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Review

Regulatory-Associated Protein of mTOR-Mediated Signaling: A Nexus Between Tumorigenesis and Disease

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Abstract: RAPTOR (regulatory-associated protein of mTOR) is a pivotal component of the mammalian target of rapamycin complex 1 (mTORC1), playing a central role in regulating cell growth, metabolism and stress responses. As a scaffold protein, RAPTOR recruits key substrates such as eukaryotic initiation factor 4E-binding protein-1 (4E-BP1) and ribosomal protein S6 kinase (S6K), facilitating their phosphorylation by mTORC1, which in turn drives protein synthesis, lipid metabolism and cellular proliferation. Its regulatory function becomes especially crucial under conditions of nutrient deprivation or stress, where it enhances the stability of the mTORC1 complex, allowing cells to adapt to fluctuating environmental cues. The hyperactivation of mTORC1, largely mediated by RAPTOR, is frequently observed in various cancers, contributing to uncontrolled cell proliferation and tumorigenesis. Moreover, RAPTOR's modulation of immune responses and metabolic pathways extends its influence beyond oncogenesis, impacting inflammatory diseases and metabolic disorders. This review meticulously elucidates RAPTOR's structure, post-translational modifications as well as its indispensable role within the mTORC1 complex, emphasizing its regulatory functions in cellular growth, metabolic adaptation, immune response and disease pathology including oncogenesis. Furthermore, it explores emergent therapeutic avenues targeting RAPTOR-mediated mTORC1 signaling, underscoring their potential to revolutionize cancer treatment and the management of related pathophysiological conditions.

Keywords: mTOR; RAPTOR; PTMs; cancer signaling; immune modulation; chemoresistance; targeted chemotherapy

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1. Introduction

Cell signaling is a complex network that governs cellular behavior, ensuring proper growth, differentiation and tissue maintenance. In cancer, disruptions in these signaling pathways can have severe consequences. Mutations or alterations in key signaling components often leading to uncontrolled cell proliferation, resistance to apoptosis and metastasis are hallmarks of cancer [1]. Aberrant signaling pathways, including mTOR, EGFR, Wnt, TNFα/β, Src, PS6K, Notch and MAPK, are commonly involved in cancer, driving tumor growth and progression [2–16]. Among these, the mTOR pathway is particularly notable

for its dysregulation, which not only contributes to tumorigenesis but also plays a key role in promoting various other disorders, including arthritis, insulin resistance, cardiovascular diseases and osteoporosis [17–22]. mTOR is a critical regulator of cellular processes such as cell proliferation, autophagy and apoptosis [23–25], integrating signals from multiple pathways to maintain cellular homeostasis [26,27].

The link between mTOR and cancer has garnered significant attention, as aberrant mTOR activation is frequently observed in tumorigenesis [28,29]. This hyperactivation promotes enhanced gene transcription, protein synthesis and uncontrolled cell proliferation in tumors [30]. Additionally, mTOR signaling plays a pivotal role in immune cell differentiation, influencing the tumor microenvironment and immune response [31] while reorganizing metabolic pathways to support the anabolic processes necessary for rapid cancer cell growth and survival. In recent years, substantial progress has been made in targeting the mTOR pathway for cancer treatment. A wide array of newly discovered mTOR inhibitors has entered clinical trials, showing promise in curbing tumor growth and improving patient outcomes [32]. Furthermore, several studies have demonstrated that combining mTOR inhibitors with other therapeutic agents can enhance anti-tumor activity, as these combinations may overcome resistance mechanisms or target multiple cancer-promoting pathways simultaneously [33–35]. Therefore, a comprehensive understanding of mTOR and its complexes is essential, as advancements in combination therapies represent a pivotal breakthrough in cancer treatment, offering promising prospects for more effective and personalized therapeutic strategies.

mTOR is a serine/threonine kinase that forms the core of two distinct complexes: mTORC1 and mTORC2, each with different functions (Figure 1). mTORC1 promotes protein synthesis and lipid biosynthesis, inhibits autophagy, responds to nutrient availability and growth factors and is sensitive to the drug rapamycin [36], while mTORC2 is involved in regulating the cytoskeleton and controlling cell survival and is less sensitive to rapamycin [37]. Structurally, mTORC1 includes mTOR, mLST8 and RAPTOR [38,39]. In contrast, mTORC2 is composed of mTOR, RICTOR, PROTOR ½, mSIN1 and mLST8 [40]. Activation of mTORC1 and mTORC2 triggers the phosphorylation of distinct sets of proteins, each playing different roles in cellular regulation. For instance, mTORC1 directly phosphorylates ribosomal protein S6 kinase 1 (S6K1) [41], enhancing protein synthesis by activating translation machinery, and it also phosphorylates eukaryotic translation initiation factor 4E-binding protein 1 (4E-BP1), which releases eIF4E to initiate cap-dependent translation [42]. This makes mTORC1 essential for controlling protein synthesis and cell growth. In contrast, mTORC2 does not regulate 4E-BP or S6K. Instead, it primarily influences cell survival, cytoskeletal organization and metabolism by phosphorylating proteins like Akt, PKC and SGK1 [43–46]. Thus, while mTORC1 governs protein synthesis, mTORC2 plays a key role in regulating cell survival and metabolic processes.

