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Research progress on the regulation mechanism of DEPTOR expression and its role in tumorigenesis

Review

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The mammalian target of rapamycin (mTOR) is a critical sensor and integrator of extracellular stimuli and intracellular signaling pathways, forming structurally and functionally distinct protein complexes (mTORC1, mTORC2, and mTORC3) with various proteins. It serves as a central regulator of vital biological processes like cell proliferation, survival, and autophagy. Numerous studies have linked mTOR pathway activation to tumor progression. DEPTOR, a common negative regulator of mTORC1 and mTORC2, exhibits complex loop regulatory mechanisms beyond simple mTOR pathway modulation. Depending on the cell type or tissue environment, DEPTOR can act as either an oncogene or a tumor suppressor gene. Given its complex role in tumorigenesis, precise regulation of DEPTOR expression across different tumor types is imperative. DEPTOR has emerged as a key focus in research on human malignant tumors. While recent years have seen through investigations into DEPTOR expression regulation in tumors, a systematic literature review is lacking. This review provides a detailed summary of the mechanisms regulating DEPTOR expression, an mTOR inhibitor in tumors, covering DNA induction, transcription, translation, and post-translational modification. Additionally, it explores the potential applications of DEPTOR/mTOR signaling axis-related compounds in tumor therapy.

Key words: mTOR signaling pathway; DEPTOR; methylation; transcription factor; microRNA; phosphorylation; ubiquitination; mTOR inhibitors

The mammalian target of rapamycin (mTOR) is an evolutionarily conserved serine/threonine protein kinase pivotal for integrating various extracellular stimulatory and intracellular signaling pathways. It forms distinct protein complexes mTORC1, mTORC2 and a recently discovered mTORC3 to regulate cellular processes like growth, survival, metabolism, autophagy, protein synthesis, and homeostasis [1–3]. In mammalian cells, mTORC1 comprises mTOR, PAPTOR, GβL, PRAS40, and DEPTOR proteins, while mTORC2 includes mTOR, RICTOR, GβL, PROTOR, SIN1, and DEPTOR (Figure 1). mTORC3 involves mTOR, ETV7, and other uncharacterized proteins (Figure 1) [2, 4, 5]. Activation of mTORC1 is primarily mediated by the PI3K/AKT and RAS/MAPK signaling pathways under the stimulation of nutrients, hormones and other external conditions, thereby phosphorylating downstream molecules like S6K1 and 4E-BP1, regulating cell growth via the translation of proteins and the synthesis of nucleotides and lipids and activating the pathways of STAT3, HIF-1α, and PP2A to promote tumor development [6]. Additionally, mTORC1 directly phosphorylates ULK1/2 and ATG13, inhibiting cellular autophagy [7]. Conversely, mTORC2, stimulated by growth factors, phosphorylates AKT, SGK, and PKC, regulating cytoskeletal reorganization, cell motility, cell proliferation, and cell survival (Figure 1) [6]. In addition, mTORC1 can negatively modulate mTORC2 and AKT via the S6K1/IRS/

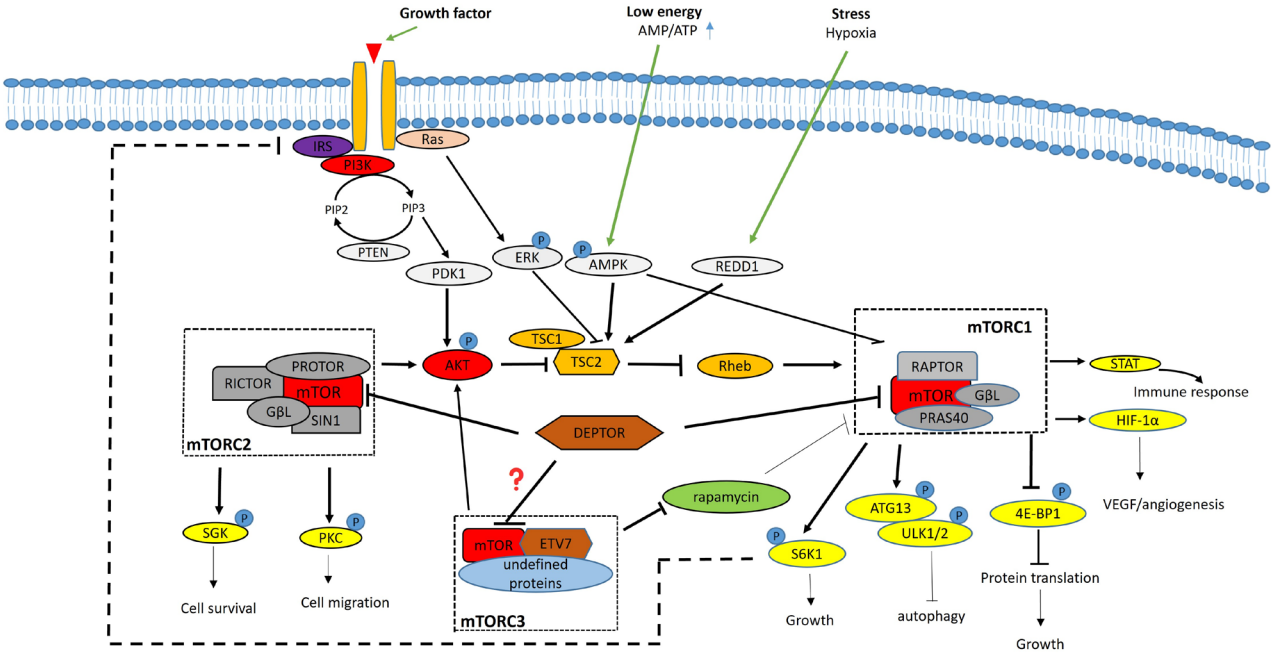

Figure 1. The mammalian target of rapamycin (mTOR) complexes and signaling pathway of mTORC1, mTORC2, and mTORC3. mTORC1 complex is composed of mTOR, RAPTOR, GβL, PRAS40, and DEPTOR proteins; mTORC2 consists of mTOR, RICTOR, GβL, PROTOR, SIN1, and DEPTOR; and mTORC3 consists of mTOR, ETV7, and several other unidentified proteins.

Table 1. Epigenetic regulation of DEPTOR in different tumor types and the postulated function with DEPTOR.

Epigenetic regulatory factors	Tumor types	Function of DEPTOR	Site of action	Ref.
ASS1	Endometrial adenocarcinoma	Decreases the cell sensitivity to arginine	H3K9me2; H3K27me3	[24]
EZH2	Human colorectal carcinoma; kidney diseases	Induces cellular autophagy; promotes apoptosis	H3K27me3	[26, 27]
AR	Prostate cancer	Tumor suppressor	ARE on intron 4 of the DEPTOR gene	[28]

PI3K pathway [8, 9]. In contrast, mTORC3, recently reported in 2018, is only known to be positively associated with tumorigenesis and rapamycin resistance in tumor cells [4]. Given the importance of the mTOR signaling pathway in the regulation of a wide range of cellular physiological functions, dysregulation of this pathway is implicated in various diseases, including metabolic disorders, ageing and cancer, where aberrant activation occurs in over 70% of cancers [10].

