancer.

NCT no.	Drug	Trial type	Tumor type	Location	Current status	Purpose	(Refs.)
NCT00555256	Rapamycin	Phase I	Advanced NSCLC	America	Completed 2012	Evaluated safety and tolerability of the combination for dose identification	(122)
NCT00818675	Ridaforolimus	Phase II, randomized discontinuation	KRAS-mutated NSCLC	America	Completed 2012	Evaluated efficacy in patients with KRAS mutations; patients with stable disease were randomized to continue drug or receive placebo	(124)
NCT00401778	Everolimus (RAD001)	Phase Ib, pre-operative	Operable NSCLC	America	Completed 2013	Evaluated target effects and safety of everolimus as a pre-operative therapy	(125)
NCT00921310	Temsirolimus	Phase I	Advanced NSCLC	America	Completed 2016	Determined maximum tolerated dose and dose-limiting toxicities of the combination	(123)
NCT05840510	Nab-sirolimus ^a	Phase I	KRASG12C-mutated NSCLC	America	Active, not recruiting (estimated completion 2026)	A dose-escalation and expansion study to determine the safety and tolerability of the combination	(126)
NCT01390818	SAR245409	Phase Ib	RAS-mutated NSCLC	America, Italy, Spain	Completed 2015	Determined the maximum tolerated dose of the dual inhibitor combination	(129)
NCT03065062	Gedatolisib (PF-05212384)	Phase I	Advanced LUSC	America	Active, not recruiting (estimated completion 2026)	A dose-finding study to evaluate safety and efficacy in patients with solid tumors	(130)
NCT01545947	CC-223	Phase I	Advanced NSCLC	America, Spain	Completed 2014	Assessed safety, tolerability and preliminary efficacy of the dual mTORC1/2 kinase inhibitor	(128)
NCT02583542	AZD2014	Phase Ib/IIa	Advanced NSCLC	Britain	Completed 2020	A dose-escalation study to determine the safety and tolerability of the combination	(127)

^aNab-sirolimus, a nanoparticle albumin-bound formulation of sirolimus, is an mTOR inhibitor used in various therapeutic contexts, particularly in oncology. LUSC, lung squamous cell carcinoma; mTORC, mTOR complex; NCT, National Clinical Trial; NSCLC, non-small cell lung cancer.

These molecules, termed selective mTOR kinase inhibitors, achieve complete blockade of both mTORC1 and mTORC2, thereby preventing phosphorylation of PKB. Third-generation inhibitors, known as RapaLink, are hybrid molecules formed

by conjugating the ATP-competitive inhibitor sapanisertib to rapalog macrocycles via diverse linker chains. Structurally, this design mimics a dual-inhibitor strategy, and such hybrid agents overcome resistance arising from monotherapy with rapalogs or ATP-competitive mTOR inhibitors. Furthermore, their multitarget activity enhances drug selectivity and therapeutic efficacy (119,120). By integrating rapamycin with mTOR kinase inhibitors, third-generation compounds exhibit superior antitumor potency and reduced off-target toxicity (Table V) (121).

Clinical investigations have explored these different generations of inhibitors. First-generation rapalogs have been evaluated extensively in combination strategies for NSCLC. Early phase trials assessed rapamycin with sunitinib (122) and temsirolimus with pemetrexed (123). Other studies examined ridaforolimus in patients with NSCLC harboring KRAS mutations (124) or evaluated everolimus in a translational study for resectable NSCLC (125). This combination approach continues to evolve with more rationale-driven pairings, such as the investigation of nab-sirolimus with the KRAS G12C inhibitor adagrasib (126). In parallel, second-generation dual mTORC1/mTORC2 kinase inhibitors have advanced into clinical studies. Initial first-in-human and dose-escalation studies have established the safety and tolerability of monotherapies such as AZD2014 (127) and CC-223 (128) in patients with advanced solid tumors. This development subsequently informed strategies to combine these potent dual inhibitors with other targeted agents, such as pairing the PI3K/mTOR inhibitor SAR245409 with the MEK inhibitor pimasertib (129) or combining the PI3K/mTOR inhibitor gedatolisib (PF-05212384) with the CDK4/6 inhibitor palbociclib (PD-0332991) (130). In summary, mTOR inhibitors demonstrate substantial promise in enhancing the efficacy of radiotherapy for lung cancer. By advancing the understanding of the molecular mechanisms underlying the mTOR signaling pathway and refining therapeutic strategies, more effective treatment regimens can be developed for patients with NSCLC, ultimately improving clinical outcomes and prognosis.

Controversies and limitations. Despite promising preclinical evidence for mTOR inhibition, several critical limitations and controversies must be addressed to ensure successful clinical translation. The key challenge lies in the notable disparity between the robust body of preclinical mechanistic evidence and the limited clinical outcomes achieved to date, which necessitates a realistic perspective on the field. Most current research comes from *in vitro* studies and xenograft models. This raises concerns about whether conclusions can be reliably generalized to heterogeneous human tumors. Furthermore, although a number of clinical trials investigating mTOR inhibitors have been completed (Table V), the results often represent preliminary phase I studies focused predominantly on determining safety and maximum tolerated dose, rather than definitive efficacy. A major therapeutic challenge stems from the complexity of the PI3K/AKT/mTOR network (131): First-generation inhibitors (rapalogs) are mostly cytostatic with modest single-agent efficacy. Their inhibition of mTORC1 fails to suppress a negative feedback loop, leading to paradoxical AKT phosphorylation and activation. This AKT activation sustains cell survival and proliferation, limiting the

clinical use of rapalogs as monotherapy and requiring combination or dual-targeting agents (45,115,132-134). Compounding this, although the PI3K/AKT/mTOR pathway is frequently dysregulated in lung cancer, the utility of biomarkers for patient selection remains context-dependent; while PIK3CA mutations have been shown to predict rapalog sensitivity in breast cancer models, PTEN loss of function is not consistently associated with sensitivity, and co-occurring oncogenic drivers (such as HER2 mutations) can further obscure predictive value (135,136). The lack of standardized, broadly validated biomarkers that account for such context-specificity still presents a notable barrier to robust patient stratification and therapeutic guidance in clinical trials.