RAPTOR is a critical component of the mTORC1 signaling pathway that regulates cell growth in response to nutrient and insulin levels [47]. This evolutionarily conserved protein plays diverse roles in cellular metabolism and growth by forming a stoichiometric complex with mTOR kinase [48]. As a scaffold protein, RAPTOR recruits substrates to mTORC1, facilitating the phosphorylation of downstream targets such as eukaryotic initiation factor 4EBP-1 and S6K, which are essential for protein synthesis and cell growth [49,50]. By enhancing S6K activity and suppressing mTOR kinase, RAPTOR helps regulate cell size and maintain mTOR protein expression [51,52]. Under conditions of nutrient deprivation or cellular stress that inhibit the mTOR signaling pathway, the interaction between RAPTOR and mTOR is enhanced, stabilizing the complex [53,54]. This stabilization is critical for maintaining the pathway's sensitivity to fluctuations in environmental conditions, thereby modulating cellular responses to ensure metabolic adaptation [55–57]. Additionally, during cellular stress, RAPTOR interacts with SPAG5 and relocates to stress granules, reducing its presence in lysosomes and modulating its activity [58]. Multiple transcript variants of RAPTOR encode different isoforms, reflecting its functional complexity in controlling cell growth, metabolism and stress responses [59,60]. Since the mTORC1 pathway is frequently

hyperactivated in tumors and RAPTOR plays a central role in this process, making it a key contributor to tumorigenesis, understanding its role is crucial.

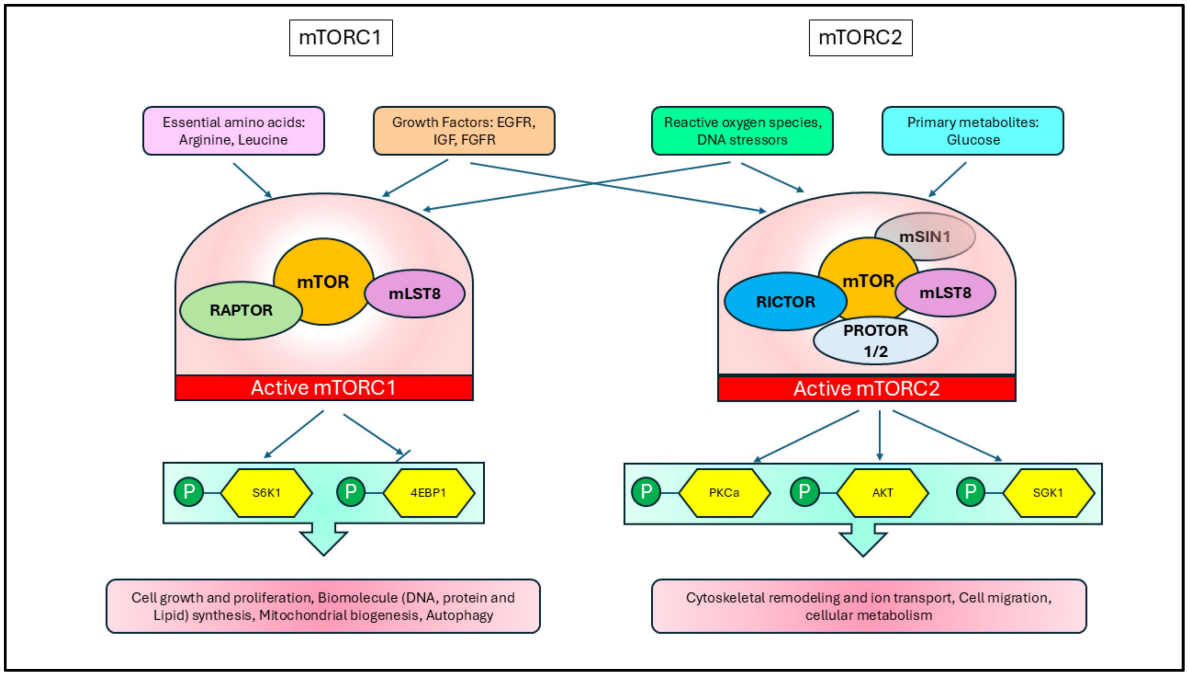


Figure 1. Components of mTOR complexes 1 and 2. mTOR exist in two distinct complexes, mTORC1 and mTORC2, each characterized by unique subunits and functions. mTORC1, the more well-studied complex, consists of the catalytic mTOR protein, RAPTOR (regulatory-associated protein of mTOR) and mLST8 (mammalian lethal with SEC13 protein 8). RAPTOR serves as a scaffold protein, essential for substrate recognition, enabling mTORC1 to regulate processes such as protein synthesis, purine and pyrimidine synthesis, autophagy, cell growth, mitochondrial biogenesis and lipid metabolism in response to nutrient and energy signals. mTORC2, on the other hand, contains mTOR, RICTOR (rapamycin-insensitive companion of mTOR), mLST8, mSIN1 (stress-activated map kinase-interacting protein 1) and PROTOR (protein observed with Rictor). mTORC2 primarily controls the phosphorylation of Akt, influencing cytoskeletal organization, cell survival and metabolism. While mTORC1 is sensitive to rapamycin, mTORC2 is generally resistant, further distinguishing their functional roles in cellular growth and homeostasis.