DEPTOR, a constituent of mTORC1 and mTORC2, is the sole known co-repressor of these complexes [11]. It interacts with mTOR's FAT domain via its C-terminal containing PDZ structural domain, inhibiting mTORC1 and mTORC2 activity (Figure 2) [12]. Theoretically, it is plausible that DEPTOR also inhibits mTORC3 (Figure 1), potentially acting as a tumor suppressor (Figure 3).

However, in certain cancers like multiple myeloma and T-cell acute lymphoblastic leukemia, high DEPTOR levels inhibit mTORC1, activating the downstream S6K1/IRS/PI3K signaling pathway, promoting AKT phosphorylation and enhancing tumor survival, displaying oncogenic properties (Figure 3) [12, 13]. Due to DEPTOR's intricate regulation of the mTOR signaling pathway and its nuanced role in tumorigenesis, precise control of its expression in different tumor types is crucial. Understanding the diverse mechanisms governing DEPTOR expression in tumors is pivotal for developing DEPTOR/mTOR signaling axis-related therapies.

Recent studies report that the mechanism of DEPTOR expression regulation in tumors is multi-faceted. A previous study has partially summarized the transcription factors and miRNAs that regulate DEPTOR expression. However, this summary is not sufficiently comprehensive. Furthermore, many of the mechanisms regulating DEPTOR expression mentioned in that article are based on predictive analyses and have not been experimentally validated [14]. In this review, we systematically summarize DEPTOR expression regulation across various tumor types, encompassing DNA

induction, transcription, translation, and post-translational modification, and explore the potential of related compounds in tumor therapy.

The regulatory mechanism of DEPTOR expression at the DNA level

Genomic alterations. Genomic alterations, including chromosome amplification and ectopic expressions, significantly influence the onset and progression of certain tumors by directly modulating the expression of genes associated with tumorigenesis [15]. In most tumors, DEPTOR expression tends to be downregulated, indicating a tumor suppressor role, consistent with the widespread activation of the mTOR signaling pathway observed in over 70% of tumors. However, in multiple myeloma, DEPTOR is overexpressed [11, 16]. Analysis of single nucleotide polymorphism data from 114 patients with multiple myeloma revealed that the copy numbers in the chromosome 8q24.12 region (where DEPTOR-encoding genes are located) was increased, leading to upregulated expression of relevant genes [17]. Similarly, a study reported increased copy numbers and elevated DEPTOR expression in 21% of 67 multiple myeloma tissues and 43 multiple myeloma cell lines within the 6 Mb region of chromosome 8q24 [18]. This upregulation of DEPTOR in multiple myeloma cells is crucial for cell survival, possibly due to DEPTOR-mediated inhibition of the downstream mTOR molecule S6K1, thereby alleviating the feedback inhibition of PI3K signaling by mTORC1 and consequently activating the PI3K and AKT signaling pathways [17]. Notably, decreased DEPTOR levels trigger apoptosis in these cells. Moreover, while DEPTOR is generally downregulated in other tumor types, amplification of the chromosomal region containing the DEPTOR locus serves as a significant marker of poor prognosis or tumor progression in certain cancer subpopulations, including breast, prostate, and lung cancers [19, 20].

Epigenetic regulation. Epigenetic modification, such as DNA and histone covalent alterations like methylation, acetylation, and glycosylation significantly influence chromatin structure and related gene expression in eukaryotes [21, 22]. Regarding the epigenetic regulation of DEPTOR, only histone methylation and acetylation modifications in its promoter region have been identified as crucial factors regulating its expression, with no reported studies on DNA methylation modifications affecting DEPTOR expression. The epigenetic regulation of DEPTOR and its postulated function in different tumor types have been compiled in Table 1.

Arginosuccinate synthase 1 (ASS1), a rate-limiting enzyme in arginine biosynthesis, exhibits low expression in many tumors, correlating with poor patient prognosis [23]. Besides, a study reported that the knockdown of ASS1 in human endometrial adenocarcinoma cells induced dimethylation and trimethylation modifications of lysine at position 9 and 27, respectively, of the H3 histone in the DEPTOR promoter region, leading to decreased DEPTOR expression [24]. Their findings suggest that ASS1 may act as an oncogene by demethylating histones in the DEPTOR promoter region rather than methylating DNA sequences, thereby enhancing DEPTOR expression and inhibiting the mTOR signaling pathway, consequently suppressing tumor cell migration and invasion. However, the specific mechanism by which ASS1 regulates histone methylation in the DEPTOR promoter region remains unexplored.

Members of the Switch/Sucrose Non-Fermentable (SWI/SNF) protein family typically regulate the transcription of related genes by altering chromatin structure. Baf60c, a SWI/SNF family member, was found to regulate histone methylation modifications in the DEPTOR promoter region [25]. Gene chip experiments and human cell studies revealed that Baf60c promotes DEPTOR expression [25]. Mechanistically, one study demonstrated that Baf60c altered the chromatin

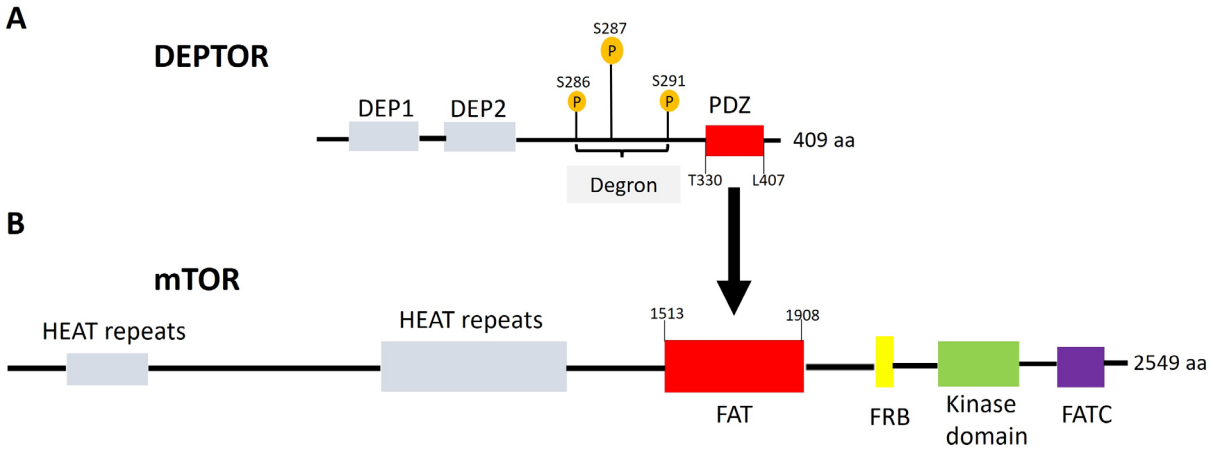

Figure 2. The PDZ domain of DEPTOR interacts with the FAT domain of mTOR. A) Overall domain of DEPTOR protein. B) Overall domain of mTOR protein.