Additionally, mTOR inhibitors are associated with a unique spectrum of adverse events, including metabolic disturbances, mucositis, fatigue, and pulmonary complications such as pneumonitis and dyspnea (137-140). Critically, the long-standing use of rapalogs as immunosuppressants in transplant patients raises concerns that their immunosuppressive properties could counteract desired anticancer effects, particularly when combining mTOR inhibition with immunotherapies designed to enhance antitumor immunity (141,142). Collectively, these limitations, from pathway redundancy and biomarker gaps to toxicity and immunological conflicts, highlight the need for further research to optimize mTOR-targeted strategies and overcome barriers to effective clinical translation.

6. Conclusion

The role of mTOR in lung cancer radioresistance has been extensively studied and well-established. The present review summarizes the mechanisms driving aberrant activation of the mTOR signaling pathway in lung cancer and its influence on radiotherapy resistance. Specifically, mTOR markedly enhances tumor cell radioresistance by regulating multiple biological processes, including cellular proliferation, autophagy, DNA repair, miRNA regulation and EMT. Furthermore, mTOR drives adaptive resistance by regulating metabolic resilience and promoting immune evasion through PD-L1 expression.

Although mTOR inhibitors hold considerable promise in lung cancer radiotherapy, several challenges remain. For example, drug resistance may arise as tumor cells evade mTOR inhibitor activity through activation of alternative signaling pathways or compensatory mechanisms. Consequently, combination therapies, such as co-administration with PI3K or MEK inhibitors, may represent effective strategies to overcome resistance. Additionally, mTOR inhibitors are associated with toxicity and side effects, including metabolic disturbances and immunosuppression, necessitating further optimization of dosing regimens and therapeutic protocols.

Acknowledgements

Not applicable.

Funding

The present study was supported by the National Natural Science Foundation of China (grant nos. 82272758 and

82273466), the Hunan Cancer Hospital Climb Plan (grant nos. ZX2020001 and ZX2020005), the Hunan Provincial Science and Technology Department (grant no. 2023ZJ1125), the Hunan Provincial Health High-Level Talent Scientific Research Project (grant no. R2023057) and the National Key Clinical Specialty Scientific Research Project (grant no. Z2023025).

Availability of data and materials

Not applicable.

Authors' contributions

XP, HL, YL, and HW conceptualized the study. XP wrote the manuscript. LY and HW reviewed the manuscript. XP, HL, YL and HW contributed to manuscript editing. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

- Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I and Jemal A: Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 74: 229-263, 2024.
- Lehrer EJ, Singh R, Wang M, Chinchilli VM, Trifiletti DM, Ost P, Siva S, Meng MB, Tchelebi L and Zaorsky NG: Safety and survival rates associated with ablative stereotactic radiotherapy for patients with oligometastatic cancer: A systematic review and meta-analysis. *JAMA Oncol* 7: 92-106, 2021.
- Gonsalves D, Ocanto A, Martín M and Couñago F: Radiotherapy in early stages of lung cancer. *Revisiónes en Cancer* 37: 133-147, 2023.
- Bao S, Wu Q, McLendon RE, Hao Y, Shi Q, Hjelmeland AB, Dewhirst MW, Bigner DD and Rich JN: Glioma stem cells promote radioresistance by preferential activation of the DNA damage response. *Nature* 444: 756-760, 2006.
- Bache M, Kadler F, Struck O, Medenwald D, Ostheimer C, Güttler A, Keßler J, Kappler M, Riemann A, Thews O, *et al*: Correlation between Circulating miR-16, miR-29a, miR-144 and miR-150, and the Radiotherapy response and survival of non-small-cell lung cancer patients. *Int J Mol Sci* 24: 12835, 2023.
- Laplante M and Sabatini DM: mTOR signaling in growth control and disease. *Cell* 149: 274-293, 2012.
- Panwar V, Singh A, Bhatt M, Tonk RK, Azizov S, Raza AS, Sengupta S, Kumar D and Garg M: Multifaceted role of mTOR (mammalian target of rapamycin) signaling pathway in human health and disease. *Signal Transduct Target Ther* 8: 375, 2023.
- Wei F, Liu Y, Guo Y, Xiang A, Wang G, Xue X and Lu Z: MiR-99b-targeted mTOR induction contributes to irradiation resistance in pancreatic cancer. *Mol Cancer* 12: 81, 2013.
- Woo Y, Lee HJ, Jung YM and Jung YJ: MTOR-mediated anti-oxidant activation in solid tumor radioresistance. *J Oncol* 2019: 5956867, 2019.
- Yu CC, Hung SK, Lin HY, Chiou WY, Lee MS, Liao HF, Huang HB, Ho HC and Su YC: Targeting the PI3K/AKT/mTOR signaling pathway as an effectively radiosensitizing strategy for treating human oral squamous cell carcinoma in vitro and in vivo. *Oncotarget* 8: 68641-68653, 2017.
- Wanigasooriya K, Tyler R, Barros-Silva JD, Sinha Y, Ismail T and Beggs AD: Radiosensitising cancer using phosphatidylinositol-3-kinase (PI3K), protein kinase B (AKT) or mammalian target of rapamycin (mTOR) inhibitors. *Cancers (Basel)* 12: 1278, 2020.
- Mardanshahi A, Gharibkandi NA, Vaseghi S, Abedi SM and Molavipordanjani S: The PI3K/AKT/mTOR signaling pathway inhibitors enhance radiosensitivity in cancer cell lines. *Mol Biol Rep* 48: 1-14, 2021.
- Feng YQ, Gu SX, Chen YS, Gao XD, Ren YX, Chen JC, Lu YY, Zhang H and Cao S: Virtual screening and optimization of novel mTOR inhibitors for radiosensitization of hepatocellular carcinoma. *Drug Des Devel Ther* 14: 1779-1798, 2020.
- Ihlamur M, Akgül B, Zengin Y, Korkut ŞV, Kelleci K and Abamor EŞ: The mTOR signaling pathway and mTOR inhibitors in cancer: Next-generation inhibitors and approaches. *Curr Mol Med* 24: 478-494, 2024.
- Vézina C, Kudelski A and Sehgal SN: Rapamycin (AY-22,989), a new antifungal antibiotic. I. Taxonomy of the producing streptomycete and isolation of the active principle. *J Antibiot (Tokyo)* 28: 721-726, 1975.
- Pignataro G, Capone D, Polichetti G, Vinciguerra A, Gentile A, Di Renzo G and Annunziato L: Neuroprotective, immunosuppressant and antineoplastic properties of mTOR inhibitors: Current and emerging therapeutic options. *Curr Opin Pharmacol*. *Curr Opin Pharmacol* 11: 378-394, 2011.
- Drenan RM, Liu X, Bertram PG and Zheng XF: FKBP12-rapamycin-associated protein or mammalian target of rapamycin (FRAP/mTOR) localization in the endoplasmic reticulum and the Golgi apparatus. *J Biol Chem* 279: 772-778, 2004.
- Helfenberger KE, Argentino GF, Benzo Y, Herrera LM, Finocchietto P and Poderoso C: Angiotensin II regulates mitochondrial mTOR pathway activity dependent on Acyl-CoA synthetase 4 in adrenocortical cells. *Endocrinology* 163: bqac170, 2022.
- Chen Y and Zhou X: Research progress of mTOR inhibitors. *Eur J Med Chem* 208: 112820, 2020.
- Ali M, Bukhari SA, Ali M and Lee HW: Upstream signalling of mTORC1 and its hyperactivation in type 2 diabetes (T2D). *BMB Rep* 50: 601-609, 2017.
- Wang G, Chen L, Qin S, Zhang T, Yao J, Yi Y and Deng L: Mechanistic target of rapamycin complex 1: From a nutrient sensor to a key regulator of metabolism and health. *Adv Nutr* 13: 1882-1900, 2022.
- Workman JJ, Chen H and Larabee RN: Environmental signaling through the mechanistic target of rapamycin complex 1: mTORC1 goes nuclear. *Cell Cycle* 13: 714-725, 2014.
- Yoon MS: The role of mammalian target of rapamycin (mTOR) in insulin signaling. *Nutrients* 9: 1176, 2017.
- Lamming DW, Ye L, Katajisto P, Goncalves MD, Saitoh M, Stevens DM, Davis JG, Salmon AB, Richardson A, Ahima RS, *et al*: Rapamycin-induced insulin resistance is mediated by mTORC2 loss and uncoupled from longevity. *Science* 335: 1638-1643, 2012.
- Sarbasov DD, Ali SM, Sengupta S, Sheen JH, Hsu PP, Bagley AF, Markhard AL and Sabatini DM: Prolonged rapamycin treatment inhibits mTORC2 assembly and Akt/PKB. *Mol Cell* 22: 159-168, 2006.
- Wang W, Tan J, Liu X, Guo W, Li M, Liu X, Liu Y, Dai W, Hu L, Wang Y, *et al*: Cytoplasmic endonuclease G promotes nonalcoholic fatty liver disease via mTORC2-AKT-ACLY and endoplasmic reticulum stress. *Nat Commun* 14: 6201, 2023.
- Peng H, Kasada A, Ueno M, Hoshii T, Tadokoro Y, Nomura N, Ito C, Takase Y, Vu HT, Kobayashi M, *et al*: Distinct roles of Rheb and Raptor in activating mTOR complex 1 for the self-renewal of hematopoietic stem cells. *Biochem Biophys Res Commun* 495: 1129-1135, 2018.
- Miricescu D, Totan A, Stanescu-Spinu II, Badoiu SC, Stefani C and Greabu M: PI3K/AKT/mTOR signaling pathway in breast cancer: From molecular landscape to clinical aspects. *Int J Mol Sci* 22: 173, 2020.
- Inoki K, Kim J and Guan KL: AMPK and mTOR in cellular energy homeostasis and drug targets. *Annu Rev Pharmacol Toxicol* 52: 381-400, 2012.