In this review, we aim to highlight the critical role of RAPTOR in regulating mTOR signaling and its involvement in a broad range of human cancers. We will be discussing RAPTOR's structural details and post-translational modifications and its role as a key scaffold protein within the mTORC1 complex to influence cancer cell signaling. Additionally, this review will explore emerging therapeutic strategies aimed at targeting RAPTOR to inhibit mTORC1 activity, with a focus on their potential to improve cancer treatments.

2. RAPTOR: Structure and Integration into mTORC1

The regulatory-associated protein of mTOR, commonly referred to as RAPTOR or KIAA1303, is an adapter protein encoded by the RPTOR gene in humans [47]. This gene produces two mRNA variants, which translate into proteins of 1335 amino acids (isoform 1) and 1177 amino acids (isoform 2); these are approximately 150 kda peptides. RAPTOR is predominantly expressed in skeletal muscle, with lower levels found in the brain, lungs, small intestine, kidneys and placenta [61–76]. Intracellularly, RAPTOR is primarily localized in the cytoplasm, lysosomes and cytoplasmic granules, with its lysosomal positioning regulated by amino acid availability [77,78].

Structurally, RAPTOR features several key domains that are essential for its function (Figure 2). It features an N-terminal catalytically inactive caspase-like domain or

RAPTOR N-terminal conserved domain (RNC), followed by HEAT repeats that form an open solenoid and seven WD40 repeats composed of about 40 amino acids terminating with tryptophan and aspartic acid (WD), which form a closed solenoid known as a beta-propeller [79,80]. RAPTOR binds to the N-HEAT/M-HEAT interface of mTOR, thereby stabilizing the complex. This interface has substrate recognition sites, known as TOR signaling (TOS) motifs, which are critical for substrate binding and regulation of mTORC1 activity [81]. This interface not only anchors RAPTOR but also links the two Rheb binding sites, where binding at one site enhances the affinity of the second, thereby contributing to the regulation of mTORC1 activity [82,83]. Recent studies on crystal structures and cryo-EM reconstructions have provided further detailed insights into how RAPTOR is integrated into the mTORC1 complex [84]. This study reveals that mTORC1 functions as a dimer composed of mTOR, mLst8 and RAPTOR heterotrimers, arranged in an antiparallel configuration of the mTOR HEAT domains extending from the FAT alpha solenoid. The N-HEAT domain, also called the "spiral" or "horn", of one mTOR interacts with the M-HEAT domain, also known as bridge, of the other mTOR polypeptide, forming a composite N-HEAT/M-HEAT interface. This surface serves as a platform for RAPTOR binding, stabilizing the dimer, although it is not essential for its maintenance. This structural organization enables RAPTOR to effectively interact with mTOR, its substrates and other regulatory proteins within the complex, such as mLST8. Together, these interactions coordinate mTORC1 activity in response to nutrients, growth factors and stress signals, ensuring proper cellular regulation [85].

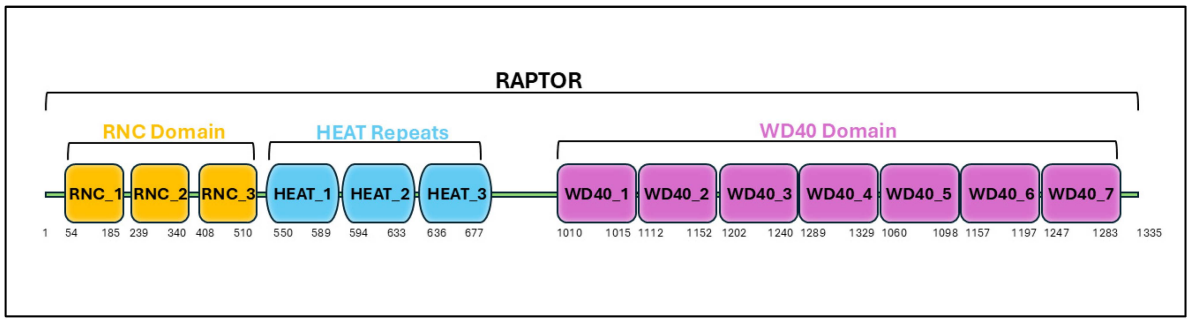


Figure 2. Structure of RAPTOR protein. The protein structure of RAPTOR is characterized by an N-terminal caspase-like domain, known as the RAPTOR N-terminal conserved (RNC) domain, which is catalytically inactive. This is followed by HEAT repeats that form an open solenoid structure. Additionally, RAPTOR contains seven WD40 repeats, each consisting of approximately 40 amino acids that end with tryptophan and aspartic acid (WD). These WD40 repeats form a closed solenoid structure known as a beta-propeller.