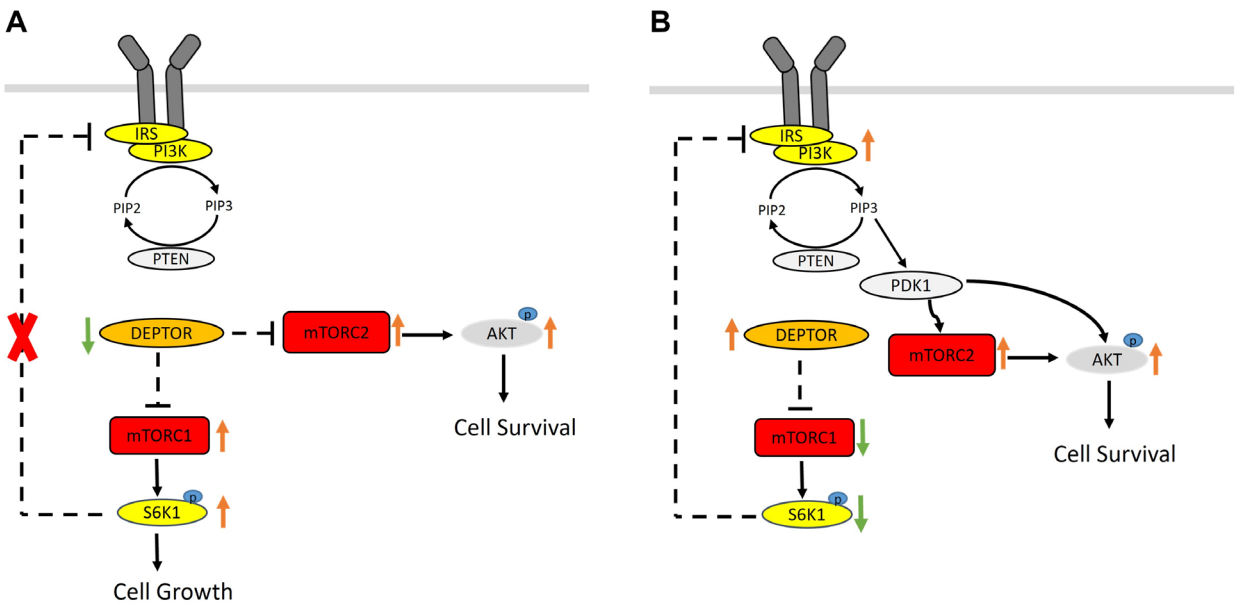

Figure 3. Depending on specific cell types or different tissue environments, DEPTOR can exhibit either oncogenic activity or tumor-suppressive effects. A) DEPTOR acts as a tumor suppressor, and B) DEPTOR acts as an oncogene.

Table 2. Regulation of DEPTOR by transcription factors in different tumor types and the postulated function with DEPTOR.

Transcription factors	Tumor types	Function of DEPTOR	Site of action	Ref.
mTORC1; mTORC2	Multiple myeloma	Oncogene	/	[11]
c-MAF/MAFB	Multiple myeloma	Oncogene	/	[11, 34, 35]
Che-1	Multiple myeloma	Oncogene	/	[37]
NOTCH1	T-ALL	Oncogene	/	[41]
P53	Multiple cancers	Suppresses cell growth and chemosensitivity	RRRC(A/T)(A/T)GYYY (0-13bp)RRR C(A/T)(A/T)GYYY	[13]
ErBb2	Breast cancer	Induces cellular autophagy	HAS (TCAAATTTC)	[44]
c-Myc	Colorectal cancer	Oncogene	E-Box sequence (CAGGTG)	[49]
ERα	Breast cancer	Tumor suppressor	ERE:AGGTCAnnnnTGACCT)-like sequences	[53]

structure and epigenetic state of DEPTOR by increasing the trimethylation modification of lysine 4 of the proximal H3 histone in the promoter region while decreasing the dimethylation of lysine 9 of the distal promoter, typical epigenetic marks associated with chromatin relaxation and transcriptional activation. Additionally, Baf60c acts as a coactivator, interacting directly with the transcription factor Six4 to co-stimulate DEPTOR expression [25]. Physiologically, Baf60c and Six4-mediated DEPTOR activation is essential for promoting the AKT signaling pathway and driving myocyte glycolysis [25].

Furthermore, another study independently demonstrated that EZH2 methyltransferase mediates the trimethylation of lysine 27 in the H3 histone within the DEPTOR promoter region, negatively regulating DEPTOR expression [26, 27]. However, in contrast to Siqi et al., Fuzheng et al. reported that the methylation modification of the DEPTOR site by EZH2 is mediated by nucleosome remodeling and metastasis-associated protein 2 in the histone deacetylase complex. Moreover, they also observed that the deletion of EZH2 in cancer cells inhibits the mTOR signaling pathway and induces cellular autophagy [26]. Conversely, the previous study observed the regulation of DEPTOR by EZH2 in renal tubular cells [27]. Treatment with 3- deazaneplanocin A (DZNep), a specific EZH2 inhibitor, elevates DEPTOR protein levels, inhibits mTORC1 and mTORC2 activities and ultimately induces apoptosis in renal tubular cells, suggesting a potential therapeutic avenue for renal protection [27].

In terms of histone acetylation modification, dihydrotestosterone (DHT), an androgen receptor (AR) activator, was found to suppress DEPTOR mRNA expression in prostate cancer cells in a time-dependent manner. Co-treatment with bicalutamide, an AR antagonist, significantly restored DEPTOR mRNA levels [28]. Further CHIP experiments

confirmed the ability of AR to bind to the androgen response element (ARE) on intron 4 of the DEPTOR gene. Additionally, acetylation modification of lysine at positions 9 and 14 of the H3 histone within this region was significantly reduced after DHT treatment [28]. Although the precise mechanism by which AR regulates H3 histone acetylation and mRNA levels on the DEPTOR intron requires further investigation, it is known that AR can recruit histone deacetylases to the ARE region of the E-cadherin gene, thereby regulating its expression [29]. Moreover, histone acetylation can promote the transcriptional activation of related genes [30]. In summary, AR likely binds to the ARE on the 4th intron of DEPTOR, recruiting histone deacetylases to this region, thus deacetylating H3 histones and inhibiting mRNA transcription; however, the related mechanism requires further experimental verification. Moreover, AR is established to play an important role in the development and progression of prostate cancer by downregulating DEPTOR levels and activating the mTORC1/S6K/cyclin D1 signaling pathway. This provides a theoretical basis for the clinical use of the AR antagonist, bicalutamide, in prostate cancer treatment.