30. Chun Y and Kim J: AMPK-mTOR signaling and cellular adaptations in hypoxia. *Int J Mol Sci* 22: 9765, 2021.
31. Lama-Sherpa TD, Jeong MH and Jewell JL: Regulation of mTORC1 by the Rag GTPases. *Biochem Soc Trans* 51: 655-664, 2023.
32. Kim SJ, DeStefano MA, Oh WJ, Wu CC, Vega-Cotto NM, Finlan M, Liu D, Su B and Jacinto E: mTOR complex 2 regulates proper turnover of insulin receptor substrate-1 via the ubiquitin ligase subunit Fbw8. *Mol Cell* 48: 875-887, 2012.
33. Sural-Fehr T, Singh H, Cantuti-Catelvetri L, Zhu H, Marshall MS, Rebiai R, Jastrzebski MJ, Givogri MI, Rasenick MM and Bongarzone ER: Inhibition of the IGF-1-PI3K-Akt-mTORC2 pathway in lipid rafts increases neuronal vulnerability in a genetic lysosomal glycosphingolipidosis. *Dis Model Mech* 12: dmm036590, 2019.
34. Lazorchak AS and Su B: Perspectives on the role of mTORC2 in B lymphocyte development, immunity and tumorigenesis. *Protein Cell* 2: 523-530, 2011.
35. Li X and Gao T: mTORC2 phosphorylates protein kinase C ζ to regulate its stability and activity. *EMBO Rep* 15: 191-198, 2014.
36. Baffi TR, Lordén G, Wozniak JM, Feichtner A, Yeung W, Kornev AP, King CC, Del Rio JC, Limaye AJ, Bogomolovas J, *et al*: mTORC2 controls the activity of PKC and Akt by phosphorylating a conserved TOR interaction motif. *Sci Signal* 14: eabe4509, 2021.
37. Carter CC, Mast FD, Olivier JP, Bourgeois NM, Kaushansky A and Aitchison JD: Dengue activates mTORC2 signaling to counteract apoptosis and maximize viral replication. *Front Cell Infect Microbiol* 12: 979996, 2022.
38. Katholnig K, Schütz B, Fritsch SD, Schörghofer D, Linke M, Sukhbaatar N, Matschinger JM, Unterleuthner D, Hirtl M, Lang M, *et al*: Inactivation of mTORC2 in macrophages is a signature of colorectal cancer that promotes tumorigenesis. *JCI Insight* 4: e124164, 2019.
39. Mehta D, Rajput K, Jain D, Bajaj A and Dasgupta U: Unveiling the role of mechanistic target of rapamycin kinase (MTOR) signaling in cancer progression and the emergence of MTOR inhibitors as therapeutic strategies. *ACS Pharmacol Transl Sci* 7: 3758-3779, 2024.
40. Qiu W, Ren M, Wang C, Fu Y and Liu Y: The clinicopathological and prognostic significance of mTOR and p-mTOR expression in patients with non-small cell lung cancer: A meta-analysis. *Medicine (Baltimore)* 101: e32340, 2022.
41. Zeng AQ, Chen X, Dai Y and Zhao JN: Betulinic acid inhibits non-small cell lung cancer by repolarizing tumor-associated macrophages via mTOR signaling pathway. *Zhongguo Zhong Yao Za Zhi* 49: 2376-2384, 2024 (In Chinese).
42. Granville CA, Warfel N, Tsurutani J, Hollander MC, Robertson M, Fox SD, Veenstra TD, Issaq HJ, Linnoila RI and Dennis PA: Identification of a highly effective rapamycin schedule that markedly reduces the size, multiplicity, and phenotypic progression of tobacco carcinogen-induced murine lung tumors. *Clin Cancer Res* 13: 2281-2289, 2007.
43. Raskova Kafkova L, Mierzwicka JM, Chakraborty P, Jakubec P, Fischer O, Skarda J, Maly P and Raska M: NSCLC: From tumorigenesis, immune checkpoint misuse to current and future targeted therapy. *Front Immunol* 15: 1342086, 2024.
44. Bang J, Jun M, Lee S, Moon H and Ro SW: Targeting EGFR/PI3K/AKT/mTOR signaling in hepatocellular carcinoma. *Pharmaceutics* 15: 2130, 2023.
45. Wu YY, Wu HC, Wu JE, Huang KY, Yang SC, Chen SX, Tsao CJ, Hsu KF, Chen YL and Hong TM: The dual PI3K/mTOR inhibitor BEZ235 restricts the growth of lung cancer tumors regardless of EGFR status, as a potent accompant in combined therapeutic regimens. *J Exp Clin Cancer Res* 38: 282, 2019.
46. Xu L, Ding R, Song S, Liu J, Li J, Ju X and Ju B: Single-cell RNA sequencing reveals the mechanism of PI3K/AKT/mTOR signaling pathway activation in lung adenocarcinoma by KRAS mutation. *J Gene Med* 26: e3658, 2024.
47. Ducray SP, Natarajan K, Garland GD, Turner SD and Egger G: The transcriptional roles of ALK fusion proteins in tumorigenesis. *Cancers (Basel)* 11: 1074, 2019.
48. Zhao T, Fan J, Abu-Zaid A, Burley SK and Zheng XFS: Nuclear mTOR signaling orchestrates transcriptional programs underlying cellular growth and metabolism. *Cells* 13: 781, 2024.
49. Zhang Q, Zhang Y, Chen Y, Qian J, Zhang X and Yu K: A Novel mTORC1/2 Inhibitor (MTI-31) inhibits tumor growth, epithelial-mesenchymal transition, metastases, and improves antitumor immunity in preclinical models of lung cancer. *Clin Cancer Res* 25: 3630-3642, 2019.