3. Post-Translational Modifications of RAPTOR and Their Role in mTOC1 Activity

Post-translational modifications (PTMs) are crucial in defining protein functionality, stability, localization and interactions within a cell [86]. These modifications, such as phosphorylation, acetylation, ubiquitination, SUMOylation and glycosylation, can alter a protein's conformation, either activating or inhibiting its enzymatic activity or binding affinity. For instance, phosphorylation can activate or suppress signaling cascades, while ubiquitination often signals for protein degradation via the proteasome [87]. PTMs ensure proteins adapt to cellular conditions and participate in processes like cell cycle regulation, apoptosis and metabolism and thus are essential for cellular homeostasis [88]. One key aspect of PTMs is their ability to influence hydrophobic interactions between amino acid residues at critical sites within a protein [89–91]. Hydrophobic interactions between non-polar residues, such as leucine, isoleucine and phenylalanine, play a significant role in protein folding, stability and function. These residues aggregate to form the hydrophobic core, stabilizing the protein's structure. PTMs near these regions can disrupt or enhance these interactions, causing changes in protein behavior. For example, phosphorylation or ubiquitination can introduce charged groups near hydrophobic residues, leading to

conformational changes that stabilize or destabilize the protein, impacting its activity. Hydrophobic interactions also influence molecular recognition, particularly in protein–protein and protein–ligand interactions. PTMs can also alter surface properties of a protein, which can affect its ability to interact with other molecules. For instance, phosphorylation may make hydrophobic regions more polar, weakening binding interactions. This mechanism led by PTMs is particularly important for signaling proteins, which contain hydrophobic domains that mediate key molecular interactions. Additionally, hydrophobic interactions at active sites influence enzyme activity and substrate specificity, while PTMs modulate these interactions and affect protein localization and function. Hydrophobic patches across proteins also signal for degradation, as PTMs can expose these regions, marking proteins for ubiquitin-mediated degradation, which regulates protein turnover. Thus, PTMs play a vital role in regulating hydrophobic interactions within proteins, impacting their folding, stability, activity, interactions, localization and degradation. By modulating these interactions, PTMs enable proteins to adapt to cellular needs, ensuring precise control over various biological processes [92]. RAPTOR is no exception when it comes to the influence of PTMs. Like many other cellular proteins, RAPTOR undergoes a variety of PTMs that are critical for its biological functions under both normal physiological conditions and in disease states. Phosphorylation is one of the most studied modifications of RAPTOR, regulating its role in mTORC1. Other modifications, such as ubiquitination and acetylation, further modulate RAPTOR's activity, localization and interactions with other proteins. These PTMs allow RAPTOR to adapt to environmental signals and cellular stresses, contributing to its regulatory involvement in energy homeostasis, nutrient sensing and inflammation. Dysregulation of RAPTOR's PTMs has been linked to various diseases, including cancer, metabolic disorders and cardiovascular diseases, underscoring the importance of proper PTM control for maintaining RAPTOR's function in both normal physiology and disease. We have illustrated major PTMs of RAPTOR in Figure 3, and in the following section, we will systematically outline the major PTMs of RAPTOR and their impact on the regulation and activity of mTORC1.