The regulation of DEPTOR expression at the transcriptional level

The most efficient mechanism for genes to exhibit differential expression across various tumor types or specific environments is through the transcriptional regulation of specific genes. Numerous transcription factors and cofactors have been identified to participate in the regulation of DEPTOR gene transcription. These transcription-associated factors respond to diverse conditions by directly binding to specific DNA sequences, such as promoters or enhancers of DEPTOR genes, thereby modulating DEPTOR gene transcription. The regulation of DEPTOR by transcription factors and the proposed functions of DEPTOR in different types of tumors have been compiled in Table 2.

mTOR signaling pathway. DEPTOR's regulation of the mTOR signaling pathway involves complex feedback loops rather than simple linear regulation. Studies have found that while DEPTOR can inhibit mTORC1 and mTORC2 activity, these complexes can also negatively regulate DEPTOR mRNA expression [11]. Similarly, other studies reported that the transforming growth factor TGF-β activates mTORC1, leading to the downregulation of DEPTOR levels [31]. Additionally, epidermal growth factor receptor (EGFR) activation downregulates DEPTOR levels by promoting downstream mTOR protein phosphorylation, with EGFR expression negatively correlated with DEPTOR in lung adenocarcinoma tissues [32]. Meanwhile, deletion of PTEN, an upstream activator of the PI3K/AKT/mTOR signaling pathway, also downregulates DEPTOR expression in various tumors [33]. However, the precise mechanism by which growth factor signaling pathways inhibit DEPTOR expression remains unclear. It appears that mTORC1 and mTORC2 play crucial roles in this process, as direct inhibition of these complexes significantly enhances DEPTOR expression [11]. Whether mTORC1 and mTORC2 regulate DEPTOR expression by degrading DEPTOR transcripts or by directly inhibiting DEPTOR transcription requires further investigation.

c-MAF and MAFB transcription factors. In multiple myeloma, where DEPTOR is frequently overexpressed, this phenomenon is often associated with increased chromosome copy numbers harboring the DEPTOR gene [16]. Further in-depth studies have revealed that this upregulation is mediated by genetic translocation of the transcription factors c-MAF and MAFB, both members of the transcription factor family regulating cell differentiation [11, 34, 35]. Consistent with this, a study on transcriptional profiling reported that high MAFB expression induces DEPTOR expression [34]. Moreover, the knockdown of c-MAF reduces both mRNA and protein levels of DEPTOR in multiple myeloma cells [34]. However, whether these two transcription factors directly or indirectly regulate DEPTOR transcription requires further investigation.

Che-1 apoptosis antagonist transcription factors and Sirt1/NAT10/Che-1 pathway. Che-1, also known as the Rb-binding protein, acts as an apoptosis-antagonizing transcription factor, regulating gene transcription by interacting with RNA polymerase II [36]. In response to various cellular stresses, such as DNA damage, hypoxia, and glucose deprivation, Che-1 undergoes phosphorylation, thereby regulating the expression of various genes to facilitate cell adaption and survival [36]. Under conditions of hypoxia and genotoxic stress, Che-1 activation promotes DEPTOR expression in cancer cells thereby negatively regulating mTOR kinase activity [37]. Specifically, upon stress induction, phosphorylated Che-1 synergizes with RNA polymerase II to directly bind to the DEPTOR promoter, facilitating its transcription and expression. Failure of Che-1 to fully phosphorylate results in its inability to bind to the DEPTOR promoter, underscoring the significance of Che-1 phosphorylation in DEPTOR expression control. Consistently, a positive correlation between Che-1 and DEPTOR expression levels was observed during multiple myeloma progression [38]. Additionally, besides promoting DEPTOR expression, Che-1 also regulates the expression of REDD1, another mTORC1 inhibitor, in stressed cells [37]. Che-1 serves as an autophagy regulator, and under conditions of adequate energy supply, NAT10 (acetyltransferase) acetylates Che-1 at K228, thereby inhibiting Che-1-mediated transcriptional activation of the downstream genes Redd1 and Deptor. Conversely, under conditions of low energy or stress, NAT10 is deacetylated by Sirt1 (NAD-dependent deacetylase), resulting in the inhibition of NAT10-activated rRNA production [39]. These observations suggest that Che-1 may increase the expression of both DEPTOR and REDD1 to ensure a high level of mTOR inhibition in response to multiple stress stimuli.

Six4 transcription factors. Six4, belonging to the SIX family of proteins, primarily participates in organ develop-

mental processes such as muscle regeneration and neurogenesis as a trans-activator [40]. Genomatix motif analysis predicted a Six4 binding site 1.6 kb upstream of the DEPTOR gene's transcription start site [25]. Chromatin immunoprecipitation experiments confirmed that Six4 acts as a transcription factor and cooperates with Baf60c to directly bind to the Six4 binding site on the DEPTOR promoter. This interaction stimulates DEPTOR expression and activates the AKT signaling pathway in myofibroblasts, promoting glycolytic metabolism [25].

NOTCH1 signaling pathway. DEPTOR exhibits high expression not only in multiple myeloma but also in T-cell leukemia (T-ALL), playing a crucial role in leukemia development [41]. Related mechanistic studies revealed a positive correlation between DEPTOR and NOTCH1 expression levels in primary T-ALL samples. NOTCH1, a proto-oncogene, acts as a transcriptional activator of DEPTOR in T-ALL cells by directly binding to its promoter, promoting its expression [41]. Elevated DEPTOR levels further activate AKT, ultimately driving T-ALL cell proliferation [41]. Notably, reducing DEPTOR levels directly induces cell death and significantly inhibits T-ALL in the xenograft animal models. These findings highlight the transcriptional control of DEPTOR and its regulation of AKT as a novel mechanism by which NOTCH1 drives T-ALL genesis, offering a new molecular basis for AKT inhibitor use in T-ALL therapy.

Oncogene P53. The tumor suppressor p53 regulates crucial biological processes such as cell cycle arrest, DNA damage repair, and apoptosis by transcriptionally activating or repressing downstream target genes in response to various cellular stresses, including DNA damage, oncogenic activation and ribosomal stress, thereby maintaining cellular stability [13]. Increasing evidence indicates that p53 induces the transcription of multiple repressors upstream of mTORC1, including PTEN, TSC2, and REDD1, leading to mTORC1 activity inhibition and exerting tumor suppressor effects [42]. Recently, one study has found that p53 can also transcriptionally activate DEPTOR to inhibit the mTOR signaling pathway [13]. The study identified a typical p53-binding motif in the DEPTOR promoter region (–196~–169) RRRC(A/T)(A/T)GYYY(0–13bp)RRRC(A/T)(A/T)GYYY (R stands for A or G, Y stands for C or T, and N stands for any nucleotide). p53 activates the transcription of the DEPTOR gene by binding directly to this region and consequently inhibiting AKT activity to suppress cell proliferation and survival [13]. Additionally, p53-enhanced DEPTOR expression attenuates the feedback inhibition of IRS1 by S6K1, further activating AKT and inducing cellular resistance to adriamycin [13]. This study unveils a novel mechanism by which p53 regulates cell proliferation, survival and sensitivity to chemotherapeutic agents through direct activation of DEPTOR expression.

Tyrosine kinase receptor ErbB2. ErbB2, a classical tyrosine kinase receptor of the EGFR family, plays a pivotal role in transmitting extracellular signals to the intracellular matrix [43]. Typically, upon cellular stimulation, ErbB2 is recruited as a co-receptor to form heterodimers with other ERBB family members (e.g., ErbB1 and ErbB3), leading to phosphorylation and activation of its kinase structural domain. This activation initiates downstream signaling pathways, including the PI3K/AKT/mTOR pathway and the MAPK pathway, promoting cell proliferation, survival, and invasion [43]. Recent studies have revealed an additional function of phosphorylated ErbB2 in breast cancer cells, wherein ErbB2 translocates to the nucleus upon phosphorylation through the nuclear localization sequences in its amino acid sequence, where it binds to the ErbB2 binding site on the DEPTOR promoter. This interaction inhibits DEPTOR gene transcription, activates the PI3K/AKT/mTOR pathway and inhibits cellular autophagy [44]. ErbB2 overexpression is observed in 20–30% of breast cancer cases and is associated with poorer patient prognosis, lymph node metastasis and drug resistance [45]. Therefore, ErbB2 serves as a biomarker for breast cancer prognosis and a therapeutic target in cancer treatment.