50. Marinov M, Ziogas A, Pardo OE, Tan LT, Dhillon T, Mauri FA, Lane HA, Lemoine NR, Zangemeister-Wittke U, Seckl MJ and Arcaro A: AKT/mTOR pathway activation and BCL-2 family proteins modulate the sensitivity of human small cell lung cancer cells to RAD001. *Clin Cancer Res* 15: 1277-1287, 2009.
51. Li X, Li C, Guo C, Zhao Q, Cao J, Huang HY, Yue M, Xue Y, Jin Y, Hu L and Ji H: PI3K/Akt/mTOR signaling orchestrates the phenotypic transition and chemo-resistance of small cell lung cancer. *J Genet Genomics* 48: 640-651, 2021.
52. He C: Activating invasion and metastasis in small cell lung cancer: Role of the tumour immune microenvironment and mechanisms of vasculogenesis, epithelial-mesenchymal transition, cell migration, and organ tropism. *Cancer Rep (Hoboken)* 7: e70018, 2024.
53. Fiorentino FP, Tokgün E, Solé-Sánchez S, Giampaolo S, Tokgün O, Jauset T, Kohno T, Perucho M, Soucek L and Yokota J: Growth suppression by MYC inhibition in small cell lung cancer cells with TP53 and RB1 inactivation. *Oncotarget* 7: 31014-31028, 2016.
54. Matsumoto M, Seike M, Noro R, Soeno C, Sugano T, Takeuchi S, Miyanaga A, Kitamura K, Kubota K and Gemma A: Control of the MYC-eIF4E axis plus mTOR inhibitor treatment in small cell lung cancer. *BMC Cancer* 15: 241, 2015.
55. Chang L, Graham PH, Ni J, Hao J, Bucci J, Cozzi PJ and Li Y: Targeting PI3K/Akt/mTOR signaling pathway in the treatment of prostate cancer radioresistance. *Crit Rev Oncol Hematol* 96: 507-517, 2015.
56. Liu N and Wang P: Development of PI3K/AKT/mTOR signaling pathway and hypofractionated radiotherapy in non-small cell lung cancer. *Chin J Clin Oncol* 40: 1196-1198, 2013 (In Chinese).
57. Glaviano A, Foo ASC, Lam HY, Yap KCH, Jacot W, Jones RH, Eng H, Nair MG, Makvandi P, Georger B, *et al*: PI3K/AKT/mTOR signaling transduction pathway and targeted therapies in cancer. *Mol Cancer* 22: 138, 2023.
58. Sarbassov DD, Guertin DA, Ali SM and Sabatini DM: Phosphorylation and regulation of Akt/PKB by the rictor-mTOR complex. *Science* 307: 1098-1101, 2005.
59. Huang J, Chen L, Wu J, Ai D, Zhang JQ, Chen TG and Wang L: Targeting the PI3K/AKT/mTOR signaling pathway in the treatment of human diseases: Current status, trends, and solutions. *J Med Chem* 65: 16033-16061, 2022.
60. Schuurbiens OC, Kaanders JH, van der Heijden HF, Dekhuijzen RP, Oyen WJ and Bussink J: The PI3-K/AKT-pathway and radiation resistance mechanisms in non-small cell lung cancer. *J Thorac Oncol* 4: 761-767, 2009.
61. Toulany M, Iida M, Keinath S, Iyi FF, Mueck K, Fehrenbacher B, Mansour WY, Schaller M, Wheeler DL and Rodemann HP: Dual targeting of PI3K and MEK enhances the radiation response of K-RAS mutated non-small cell lung cancer. *Oncotarget* 7: 43746-43761, 2016.
62. Zhang T, Cui GB, Zhang J, Zhang F, Zhou YA, Jiang T and Li XF: Inhibition of PI3 kinases enhances the sensitivity of non-small cell lung cancer cells to ionizing radiation. *Oncol Rep* 24: 1683-1689, 2010.
63. Chen K, Shang Z, Dai AL and Dai PL: Novel PI3K/Akt/mTOR pathway inhibitors plus radiotherapy: Strategy for non-small cell lung cancer with mutant RAS gene. *Life Sci* 255: 117816, 2020.
64. Kim SY, Jeong EH, Lee TG, Kim HR and Kim CH: The combination of trametinib, a MEK inhibitor, and temsirolimus, an mTOR Inhibitor, radiosensitizes lung cancer cells. *Anticancer Res* 41: 2885-2894, 2021.
65. He GH, Xing DJ, Jin D, Lu Y, Guo L, Li YL and Li D: Scutellarin improves the radiosensitivity of non-small cell lung cancer cells to iodine-125 seeds via downregulating the AKT/mTOR pathway. *Thorac Cancer* 12: 2352-2359, 2021.
66. Sebastian NT, Webb A, Shilo K, Robb R, Xu-Welliver M, Haglund K, Brownstein J, DeNicola GM, Shen C and Williams TM: A PI3K gene expression signature predicts for recurrence in early-stage non-small cell lung cancer treated with stereotactic body radiation therapy. *Cancer* 129: 3971-3977, 2023.
67. Choi EJ, Ryu YK, Kim SY, Wu HG, Kim JS, Kim IH and Kim IA: Targeting epidermal growth factor receptor-associated signaling pathways in non-small cell lung cancer cells: Implication in radiation response. *Mol Cancer Res* 8: 1027-1036, 2010.
68. Holler M, Grottke A, Mueck K, Manes J, Jücker M, Rodemann HP and Toulany M: Dual Targeting of Akt and mTORC1 impairs repair of DNA double-strand breaks and increases radiation sensitivity of human tumor cells. *PLoS One* 11: e0154745, 2016.