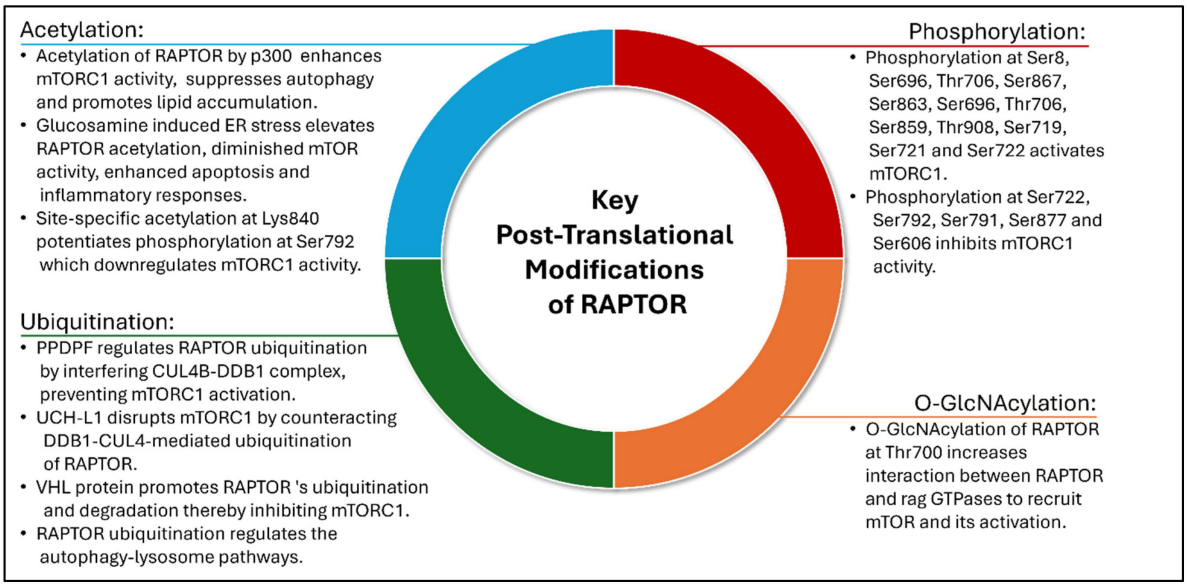


Figure 3. Major PTMs of RAPTOR protein. RAPTOR undergoes several PTMs that tightly regulate mTORC1 activity. Both phosphorylation and acetylation can either enhance mTORC1 activation or suppress its activity, depending on the specific phosphorylation/acetylation site. O-GlcNAcylation strengthens RAPTOR's interaction with Rag GTPases, promoting mTORC1 activation. Ubiquitination, regulated by factors like PPDPF, UCH-L1 and VHL protein, modulates RAPTOR stability, influencing both mTORC1 activity and autophagy pathways.

3.1. Phosphorylation PTMs of RAPTOR

RAPTOR undergoes multiple key PTMs that regulate its function and stability within the mTORC1 signaling pathway. Phosphorylation is the major and critical PTM for RAPTOR, which plays a pivotal role in modulating its interactions with mTOR and other regulatory proteins, thereby influencing mTORC1 activity. One of the previous studies identified Ser696 and Thr706 as key phosphorylation sites on RAPTOR during mitosis, with the kinase cdc2/CDK1 responsible for their phosphorylation [93,94]. This phosphorylation by CDK1 is crucial for activation of mTORC1 during mitosis to support mitotic progression and the biosynthetic demands of cell division. In contrast, phosphorylation of RAPTOR at Ser722 and Ser792 by AMP-activated protein kinase (AMPK) happens under conditions of low nutrient availability or metabolic stress [95]. This phosphorylation reduces the interaction between RAPTOR and mTORC1, leading to decreased mTORC1 activity. This, in turn, inhibits anabolic processes like protein synthesis and cell growth. In contrast, another study identifies six phosphorylation sites on RAPTOR organized in two clusters. Among them, Ser867 (Ser863 in some studies) serves as a pivotal regulatory site [96]. Phosphorylation of Ser867 is stimulated by insulin via the PI3K/TSC/Rheb pathway and this phosphorylation event acts as a "master switch", enabling further phosphorylation of nearby residues like Ser859 and Ser855 on RAPTOR. These phosphorylation events on RAPTOR are crucial for mTORC1's kinase activity, particularly its ability to phosphorylate the downstream substrate 4E-BP1.

Another study demonstrated that mTOR phosphorylates RAPTOR at Ser863 both with insulin stimulating this phosphorylation and with the inhibitor rapamycin blocking it [97]. Mutation of RAPTOR at Ser863 significantly reduced mTORC1 activity, both in cell-based experiments and in vitro kinase assays. Furthermore, the Ser863 mutant of RAPTOR impaired the ability of Rheb to enhance the phosphorylation of S6K. Moreover, Nemo-like kinase (NLK) phosphorylates RAPTOR at S863, disrupting its interaction with the Rag GTPase, which is crucial for mTORC1 recruitment to the lysosome [98]. Interestingly, ERK1/2 plays a critical role in regulating mTORC1 activity by interacting with and phosphorylating RAPTOR both in vivo and in vitro. Mass spectrometry identified three proline-directed sites in RAPTOR, Ser8, Ser696 and Ser863, as direct targets of ERK1/2 phosphorylation. [99]. Mutational analysis of these phosphorylation sites revealed that ERK1/2-mediated phosphorylation of RAPTOR enhances mTORC1 activity and promotes signaling to downstream substrates, such as 4E-BP1, highlighting its importance in mTORC1 regulation

Phosphorylation of RAPTOR at Ser791 by protein kinase A (PKA) plays a critical inhibitory role in mTORC1 activity, particularly in response to G-protein coupled receptor (GPCR) signaling through Gαs proteins [100,101]. GPCR activation increases cyclic AMP (cAMP), which in turn activates PKA. Once activated, PKA directly phosphorylates RAPTOR at Ser791, leading to a reduction in mTORC1 activity. Mutation of RAPTOR at Ser791 prevents its phosphorylation and restores mTORC1 activity even in the presence of PKA activation, showing that Ser791 phosphorylation is necessary for PKA-mediated inhibition of the complex. Phosphorylation of RAPTOR at Ser696, Thr706 and Ser863 by JNK (c-Jun N-terminal kinase) plays a significant role in regulating mTORC1 activity in response to osmotic stress [102]. The research demonstrates that under osmotic stress conditions, JNK phosphorylates RAPTOR at these specific sites, as identified through liquid chromatography–tandem mass spectrometry (LC-MS/MS). JNK directly interacts with and phosphorylates RAPTOR both in vitro and in cells, and specific inhibition of JNK effectively abolishes RAPTOR phosphorylation at these sites. Phosphorylation of RAPTOR at Ser877 by TANK-binding kinase 1 (TBK1) plays a key role in inhibiting mTORC1 activity, particularly in the context of cellular growth and autophagy regulation [103]. TBK1, traditionally known for its role in the innate immune system, has been identified as a modulator of mTOR, which is crucial for promoting cell growth and inhibiting autophagy. When utilizing kinase assays and mass spectrometry, it was revealed that TBK1 phosphorylates RAPTOR at Ser877 both under normal conditions and in response to pathogen-associated molecules that activate TBK1. Phosphorylation at Ser877 was inversely linked to mTORC1 activity, with higher