NF-κB signaling pathway. The nuclear factor NF-κB complex comprises multicomponent proteins and functions as an inducible transcription factor involved in diverse biological processes, including cell proliferation, immune response, inflammation, cell survival and tumorigenesis [46]. The most common form of NF-κB is a heterodimer formed by the p65 and p50 proteins. In its inactive state, this dimer binds to IκBs inhibitory proteins, masking the nuclear localization signal (NLS) on p65 and p50 [46]. Stimulation by pro-inflammatory factors, such as cytokines, pathogens and hazard-associated molecules, activates the IKK protein complex, which phosphorylates IκBs inhibitory proteins, leading to their degradation by the ubiquitin-proteasome system and unmasking of the NLS, allowing NF-κB translocation to the nucleus [47, 48]. Furthermore, another study has shown that DEPTOR mRNA and protein levels were significantly reduced in a mouse model of LPS-induced hepatic inflammation, accompanied by mTOR signaling pathway activation [46]. Mechanistically, after inflammatory signals activate the NF-κB signaling pathway, the p65 active subunit of the NF-κB complex directly binds to the –145/–127 region on the DEPTOR promoter, thereby repressing DEPTOR gene transcription [46]. This study suggests that DEPTOR plays a crucial role in regulating hepatic inflammatory responses through the mTOR signaling pathway.

Wnt/β-Catenin/c-Myc signaling pathway. The Wnt/β-Catenin signaling pathway drives colorectal cancer progression by upregulating downstream target genes like the proto-oncogene c-Myc [49]. However, the key downstream targets that mediate the oncogenic role of c-Myc in colorectal cancer remain unexplored. Recent studies have identified DEPTOR, an mTOR inhibitor, as a direct target of Wnt/β-Catenin/c-Myc signaling in colorectal cancer cells [49]. c-Myc recognizes and binds to the E-Box sequence (5'-CAGGTG-3') in the –1131/–779 region of the DEPTOR promoter, stimulating

DEPTOR mRNA transcription and expression [49]. Intriguingly, high DEPTOR expression is observed in colorectal cancer cells, and DEPTOR knockdown reduces Bmi1 expression and inhibits colorectal cancer cell proliferation. These findings suggest that DEPTOR exerts a tumor-promoting role in colorectal cancer. Furthermore, co-targeting Wnt/β-Catenin and mTOR signaling pathways simultaneously enhances the anticancer effects, providing a theoretical basis for the synergistic combination of Wnt and mTOR inhibitors for treating colorectal cancer with elevated c-Myc levels.

Glucocorticoid receptor GR and transcriptional co-repressor Brd2. Numerous studies have underscored the significance of mTORC1 in the regulation of lipid metabolism and adipogenesis [50]. David et al. discovered that DEPTOR inhibits mTORC1 kinase activity. Subsequently, it was discovered that glucocorticoids regulate DEPTOR expression during adipogenesis [50]. Bioinformatics analysis identified a conserved glucocorticoid response element (GRE) in the DEPTOR promoter region. Upon glucocorticoid stimulation, the glucocorticoid receptor binds to the GRE element on the DEPTOR promoter, promoting its expression. Elevated DEPTOR levels activate the pro-adipogenic AKT/PKB-PPAR-γ signaling axis by inhibiting mTORC1-mediated feedback inhibition of insulin signaling [50]. Additionally, another study reported that a transcriptional co-repressor Brd2 regulates the insulin signaling pathway by repressing GR binding to the DEPTOR promoter, thus inhibiting DEPTOR expression [51].

Estrogen receptor ERα. Estrogen receptors (ERs), including ERα and ERβ (both of which require binding to estrogen to be activated), play crucial roles in breast cancer progression [52, 53]. Activated ERα and ERβ serve as transcription factors to regulate the expression of downstream target genes and the activation of oncogenic signaling pathways such as PI3K/AKT/mTOR in the cytoplasm [52, 53]. ER-positive breast cancer accounts for up to 75% of cases, highlighting its significance in breast cancer progression [53]. Notably, in breast cancer cells ERα directly promotes DEPTOR expression to counterbalance estrogen activation of the PI3K/AKT/mTOR signaling pathway [53]. Moreover, target genes regulated by ERα typically harbor more than one estrogen response element (ERE: AGGTCAnnnnTGACCT)-like sequences in their proximal promoter regions and/or within 200 kbp of the transcription start site [53]. Currently, three ERE-similar sequences have been identified within 100 kbp of the DEPTOR transcriptional start site, potentially cooperating as enhancers to facilitate ERα recruitment to the proximal promoter region, thus ensuring the transcriptional regulation of the DEPTOR gene. However, the specific regulatory mechanism of ERα on DEPTOR requires further study. Overall, combining mTOR inhibitors with endocrine therapy may offer a more effective treatment strategy for patients with advanced ER-positive breast cancer.

mRNA level-related regulatory mechanisms of post-transcriptional DEPTOR

The DEPTOR mRNA is regulated by RNA-binding proteins and micro-RNAs (miRNAs), which contribute to the alteration of DEPTOR protein content in cancer cells. Relevant miRNAs are compiled in Table 3.

PUM1 inhibits DEPTOR transcript degradation. RNA-binding proteins (RBPs) directly interact with RNA, exerting regulatory control over gene expression post-transcriptionally. These proteins engage in various processes such as pre-mRNA cleavage, mRNA stability maintenance, and translation, thereby influencing the expression of target [54]. PUM1 is a sequence-specific RBP that binds with high affinity and specificity to RNA sequences known as the Pumilio Response Element (PRE), modulating the response of the corresponding mRNA [55]. The PRE sequence, 5'-UGUANAUA-3', where N represents any nucleotide, serves as a binding site for PUM1. Furthermore, transcriptome sequencing and differential gene expression analysis identified PRE sequences on DEPTOR mRNA in gastric cancer cells, suggesting DEPTOR mRNA as a target of PUM1 [55]. Moreover, RNA immunoprecipitation experiments confirmed PUM1 binding to the 3'-untranslated region (UTR) of DEPTOR mRNA, facilitating its translational expression by inhibiting mRNA degradation [55]. Physiologically, PUM1-mediated upregulation of DEPTOR disrupts the normal inhibitory feedback between mTORC1 and PI3K, leading to sustained activation of the PI3K/AKT signaling pathway and promoting glycolytic metabolism in gastric cancer cells [55]. Overall, the findings of the above studies unveil the significance of the PUM1/DEPTOR signaling axis in gastric cancer progression, offering novel targeting mechanisms and therapeutic strategies for gastric cancer treatment.