69. Zhang P, He D, Song E, Jiang M and Song Y: Celecoxib enhances the sensitivity of non-small-cell lung cancer cells to radiation-induced apoptosis through downregulation of the Akt/mTOR signaling pathway and COX-2 expression. *PLoS One* 14: e0223760, 2019.
70. Xiong L, Tan B, Lei X, Zhang B, Li W, Liu D and Xia T: SIRT6 through PI3K/Akt/mTOR signaling pathway to enhance radiosensitivity of non-small cell lung cancer and inhibit tumor progression. *IUBMB Life* 73: 1092-1102, 2021.
71. Hamid MB, Serafin AM and Akudugu JM: Selective therapeutic benefit of X-rays and inhibitors of EGFR, PI3K/mTOR, and Bcl-2 in breast, lung, and cervical cancer cells. *Eur J Pharmacol* 912: 174612, 2021.
72. Levine B and Kroemer G: Autophagy in the pathogenesis of disease. *Cell* 132: 27-42, 2008.
73. Biswas U, Roy R, Ghosh S and Chakrabarti G: The interplay between autophagy and apoptosis: Its implication in lung cancer and therapeutics. *Cancer Lett* 585: 216662, 2024.
74. Gargalionis AN, Papavassiliou KA and Papavassiliou AG: Implication of mTOR Signaling in NSCLC: Mechanisms and therapeutic perspectives. *Cells* 12: 2014, 2023.
75. Loizzo D, Pandolfo SD, Rogers D, Cerrato C, di Meo NA, Autorino R, Mirone V, Ferro M, Porta C, Stella A, *et al*: Novel insights into autophagy and prostate cancer: A comprehensive review. *Int J Mol Sci* 23: 3826, 2022.
76. Wang J, Gong M, Fan X, Huang D, Zhang J and Huang C: Autophagy-related signaling pathways in non-small cell lung cancer. *Mol Cell Biochem* 477: 385-393, 2022.
77. Kim KW, Hwang M, Moretti L, Jaboin JJ, Cha YI and Lu B: Autophagy upregulation by inhibitors of caspase-3 and mTOR enhances radiotherapy in a mouse model of lung cancer. *Autophagy* 4: 659-668, 2008.
78. Fei HR, Tian H, Zhou XL, Yang MF, Sun BL, Yang XY, Jiao P and Wang FZ: Inhibition of autophagy enhances effects of PF-04691502 on apoptosis and DNA damage of lung cancer cells. *Int J Biochem Cell Biol* 78: 52-62, 2016.
79. Yan J, Xie Y, Wang F, Chen Y, Zhang J, Dou Z, Gan L, Li H, Si J, Sun C, *et al*: Carbon ion combined with tigecycline inhibits lung cancer cell proliferation by inducing mitochondrial dysfunction. *Life Sci* 263: 118586, 2020.
80. Kim KW, Moretti L, Mitchell LR, Jung DK and Lu B: Combined Bcl-2/mammalian target of rapamycin inhibition leads to enhanced radiosensitization via induction of apoptosis and autophagy in non-small cell lung tumor xenograft model. *Clin Cancer Res* 15: 6096-6105, 2009.
81. Kim EJ, Jeong JH, Bae S, Kang S, Kim CH and Lim YB: mTOR inhibitors radiosensitize PTEN-deficient non-small-cell lung cancer cells harboring an EGFR activating mutation by inducing autophagy. *J Cell Biochem* 114: 1248-1256, 2013.
82. Kim KW, Myers CJ, Jung DK and Lu B: NVP-BEZ-235 enhances radiosensitization via blockade of the PI3K/mTOR pathway in cisplatin-resistant non-small cell lung carcinoma. *Genes Cancer* 5: 293-302, 2014.
83. Liang N, Zhong R, Hou X, Zhao G, Ma S, Cheng G and Liu X: Ataxia-telangiectasia mutated (ATM) participates in the regulation of ionizing radiation-induced cell death via MAPK14 in lung cancer H1299 cells. *Cell Prolif* 48: 561-572, 2015.
84. Zhang X, Ji J, Yang Y, Zhang J and Shen L: Stathmin1 increases radioresistance by enhancing autophagy in non-small-cell lung cancer cells. *Oncotargets Ther* 9: 2565-2574, 2016.
85. Lai C, Zhang J, Tan Z, Shen LF, Zhou RR and Zhang YY: Maf1 suppression of ATF5-dependent mitochondrial unfolded protein response contributes to rapamycin-induced radio-sensitivity in lung cancer cell line A549. *Aging (Albany NY)* 13: 7300-7313, 2021.
86. He B, Zhao Z, Cai Q, Zhang Y, Zhang P, Shi S, Xie H, Peng X, Yin W, Tao Y and Wang X: MiRNA-based biomarkers, therapies, and resistance in cancer. *Int J Biol Sci* 6: 2628-2647, 2020.
87. Lu J, Getz G, Miska EA, Alvarez-Saavedra E, Lamb J, Peck D, Sweet-Cordero A, Ebert BL, Mak RH, Ferrando AA, *et al*: MicroRNA expression profiles classify human cancers. *Nature* 435: 834-838, 2005.
88. Volinia S, Calin GA, Liu CG, Ambs S, Cimmino A, Petrocca F, Visone R, Iorio M, Roldo C, Ferracin M, *et al*: A microRNA expression signature of human solid tumors defines cancer gene targets. *Proc Natl Acad Sci USA* 103: 2257-2261, 2006.
89. Avvari S, Prasad DKV and Khan IA: Role of MicroRNAs in cell growth proliferation and tumorigenesis. In: *Role of MicroRNAs in Cancers*. Prasad D and Santosh Sushma P (eds). Springer, Singapore, pp37-51, 2022.