Ser877 phosphorylation reducing mTOR signaling. Cells with a mutant RAPTOR lacking Ser877 phosphorylation showed increased mTORC1 activity, highlighting its inhibitory role.

Phosphorylation of RAPTOR at Ser859 by glycogen synthase kinase-3 (GSK3) plays a pivotal role in regulating mTORC1 activity, particularly in response to amino acid availability [104]. GSK3 directly phosphorylates RAPTOR, a scaffold protein of the mTORC1 complex, at Ser859, which is crucial for maintaining the functional interaction between mTOR and RAPTOR. This interaction is essential for the phosphorylation of downstream mTORC1 targets such as p70S6K1 (ribosomal S6 kinase 1) and ULK1 (uncoordinated-51-like kinase 1). Inhibition of GSK3, either through pharmacological agents or gene silencing or mutation of RAPTOR at Ser859 (S859A), disrupts the mTOR–RAPTOR interaction. This disruption results in a marked reduction in mTORC1 activity, even in the presence of amino acids, leading to decreased phosphorylation of mTORC1 substrates. Another study suggests that phosphorylation of RAPTOR at Thr908 by intestinal cell kinase (ICK) plays a critical role in modulating mTORC1 activity, both in vitro and in vivo. [75]. Phosphorylation of RAPTOR at Thr908 by ICK is crucial for mTORC1 activation in response to insulin and nutrient starvation, particularly when the small GTP-binding protein Rheb is overexpressed. The RAPTOR T908A mutant impairs mTORC1 activation but does not disrupt the structural integrity of the mTORC1 complex. Interestingly, phosphorylation of RAPTOR at Ser855, Ser859 and Ser792 by ULK1 plays a crucial role in inhibiting mTORC1 activity, particularly in the context of autophagy regulation [105]. ULK1, a key kinase in autophagy initiation, induces multisite phosphorylation of RAPTOR both in vivo and in vitro, with strong phosphorylation at Ser855 and Ser859 and moderate phosphorylation at Ser792. Despite increased mTORC1 activity markers, such as enhanced RAPTOR phosphorylation at Ser863 and mTOR autophosphorylation at Ser2481, ULK1 overexpression paradoxically inhibits mTORC1 phosphorylation of downstream targets like S6K1 and 4E-BP1. The research suggests that ULK1 does not disrupt mTORC1 complex interactions but impairs RAPTOR's ability to bind substrates, particularly 4E-BP1. This reduces mTORC1's capacity to phosphorylate key targets. ULK1 knockdown via shRNA increases mTORC1 substrate phosphorylation and decreases RAPTOR phosphorylation at Ser859 and Ser792, confirming ULK1's inhibitory role.

Phosphorylation of RAPTOR at Ser606 by LATS1 and LATS2, key kinases in the Hippo pathway, inhibits mTORC1 activity by disrupting RAPTOR's interaction with Rheb, reducing mTORC1 signaling and limiting cell growth. [106]. A phosphomimetic RAPTOR-S606D mutation significantly decreases cell size and proliferation. In RAPTORD/D knock-in mice, mimicking Ser606 phosphorylation results in smaller livers and hearts, with strong inhibition of mTORC1 signaling, even when the Hippo pathway is suppressed. This phosphorylation links the Hippo pathway to mTORC1 regulation, regulating organ growth in response to cellular and environmental signals. Phosphorylation of RAPTOR at Ser863 and Ser771 by the p38β-PRAK pathway plays a significant role in regulating mTORC1 activity, particularly in response to specific stress conditions like arsenite exposure [107]. Activation of p38β leads to its interaction with RAPTOR, a key component of mTORC1, resulting in the phosphorylation of RAPTOR at Ser863 and Ser771. This phosphorylation enhances mTORC1 activity in response to arsenite specifically, which was not observed with other stimuli like insulin, nutrients, anisomycin or H_2O_2. Another study showed that the phosphorylation of RAPTOR at Ser719, Ser721 and Ser722 by RSK (p90 ribosomal S6 kinase) is essential for regulating mTORC1 activity, revealing a novel mechanism through which the Ras/MAPK pathway modulates mTOR signaling. [108]. Moreover, another study identified several phosphorylation sites on RAPTOR, including Ser696, Thr706, Ser721, Ser722, Ser855, Ser859, Ser863, Thr865 and Ser877. [109]. Insulin treatment increases phosphorylation at Ser696, Ser855, Ser863 and Thr865 while suppressing phosphorylation at Ser722. Notably, Ser696 phosphorylation is regulated by the MAPK pathway and remains unaffected by mTOR inhibition with rapamycin. Inhibiting MAPK reduces insulin-stimulated phosphorylation of Ser696, underscoring MAPK's direct role in this process. Mutating Ser696 to alanine disrupts downstream mTOR signaling, particularly the phosphorylation of p70S6 kinase, essential for protein synthesis. Furthermore, the convergence of the MAPK and PI3K

pathways at mTORC1 is evident, as inhibitors of these pathways reduce insulin-stimulated RAPTOR phosphorylation.