Table 3. Regulation of DEPTOR by miRNAs in different tumor types and the postulated function with DEPTOR.

miRNAs	Tumor types	Function of DEPTOR	Site of action	Ref.
miR-135b	Multiple myeloma	Oncogene	AAGCCAU	[34]
miR-642a	Multiple myeloma	Oncogene	GAGGGAA	[34]
miR-155	Breast cancer; Diffuse large B-cell lymphoma	Tumor suppressor	AGCAUUAA	[57-59]
miR-671-3p	Breast cancer	Tumor suppressor	GAACCGG	[66]
miR-592	Medulloblastoma	Tumor suppressor	UGACACA	[67]

Regulation of DEPTOR mRNA by miRNAs. miRNAs are short, non-coding single-stranded RNAs typically comprising 19-25 nucleotides. They regulate gene expression by binding, usually in a partially complementary manner, to the 3'-UTR region of target mRNAs, leading to mRNA degradation and translation repression [56]. miRNAs represent a crucial mode of post-transcriptional gene regulation.

miR-135b and miR-642a. In the context of multiple myeloma (especially in patients carrying the c-MAF and MAFB translocations), where DEPTOR is frequently overexpressed, reduced expression of miR-135b and miR-642a contributes significantly to DEPTOR upregulation [34]. *In silico* analysis indicated that DEPTOR mRNA may be a direct target of miR-135b and miR-642a. Luciferase gene reporter experiments confirmed that miR-135b and miR-642a directly bind to DEPTOR mRNA, resulting in DEPTOR protein downregulation and subsequent plasma cell dedifferentiation [34].

miR-155. Independent studies have revealed that miR-155, a miRNA with multiple roles in physiological and pathological processes, can regulate DEPTOR expression in breast cancer cells and diffuse large B-cell lymphoma, which in turn affects mTOR signaling pathway activity [57–59]. In the corresponding cell lines, the overexpression of miR-155 inhibited DEPTOR expression. Site-directed mutagenesis identified a binding site for miR-155 in the 3'-UTR of DEPTOR mRNA. Mutation of this site inhibited miR-155-mediated regulation of DEPTOR protein expression, underscoring the specific interaction between miR-155 and DEPTOR mRNA [57–59].

miR-181a. TGFβ stimulation is implicated in cell hypertrophy and matrix protein increase in various renal diseases including diabetic nephropathy [60]. Studies report that in thylakoid cells, TGFβ promotes mTOR signaling pathway activity by inhibiting DEPTOR expression, yet the precise mechanism remains unclear [61]. Meanwhile, another research group demonstrated that TGFβ downregulates DEPTOR protein levels by upregulating miR-181a expression in thylakoid cells [62]. A partially complementary sequence to miR-181a exists in the 3'-UTR of DEPTOR mRNA. Enhanced miR-181a levels elevate mTORC1 and mTORC2 activity by downregulating DEPTOR expression, thereby promoting 4EBP-1 and eEF2 phosphorylation, which fosters protein synthesis and thylakoid hypertrophy [62].

miR-182. Numerous studies have demonstrated the pivotal role of miRNAs in the repair of tissues and organs post-injury [63]. Notably, miR-182 expression is downregulated in intestinal ischemia/reperfusion (I/R) injury [64]. Upregulation of miR-182 mitigates intestinal injury, decreases autophagy levels and DEPTOR expression and enhances mTOR signaling pathway activity post I/R [64]. Bioinformatics analysis coupled with dual luciferase reporter gene assays corroborated miR-182 targeting of the 3'-UTR region of DEPTOR mRNA, thereby downregulating DEPTOR levels. Importantly, DEPTOR is instrumental in miR-182-mediated gut protection regulation [64].

miR-671-3p. Breast cancer is the most prevalent female malignant tumor worldwide, with rising incidence rates in recent years and an increasing trend toward the younger population [65]. The discovery of metastasis-associated miRNAs has provided new ideas for studying breast cancer metastasis. Studies have shown that overexpression of miR-671-3p significantly inhibited the proliferation and invasive migration ability of breast cancer cells, whereas the inhibition of miR-671-3p expression had opposite effects on these functions [66]. Further mechanistic studies demonstrated that the DEPTOR protein is a direct target gene of miR-671-3p. Moreover, a complementary sequence within the 3'-UTR of DEPTOR mRNA facilitates miR-671-3p-mediated downregulation of DEPTOR expression, influencing breast cancer cell behavior [66]. This study underscores the potential of miR-671-3p expression levels as diagnostic indicators and therapeutic targets in the early diagnosis and treatment of breast cancer.

miR-592. Medulloblastoma, a prevalent pediatric brain malignancy, encompasses four molecular subgroups, namely WNT, SHH, Group 3, and Group 4 [67]. miR-592 expression in Group 3 subgroup medulloblastoma attenuates non-anchored cell growth, invasiveness, and tumorigenicity [67]. DEPTOR is a potential target of miR-592, with a complementary sequence identified in the 3'-UTR of DEPTOR mRNA [67]. Further studies revealed that miR-592-mediated reduction in DEPTOR expression activates the mTORC1 and mTORC2 complexes in medulloblastoma cells. Interestingly, miR-592 expression reduced AKT kinase activity, which could be attributed to the activation of inhibitory feedback loops in the mTOR signaling pathway [67]. Additionally, miR-592 expression upregulated ERK1/ERK2 kinase activity, resulting in the activation of the MAPK signaling pathway. Thus, miR-592 overexpression is a potential driver of medulloblastoma, which confers its characteristic neuronal differentiation-related gene expression profiles by activating the mTOR and MAPK signaling pathways.

miR-96-5p. A recent study unveiled DEPTOR as a regulatory target of miR-96-5p [68]. The expression of miR-96-5p and DEPTOR showed a negative correlation in nasal mucosal tissues of patients with allergic rhinitis [68]. Decreased miR-96-5p expression in an allergic rhinitis cell model inhibited pro-inflammatory cytokine expression and mTOR/NF-κB signaling pathway by targeting DEPTOR [68]. Bioinformatics combined with dual luciferase assays and RNA immunoprecipitation experiments collectively confirmed DEPTOR as a direct target of miR-96-5p. Thus, miR-96-5p holds promise as a diagnostic marker and therapeutic target for allergic rhinitis.

Related mechanisms of post-translational modifications regulating DEPTOR levels and activity

Post-translational modification encompasses the chemical alterations of proteins following transcription and transla-

tion, catalyzed by various enzymes. These modifications, including ubiquitination, phosphorylation, and methylation, play crucial regulatory roles in protein stability, activation, localization, and interactions. DEPTOR proteins undergo diverse post-translational modification mechanisms, impacting the occurrence and progression of numerous tumors.

Ubiquitination and deubiquitination modifications regulate DEPTOR protein levels. Ubiquitination serves as a fundamental mechanism for protein degradation via the proteasome system, thereby regulating protein abundance and activity [69]. The ubiquitination modification of proteins involves a three-step enzymatic reaction catalyzed by the E1 ubiquitin activating enzyme, E2 ubiquitin coupling enzyme and E3 ubiquitin ligase, with E3 ubiquitin ligase playing a key role in substrate recognition and ubiquitination [69]. Several E3 ubiquitin ligases targeting DEPTOR proteins have been listed in Table 4.