90. Chen Y, Li WW, Peng P, Zhao WH, Tian YJ, Huang Y, Xia S and Chen Y: mTORC1 inhibitor RAD001 (everolimus) enhances non-small cell lung cancer cell radiosensitivity in vitro via suppressing epithelial-mesenchymal transition. *Acta Pharmacol Sin* 40: 1085-1094, 2019.
91. Yuan Y, Liao H, Pu Q, Ke X, Hu X, Ma Y, Luo X, Jiang Q, Gong Y, Wu M, *et al*: miR-410 induces both epithelial-mesenchymal transition and radioresistance through activation of the PI3K/mTOR pathway in non-small cell lung cancer. *Signal Transduct Target Ther* 5: 85, 2020.
92. Li T, Wei L, Zhang X, Fu B, Zhou Y, Yang M, Cao M, Chen Y, Tan Y, Shi Y, *et al*: Serotonin Receptor HTR2B facilitates colorectal cancer metastasis via CREB1-ZEB1 axis-mediated epithelial-mesenchymal transition. *Mol Cancer Res* 22: 538-554, 2024.
93. Chen Y, Liao W, Yuan A, Xu H, Yuan R and Cao J: MiR-181a reduces radiosensitivity of non-small-cell lung cancer via inhibiting PTEN. *Panminerva Med* 64: 374-383, 2022.
94. Jiang LP, He CY and Zhu ZT: Role of microRNA-21 in radiosensitivity in non-small cell lung cancer cells by targeting PDCD4 gene. *Oncotarget* 8: 23675-23689, 2017.
95. Huang M, Li T, Wang Q, Li C, Zhou H, Deng S, Lv Z, He Y, Hou B and Zhu G: Silencing circPVT1 enhances radiosensitivity in non-small cell lung cancer by sponging microRNA-1208. *Cancer Biomark* 31: 263-279, 2021.
96. Yin H, Ma J, Chen L, Piao S, Zhang Y, Zhang S, Ma H, Li Y, Qu Y, Wang X and Xu Q: MiR-99a enhances the radiation sensitivity of non-small cell lung cancer by targeting mTOR. *Cell Physiol Biochem* 46: 471-481, 2018.
97. Meng X, Sun Y, Liu S and Mu Y: miR-101-3p sensitizes lung adenocarcinoma cells to irradiation via targeting BIRC5. *Oncol Lett* 21: 282, 2021.
98. Li Z, Qu Z, Wang Y, Qin M and Zhang H: miR-101-3p sensitizes non-small cell lung cancer cells to irradiation. *Open Med (Wars)* 15: 413-423, 2020.
99. Tang Y, Cui Y, Li Z, Jiao Z, Zhang Y, He Y, Chen G, Zhou Q, Wang W, Zhou X, *et al*: Radiation-induced miR-208a increases the proliferation and radioresistance by targeting p21 in human lung cancer cells. *J Exp Clin Cancer Res* 35: 7, 2016.
100. Deng H, Chen Y, Li P, Hang Q, Zhang P, Jin Y and Chen M: PI3K/AKT/mTOR pathway, hypoxia, and glucose metabolism: Potential targets to overcome radioresistance in small cell lung cancer. *Cancer Pathog Ther* 1: 56-66, 2023.
101. Liu B, Huang ZB, Chen X, See YX, Chen ZK and Yao HK: Mammalian target of rapamycin 2 (MTOR2) and C-MYC modulate glucosamine-6-phosphate synthesis in glioblastoma (GBM) cells through glutamine: fructose-6-phosphate aminotransferase 1 (GFAT1). *Cell Mol Neurobiol* 39: 415-434, 2019.
102. Deng H, Chen Y, Wang L, Zhang Y, Hang Q, Li P, Zhang P, Ji J, Song H, Chen M and Jin Y: PI3K/mTOR inhibitors promote G6PD autophagic degradation and exacerbate oxidative stress damage to radiosensitize small cell lung cancer. *Cell Death Dis* 14: 652, 2023.
103. Cardnell RJ, Feng Y, Mukherjee S, Diao L, Tong P, Stewart CA, Masroopour F, Fan Y, Nilsson M, Shen Y, *et al*: Activation of the PI3K/mTOR pathway following PARP Inhibition in small cell lung cancer. *PLoS One* 11: e0152584, 2016.
104. Knelson EH, Patel SA and Sands JM: PARP inhibitors in small-cell lung cancer: Rational combinations to improve responses. *Cancers (Basel)* 13: 727, 2021.
105. Kim WY, Oh SH, Woo JK, Hong WK and Lee HY: Targeting heat shock protein 90 overrides the resistance of lung cancer cells by blocking radiation-induced stabilization of hypoxia-inducible factor-1alpha. *Cancer Res* 69: 1624-1632, 2009.
106. Subtil FS, Wilhelm J, Bill V, Westholt N, Rudolph S, Fischer J, Scheel S, Seay U, Fournier C, Taucher-Scholz G, *et al*: Carbon ion radiotherapy of human lung cancer attenuates HIF-1 signaling and acts with considerably enhanced therapeutic efficiency. *FASEB J* 28: 1412-1421, 2014.
107. Jung MJ, Rho JK, Kim YM, Jung JE, Jin YB, Ko YG, Lee JS, Lee SJ, Lee JC and Park MJ: Upregulation of CXCR4 is functionally crucial for maintenance of stemness in drug-resistant non-small cell lung cancer cells. *Oncogene* 32: 209-221, 2013.
108. Dodson M, Dai W, Anandhan A, Schmidlin CJ, Liu P, Wilson NC, Wei Y, Kitamura N, Galligan JJ, Ooi A, *et al*: CHML is an NRF2 target gene that regulates mTOR function. *Mol Oncol* 16: 1714-1727, 2022.