Collectively, these phosphorylation modifications are crucial for the proper functioning of mTORC1, as they regulate RAPTOR's interactions and signaling capacity, influencing cell growth, metabolism and stress responses.

3.2. Ubiquitination PTMs on RAPTOR

Ubiquitination of RAPTOR plays a pivotal role in regulating mTORC1 activity, influencing its stability, interactions within the mTOR complex and downstream signaling. One significant regulator is UCH-L1, which disrupts mTORC1 by counteracting the DDB1-CUL4-mediated ubiquitination of RAPTOR [110]. This disruption reduces the activity of mTORC1 toward targets such as S6K and 4E-BP1 while increasing mTORC2 activity. This balance between mTORC1 and mTORC2 is essential for cellular processes like neuroprotection and tumor suppression. Another mechanism involves the von Hippel–Lindau (VHL) protein, which promotes RAPTOR's ubiquitination and degradation, thereby inhibiting mTORC1 signaling. This is particularly crucial in clear cell renal cell carcinoma, where the loss of VHL leads to hyperactive mTORC1 signaling, contributing to disease progression [71]. Furthermore, pancreatic progenitor cell differentiation and proliferation factor (PPDPF) regulates RAPTOR ubiquitination by interfering with the CUL4B-DDB1 complex, preventing RAPTOR activation [111]. Interestingly, ubiquitination of RAPTOR plays a crucial role in modulating the autophagy–lysosome pathway. In GCD2 corneal fibroblasts with mutant-TGFBIp accumulation, reduced levels of RAPTOR were associated with delayed autophagic clearance of mutant proteins [77]. Treatment with MG132, a ubiquitin/proteasome system inhibitor, significantly increased both total and ubiquitinated RAPTOR levels, suggesting that RAPTOR's ubiquitination status directly influences autophagy. However, despite increased autophagic activity, indicated by elevated LC3-II levels, mutant-TGFBIp continued to accumulate in autophagosomes and lysosomes. This implies that impaired RAPTOR function due to altered ubiquitination may contribute to defective autophagy and protein clearance, resulting in pathogenic protein accumulation in GCD2 corneal fibroblasts. Thus, RAPTOR ubiquitination is closely linked to its regulation of mTORC1 activity, with broad implications for diseases characterized by dysregulated mTOR signaling, including cancer, neurodegenerative disorders and metabolic diseases.

3.3. Acetylation PTMs of RAPTOR

Acetylation of the RAPTOR protein plays a crucial role in modulating mTORC1 activity, particularly in response to changes in nutrient availability. Inhibition of fatty acid oxidation (FAO) leads to increased acetyl-CoA production, which activates mTORC1 through GCN5-dependent acetylation of RAPTOR [112]. Additionally, p300, a key acetyltransferase, shuttles between the nucleus and cytoplasm in response to nutrient levels, controlling RAPTOR acetylation [113]. Under nutrient-rich conditions, p300 acetylates RAPTOR, activating mTORC1 and suppressing autophagy. In contrast, during nutrient deprivation, p300 relocates to the nucleus, decreases RAPTOR acetylation and reduces mTORC1 activity, thereby promoting autophagy [114]. This nutrient-sensitive mechanism is also implicated in pathological conditions such as non-alcoholic fatty liver disease (NAFLD), where Bisphenol S (BPS) exposure drives EP300-dependent acetylation of RAPTOR, blocking autophagy and contributing to lipid accumulation [115,116]. These findings underscore the importance of RAPTOR acetylation in balancing mTORC1 activity, autophagy and metabolic regulation across various physiological and pathological states.

Additionally, acetylation of RAPTOR at Lys840 plays a pivotal role in regulating mTORC1 activity, particularly in relation to the modulation of gastric hormone expression. Inhibition of histone deacetylase 5 (HDAC5) through sodium valproate, trichostatin A or siHDAC5 leads to increased acetylation of RAPTOR at Lys840, which in turn enhances phosphorylation at Ser792 [117]. This phosphorylation event suppresses mTORC1 signaling. Conversely, a RAPTOR mutant that lacks the Lys840 acetylation site exhibits reduced Ser792

phosphorylation, leading to enhanced mTORC1 activity. This highlights the importance of Lys840 acetylation in negatively regulating mTORC1 signaling. This regulatory mechanism affects the levels of ghrelin and nucleobindin 2/nesfatin-1, two gastric hormones involved in the energy balance. Increased acetylation of RAPTOR Lys840 and the subsequent suppression of mTORC1 signaling results in elevated ghrelin levels and reduced nesfatin-1 expression. These findings suggest that HDAC5 regulates mTORC1 through Lys840 acetylation, which has broader implications for energy homeostasis and hormone regulation.