Three independent groups concurrently discovered that the $SCF^{\beta\text{-}TrCP}$ E3 ligase complex orchestrates the ubiquitination and subsequent degradation of DEPTOR [19, 70, 71]. The β-TrCP subunit in the $SCF^{\beta\text{-}TrCP}$ complex recognizes a specific degradation motif, termed the β-TrCP degradation motif, which includes the DSGXXS sequence or its variants (DSG/EEG/SSG/TSGXXS/E/D) [72]. Notably, the β-TrCP degradation motif is also present in the DEPTOR amino acid sequence, with different molecular mechanisms reported by the three independent groups for the ubiquitination of DEPTOR [12]. The model proposed by Shanshan et al. suggests that mTOR phosphorylates the S293 and S299 sites on DEPTOR under mitogen stimulation, which, in turn, promotes the phosphorylation of Ser286, Ser287, and Ser291 in the β-TrCP degradation motifs by kinase CK I α and consequently resulting in the ubiquitination and degradation of DEPTOR by $SCF^{\beta\text{-}TrCP}$ [19]. Similarly, Daming et al. revealed that mTOR first pre-phosphorylates Ser293, Tyr295, and Ser299 on DEPTOR before CKIα- mediated phosphorylation of Ser286 and Ser287 in the β-TrCP degradation motifs [70]. Conversely, Yongchao et al. found that Ser286, Ser287, and Ser291 sites in the β-TrCP degradation motif of DEPTOR were phosphorylated by S6K1 and RSK1 [71]. However, specific inhibitors of S6K1 fail to inhibit the degradation of DEPTOR, suggesting that the regulation of DEPTOR by S6K1 is controversial [70]. The above study used rapamycin to block S6K1 activity, wherein the inhibition of DEPTOR phosphorylation could also result from reduced mTORC1 activity. Moreover, the regulation of DEPTOR phosphorylation and degradation by RSK1 may also be indirect. RSK1 has been reported to activate mTORC1 by phosphorylating TSC2, with RSK1 inhibition indirectly reducing DEPTOR phosphorylation by decreasing mTORC1 activity [73]. Overall, the proposed mechanisms of DEPTOR degradation require further investigation.

Recent study suggests that DEPTOR might serve as a substrate for Cul5/Elongin B E3 ubiquitin ligase [74]. They suggested that the autophagy-regulating factor AMBRA1 binds to and inhibits Cul5, leading to the accumulation of DEPTOR and subsequent mTOR inactivation [74]. However, the precise mechanism underlying Cul5/Elongin B E3 ubiquitination in DEPTOR degradation requires further elucidation.

Recently, it was reported that the E2 ubiquitin-coupled enzyme UBE2C is crucial for the growth of lung cancer cells harboring the Kras mutation and for lung carcinogenesis [75]. Briefly, in lung cancer cells, UBE2C combined with the E3 ubiquitin ligase APC/C^{CDH1} ubiquitinates DEPTOR and induces its degradation, thereby regulating lung cancer progression [75]. Notably, their study also found that DEPTOR protein levels fluctuated with the progression of the cell cycle, being lowest in the G1 phase, coinciding with the high activity of APC/C^{CDH1}. Moreover, the fluctuation of DEPTOR protein levels was dependent on UBE2C and APC/C^{CDH1} rather than $SCF^{\beta\text{-}TrCP}$ [75]. Therefore, targeting UBE2C and APC/C^{CDH1} may present a novel strategy for treating lung cancer associated with Kras mutations.

Protein ubiquitination is a reversible process, and DEPTORs modified by ubiquitination can also be deubiquitinated to maintain equilibrium by various mechanisms. The deubiquitinating enzymes targeting DEPTOR and postulated function with DEPTOR in different types of tumors have been listed in Table 5.

Firstly, it was reported that the demethylase KDM4A significantly reduces DEPTOR ubiquitination mediated by $SCF^{\beta\text{-}TrCP}$, thereby enhancing its protein level [76]. Interestingly, this process relies on the demethylation activity of KDM4A. However, the specific substrates of KDM4A-mediated demethylation and its regulatory mechanism in DEPTOR ubiquitination remain unclear. Secondly, under conditions of amino acid deprivation, the protease OTUB1 inhibits mTORC1 activity by binding to DEPTOR through its N-terminal structural domain and mediating its deubiquitination, thereby stabilizing DEPTOR protein levels [77]. Similarly, another study identified a novel gene, UBTOR, which stabilizes DEPTOR in the mTOR complex by reducing

Table 4. Ubiquitination enzymes targeting DEPTOR and the postulated function with DEPTOR.

Ubiquitination enzymes	Tumor types	Function of DEPTOR	Site of action	Ref.
$SCF^{\beta\text{-}TrCP}$ E3 ligase	Multiple cancers	Inhibits mTOR activity	(DSG/EEG/SSG/TSGXXS/E/D)	[19, 70, 71]
Cul5/Elongin B	/	Inhibits mTOR activity	/	[74]
UBE2C	Kras mutation-associated lung cancer	Tumor suppressor	/	[75]

its ubiquitination as a deubiquitinating enzyme. Mechanistic findings suggest that UBTOR, a deubiquitinating enzyme, binds to DEPTOR through its N-terminal UBTOR$^{1\text{-}467}$ and reduces the ubiquitination of DEPTOR, thereby stabilizing the expression level of DEPTOR [78]. Additionally, a study published in 2022 identified another deubiquitinating enzyme, USP7, which removes ubiquitin modifications from DEPTOR [79]. Specifically, the phosphorylation of the Ser235 site on DEPTOR by ERK1 recruits USP7, maintaining its interaction and protecting DEPTOR from polyubiquitination and subsequent proteasomal degradation [79]. Recently, a new study discovered that Numb, a multifunctional adaptor protein, binds to the adaptor protein SKP1, thereby blocking its interaction with β-TrCP, a component of SCF$^{\beta\text{-TrCP}}$. This interaction inhibits the ubiquitination of DEPTOR, thereby promoting autophagy [80].

Phosphorylation modifications regulate DEPTOR protein activity. In addition to the above phosphorylation modifications directly related to DEPTOR ubiquitination and deubiquitination, DEPTOR is also regulated by a variety of other phosphorylated kinases. The phosphorylation kinases of DEPTOR and its proposed functions in different types of tumors have been listed in Table 6.

In cardiomyocytes, P38γ mediates the phosphorylation of four amino acid sites on DEPTOR (Ser145, Ser244, Ser265, and Ser293) while p38δ mediates the phosphorylation at two sites (Ser265 and Thr321). These phosphorylation events promote DEPTOR degradation, ultimately controlling cardiac size [81]. However, the precise mechanism by which P38γ and p38δ synergistically phosphorylate DEPTOR, whether they form a heterodimer, and the subsequent steps in DEPTOR degradation require further investigations.