109. Zheng H, Wang M, Wu J, Wang ZM, Nan HJ and Sun H: Inhibition of mTOR enhances radiosensitivity of lung cancer cells and protects normal lung cells against radiation. *Biochem Cell Biol* 94: 213-220, 2016.
110. Lastwika KJ, Wilson W III, Li QK, Norris J, Xu H, Ghazarian SR, Kitagawa H, Kawabata S, Taube JM, Yao S, *et al*: Control of PD-L1 expression by oncogenic activation of the AKT-mTOR pathway in non-small cell lung cancer. *Cancer Res* 76: 227-238, 2016.
111. Xiao P, Sun LL, Wang J, Han RL, Ma Q and Zhong DS: LKB1 gene inactivation does not sensitize non-small cell lung cancer cells to mTOR inhibitors in vitro. *Acta Pharmacol Sin* 36: 1107-1112, 2015.
112. Li H, Li X, Liu S, Guo L, Zhang B, Zhang J and Ye Q: Programmed cell death-1 (PD-1) checkpoint blockade in combination with a mammalian target of rapamycin inhibitor restrains hepatocellular carcinoma growth induced by hepatoma cell-intrinsic PD-1. *Hepatology* 66: 1920-1933, 2017.
113. Dong L, Lv H, Li W, Song Z, Li L, Zhou S, Qiu L, Qian Z, Liu X, Feng L, *et al*: Co-expression of PD-L1 and p-AKT is associated with poor prognosis in diffuse large B-cell lymphoma via PD-1/PD-L1 axis activating intracellular AKT/mTOR pathway in tumor cells. *Oncotarget* 7: 33350-33362, 2016.
114. Chiarini F, Evangelisti C, McCubrey JA and Martelli AM: Current treatment strategies for inhibiting mTOR in cancer. *Trends Pharmacol Sci* 36: 124-135, 2015.
115. Mohindra NA and Platanius LC: Catalytic mammalian target of rapamycin inhibitors as antineoplastic agents. *Leuk Lymphoma* 56: 2518-2523, 2015.
116. Ushijima H, Suzuki Y, Oike T, Komachi M, Yoshimoto Y, Ando K, Okonogi N, Sato H, Noda SE, Saito J and Nakano T: Radio-sensitization effect of an mTOR inhibitor, temsirolimus, on lung adenocarcinoma A549 cells under normoxic and hypoxic conditions. *J Radiat Res* 56: 663-668, 2015.
117. Chen H, Ma Z, Vanderwaal RP, Feng Z, Gonzalez-Suarez I, Wang S, Zhang J, Roti Roti JL, Gonzalo S and Zhang J: The mTOR inhibitor rapamycin suppresses DNA double-strand break repair. *Radiat Res* 175: 214-224, 2011.
118. Waqar SN, Robinson C, Bradley J, Goodgame B, Rooney M, Williams K, Gao F and Govindan R: A phase I study of temsirolimus and thoracic radiation in non-small-cell lung cancer. *Clin Lung Cancer* 15: 119-123, 2014.
119. Waldner M, Fantus D, Solari M and Thomson AW: New perspectives on mTOR inhibitors (rapamycin, rapalogs and TORKinibs) in transplantation. *Br J Clin Pharmacol* 82: 1158-1170, 2016.
120. Dancey J: MTOR signaling and drug development in cancer. *Nat Rev Clin Oncol* 7: 209-219, 2010.
121. Occhiuzzi MA, Lico G, Ioele G, De Luca M, Garofalo A and Grande F: Recent advances in PI3K/PKB/mTOR inhibitors as new anticancer agents. *Eur J Med Chem* 246: 114971, 2023.
122. Waqar SN, Gopalan PK, Williams K, Devarakonda S and Govindan R: A phase I trial of sunitinib and rapamycin in patients with advanced non-small cell lung cancer. *Chemotherapy* 59: 8-13, 2013.
123. Waqar SN, Bagstrom MQ, Morgensztern D, Williams K, Rigden C and Govindan R: A Phase I Trial of temsirolimus and pemtrexed in patients with advanced non-small cell lung cancer. *Chemotherapy* 61: 144-147, 2016.
124. Riely GJ, Brahmer J, Planchard D, Crinò L, Doebele RC, Lopez LAM, Gettinger SN, Schumann C, Li X, Atkins BM, *et al*: A randomized discontinuation phase II trial of ridaforolimus in non-small cell lung cancer (NSCLC) patients with KRAS mutations. *J Clin Oncol* 30 (Suppl 15): 7532, 011.
125. National Library of Medicine: Adagrasib in Combination With Nab-Sirolimus in Patients With Advanced Solid Tumors and Non-Small Cell Lung Cancer With a KRAS G12C Mutation (KRISTAL-19). *ClinicalTrials.gov* ID NCT05840510. <https://clinicaltrials.gov/study/NCT05840510>.
126. Owonikoko TK, Ramalingam SS, Miller DL, Force SD, Sica GL, Mendel J, Chen Z, Rogatko A, Tighiouart M, Harvey RD, *et al*: A translational, pharmacodynamic, and pharmacokinetic phase IB clinical study of everolimus in resectable non-small cell lung cancer. *Clin Cancer Res* 21: 1859-1868, 2015.
127. Bendell JC, Kelley RK, Shih KC, Grabowsky JA, Bergsland E, Jones S, Martin T, Infante JR, Mischel PS, Matsutani T, *et al*: A phase I dose-escalation study to assess safety, tolerability, pharmacokinetics, and preliminary efficacy of the dual mTORC1/mTORC2 kinase inhibitor CC-223 in patients with advanced solid tumors or multiple myeloma. *Cancer* 121: 3481-3490, 2015.
128. Basu B, Dean E, Puglisi M, Greystoke A, Ong M, Burke W, Cavallin M, Bigley G, Womack C, Harrington EA, *et al*: First-in-human pharmacokinetic and pharmacodynamic study of the dual mTORC 1/2 inhibitor AZD2014. *Clin Cancer Res* 21: 3412-3419, 2015.
129. Heist RS, Infante JR, Campana F, Egile C, Jego V, Damstrup L, Mita M, Grande E and Rizv N: 4430-Pimasertib (Pim) and Sar245409 (Sar)-a Mek and Pi3K/Mtor inhibitor combination: A Phase Ib trial with expansions in selected genotype-defined solid tumors. *Ann Oncol* 25 (Suppl 4): iv146, 2014.
130. National Library of Medicine: Study of the CDK4/6 Inhibitor Palbociclib (PD-0332991) in Combination With the PI3K/mTOR Inhibitor Gedatolisib (PF-05212384) for Patients With Advanced Squamous Cell Lung, Pancreatic, Head & Neck and Other Solid Tumors. *ClinicalTrials.gov* ID NCT03065062. <https://clinicaltrials.gov/study/NCT03065062>.
131. McCay J and Gribben JG: PI3 kinase, AKT, and mTOR inhibitors. In: *Precision Cancer Therapies*. O'Connor OA, Ansell SM and Seymour JF(eds). Vol 1. John Wiley & Sons, Inc., pp113-129, 2023.
132. Saran U, Foti M and Dufour JF: Cellular and molecular effects of the mTOR inhibitor everolimus. *Clin Sci (Lond)* 129: 895-914, 2015.
133. Rodrik-Outmezguine VS, Okaniwa M, Yao Z, Novotny CJ, McWhirter C, Banaji A, Won H, Wong W, Berger M, de Stanchina E, *et al*: Overcoming mTOR resistance mutations with a new-generation mTOR inhibitor. *Nature* 534: 272-276, 2016.
134. Porcelli L, Quatralo AE, Mantuano P, Silvestris N, Rolland JF, Biancolillo L, Paradiso A and Azzariti A: Synergistic antiproliferative and antiangiogenic effects of EGFR and mTOR inhibitors. *Curr Pharm Des* 19: 918-926, 2013.
135. Weigelt B, Warne PH and Downward J: PIK3CA mutation, but not PTEN loss of function, determines the sensitivity of breast cancer cells to mTOR inhibitory drugs. *Oncogene* 30: 3222-3233, 2011.
136. Sanaei MJ, Razi S, Pourbagheri-Sigaroodi A and Bashash D: The PI3K/Akt/mTOR pathway in lung cancer; oncogenic alterations, therapeutic opportunities, challenges, and a glance at the application of nanoparticles. *Transl Oncol* 18: 101364, 2022.
137. Papadimitrakopoulou VA, Soria JC, Jappe A, Jehl V, Klimovsky J and Johnson BE: Everolimus and erlotinib as second- or third-line therapy in patients with advanced non-small-cell lung cancer. *J Thorac Oncol* 7: 1594-1601, 2012.
138. Ponticelli C: The pros and the cons of mTOR inhibitors in kidney transplantation. *Expert Rev Clin Immunol* 10: 295-305, 2015.
139. Boers-Doets CB, Raber-Durlacher JE, Treister NS, Epstein JB, Arends AB, Wiersma DR, Lalla RV, Logan RM, van Erp NP and Gelderblom H: Mammalian target of rapamycin inhibitor-associated stomatitis. *Future Oncol* 9: 1883-1892, 2013.
140. Gartrell BA, Ying J, Sivendran S, Boucher KM, Choueiri TK, Sonpavde G, Oh WK, Agarwal N and Galsky MD: Pulmonary complications with the use of mTOR inhibitors in targeted cancer therapy: A systematic review and meta-analysis. *Target Oncol* 9: 195-204, 2014.
141. Gaumann A, Schlitt HJ and Geissler EK: Immunosuppression and tumor development in organ transplant recipients: The emerging dualistic role of rapamycin. *Transpl Int* 21: 207-217, 2008.
142. El Hage A and Dormond O: Combining mtor inhibitors and T cell-based immunotherapies in cancer treatment. *Cancers (Basel)* 13: 1359, 2021.