Recently, by using adventitious protein biotin labeling and assay experiments, a study proposed a novel mechanism for regulating DEPTOR activity using [82]. They discovered that spleen tyrosine kinase (SYK) phosphorylates the Tyr289 site on DEPTOR in an ephrin receptor-dependent manner. This phosphorylation disrupts the interaction between DEPTOR and mTOR kinases, leading to rapid and sustained activation of mTORC1 and mTORC2 [82]. Notably, Tyr289 is situated within the β-TrCP degradation motif involved in DEPTOR degradation. It is plausible that phosphorylation at this site may interfere with other post-translational modifications in this region, potentially blocking CKIα/β-TrCP-mediated DEPTOR degradation. However, further experimental validation is necessary to confirm this hypothesis and elucidate its implications fully.

Glycine N-methyltransferase regulates DEPTOR activity. Glycine N-methyltransferase (GNMT) is a folate-binding protein known to regulate the ratio of S-adenosylmethionine to S-adenosylhomocysteine and acts as a tumor suppressor in hepatocellular carcinoma [83]. Recent research has revealed that GNMT interacts with DEPTOR through its C-terminal region, binding to the PDZ structural domain of DEPTOR [84]. This interaction has been shown to neutralize the activation of AKT by DEPTOR. However, the precise mechanism by which GNMT regulates DEPTOR activity remains to be fully elucidated, necessitating further investigation in follow-up studies.

Research progress on DEPTOR/mTOR signaling axis-related compounds

The role of DEPTOR in cancer remains contentious, as it can exhibit oncogenic or tumor-suppressive activities depending on the specific cell or tumor type. However, emerging evidence suggests that DEPTOR may act as an oncogene in certain cancers such as multiple myeloma and T-cell leukemia [11, 41]. Consequently, pharmacological inhibition of DEPTOR could hold promise for the treatment of such tumors. NSC12640 is one such compound identified to bind to the PDZ-binding domain of DEPTOR disrupting its interaction with mTOR [85]. Studies have indicated that multiple myeloma cells with high DEPTOR expression are highly sensitive to NSC12640 [85].

Table 5. Deubiquitinating enzymes targeting DEPTOR and the postulated function with DEPTOR.

Deubiquitinating enzymes	Tumor types	Function of DEPTOR	Ref.
KDM4A	Glioma; Acute myeloid leukemia	Tumor suppressor	[76]
OTUB1	Multiple cancers	Tumor suppressor	[77]
UBTOR	Glioblastoma	Tumor suppressor	[78]
USP7	Multiple myeloma	Oncogene	[79]

Table 6. Phosphorylation modification and the postulated function with DEPTOR in different tumor types.

Phosphokinase	Tumor types	Function of DEPTOR	Site of action	Ref.
mTOR	Glioma	Tumor suppressor	Ser293; Tyr295; Ser299	[70]
CKIα	Glioma	Tumor suppressor	Ser286; Ser287	[70]
S6K1/RSK1	Breast cancer	Tumor suppressor	Ser286, Ser287; Ser291	[71]
SYK	Multiple cancers	Tumor suppressor	Tyr289	[82]

Given the relatively clear role of the mTOR signaling pathway in promoting tumorigenesis, the development of relevant compounds that directly target the inhibition of mTOR for tumor therapy seems to be a more feasible and promising avenue. Consequently, efforts have focused on developing inhibitors that directly target mTOR for cancer therapy. The first-generation mTOR inhibitors, including rapamycin and its derivatives such as everolimus, temsirolimus, and lidafonil [1, 86], primarily target mTORC1 but have limited impact on mTORC2. Among them, everolimus has been used in the treatment of HER2-positive breast cancer and neuroendocrine tumors, while temsirolimus is used in the treatment of advanced renal cell carcinoma. Additionally, lidafonil has been used in the treatment of renal cell carcinoma, breast cancer, and other tumors [1, 87]. However, adverse effects of immunosuppression, such as infections and gastrointestinal disorders, have limited the use of such drugs. To achieve more comprehensive mTOR inhibition, second-generation mTOR inhibitors have been developed, targeting both mTORC1 and mTORC2 [88]. Such inhibitors are small molecule ATP analogues that compete with ATP to occupy the kinase active site of mTOR, such as Torin 1, Ku-0063794, AZD8055, and XL388 [1, 3, 89]. However, their efficacy in large-scale clinical trials remains to be fully established, delaying their clinical approval. To address the issue of drug resistance in terms of first- and second-generation inhibitors, a third-generation mTOR inhibitor, Rapalink-1, was developed by combining the target of first- and second-generation mTOR inhibitors [90, 91]. Rapalink-1 demonstrated potent anticancer activity *in vitro*; however, further research is required before it can progress to clinical trials. This approach provides new avenues for the development of anticancer drugs. Ongoing research into compounds targeting the DEPTOR/mTOR signaling axis holds potential for novel approaches to cancer treatment. Future clinical studies will be crucial in determining the efficacy and safety profiles of these compounds in cancer treatment.

In summary, almost 15 years have elapsed since the discovery of the DEPTOR protein in 2009. Over this time, numerous laboratories have illuminated the importance of this protein in tumorigenesis and progression, unravelling its related regulatory mechanisms. This review underscores that the expression and activity of DEPTOR are subject to regulation at multiple levels, including DNA induction, transcription, translation, and post-translational modification. However, many questions persist in the field of DEPTOR function and expression regulation. Firstly, diverse mechanisms govern DEPTOR expression across different tissue types and tumor types, such as intestinal ischemia/reperfusion injury, nasal mucosal tissues, cardiomyocytes, as well as lung and breast cancers. Given that DEPTOR function is dependent on specific cell types and tissue environments, future investigations must discern whether these mechanisms apply universally across tumor types or if certain pathways are tumor-type-dependent or environment-specific.

Moreover, while DEPTOR largely relies on mTOR function to exert its biological activity during pathophysiological processes, recent studies have unveiled potential functions of DEPTOR independent of the mTOR signaling pathway. DEPTOR can regulate the phosphorylation levels of the MAPK signaling pathway and the pERK1/2 (T202/Y204) sites alone without crosstalk with the mTOR signaling pathway [92]. Additionally, DEPTOR can translocate to the nucleus and bind to the promoter regions of genes associated with endoplasmic reticulum homeostasis to act as a transcriptional regulator [93]. These new features underscore the importance of elucidating DEPTOR's mechanisms in anticancer therapy. However, further research is imperative to fully grasp the precise mechanism of DEPTOR's action in different tumors and identify all regulated pathways, enabling personalized treatments for tumors with different characteristics.

Currently, mTOR signaling pathways and their roles in tumors remain incompletely understood. For example, in addition to the mTORC1 and mTORC2 complexes, mTOR has also been found to form mTORC3 with ETV7 and other unknown proteins. Research on the role of this new type of complex in tumor development and progression is still in its infancy. Moreover, while various drugs targeting the mTOR signaling pathway are clinically available, their clinical efficacy often falls short of expectations, with tumor recurrence or drug resistance posing ongoing challenges. Additionally, the side effects of mTOR inhibitor therapy warrant consideration. These issues necessitate further analysis in future studies. Advancements are anticipated in understanding the molecular network of the mTOR signaling pathway, as well as elucidating the side effects and potential resistance mechanisms of mTOR-targeted cancer therapy. Ultimately these endeavors aim to develop safer and more efficient oncology therapeutic drugs for the benefit of patients.

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