Moreover, acetylation of RAPTOR protein plays a significant role in regulating ER stress and endothelial dysfunction in atherosclerosis. Glucosamine (GlcN) treatment in endothelial cells induces ER stress, leading to increased expression of apoptotic and pro-inflammatory/pro-thrombotic markers [118]. This stress is associated with increased RAPTOR acetylation, stimulating mTORC1-dependent protein synthesis and worsening cellular stress. However, treatment with SRT1720, which modulates RAPTOR acetylation, alleviated ER stress and reversed the pro-apoptotic and inflammatory effects of GlcN. By controlling RAPTOR acetylation to inhibit mTORC1 activity, SRT1720 mitigates ER overload and restores cellular balance. These findings underscore the critical role of RAPTOR acetylation in linking mTORC1 activity to ER stress and suggest potential therapeutic strategies for endothelial dysfunction and atherosclerosis through pathway modulation.

In conclusion, RAPTOR acetylation is crucial for modulating mTORC1 activity in response to nutrient availability, influencing processes such as autophagy and energy regulation. Its role in both physiological and pathological contexts highlights its potential as a therapeutic target for conditions like atherosclerosis and metabolic disorders.

3.4. Additional PTMs Crucial for RAPTOR Regulation

O-GlcNAcylation is a reversible PTM where N-acetylglucosamine (GlcNAc) is added to serine or threonine residues on proteins by O-GlcNAc transferase (OGT). O-GlcNAcase (OGA) removes the modification, allowing dynamic regulation. Similar to phosphorylation, it plays a key role in controlling protein function, stability, localization and interactions. O-GlcNAcylation of RAPTOR at threonine 700 plays a crucial role in regulating mTORC1 activity in response to glucose levels [119]. This modification at threonine 700 enhances the interaction between RAPTOR and Rag GTPases, which are critical for the recruitment of mTORC1 to the lysosomal surface, a key step for mTORC1 activation. As a result, mTORC1 is effectively activated, promoting anabolic processes such as protein synthesis. Additionally, the research shows that AMPK-mediated phosphorylation of RAPTOR inhibits O-GlcNAcylation at threonine 700, thereby suppressing the RAPTOR–Rag interactions and preventing mTORC1 activation. This mechanism highlights the fine-tuned balance between glucose signaling and cellular energy status, where O-GlcNAcylation of RAPTOR serves as a key sensor to ensure proper mTORC1 activation in response to available glucose.

SUMOylation, a PTM involving the attachment of small ubiquitin-like modifiers (SUMOs) to target proteins, plays a pivotal role in the regulation of mTOR signaling. In particular, the SUMOylation of key components such as GβL (mLST8), a core subunit of both mTORC1 and mTORC2 complexes, significantly influences the assembly and stability of these complexes [120]. SUMOylation of specific lysine residues on GβL (such as K86, K215 and K305) is crucial for proper mTOR complex formation, essential for nutrient sensing and signaling. SUMO depletion destabilizes mTOR–RAPTOR and mTOR–Rictor interactions, reducing mTORC1 and mTORC2 activity and impairing nutrient-induced mTOR signaling. Disruption of SUMOylation diminishes downstream target activation and affects metabolic regulation, with links to diseases like Huntington's and obesity. Targeting SUMOylation may offer therapeutic strategies for conditions involving dysregulated mTOR signaling.

In conclusion, the PTMs of RAPTOR protein play a pivotal role in regulating mTORC1 activity, balancing autophagy and influencing metabolic pathways across various physiological and pathological conditions such as protein synthesis, apoptosis and inflammation, especially under stress conditions like ER stress. Collectively, these modifications enable

RAPTOR to dynamically respond to changes in cellular conditions, including nutrient availability, stress and growth signals. Table 1 summarizes site-specific PTMs on RAPTOR and its role in modulating mTOR activity. By modulating RAPTOR's role in mTORC1 signaling, PTMs are essential for maintaining cellular homeostasis, growth and metabolism, and their dysregulation can contribute to oncogenesis.

Table 1. Summary of site-specific PTMs of RAPTOR.

PTM Type	Site	Functional Relevance of PTM	Reference
Phosphorylation	Ser722, Ser792	This phosphorylation by AMPK stabilizes the interaction between RAPTOR and mTORC1, causing inhibition of mTORC1	[95]
	Ser8	This phosphorylation by ERK1/2 enhances mTORC1 activity	[99]
	Ser696	This phosphorylation by CDK1 and ERK1/2 promotes mTORC1 activity and signaling to downstream substrates, such as 4E-BP1	[93,99]
	Thr706	This phosphorylation by CDK1 is crucial for activation of mTORC1 during mitosis to support mitotic progression and the biosynthetic demands of cell division	[93]
	Ser867	Phosphorylation of Ser867 is stimulated by insulin via the PI3K/TSC/Rheb pathway, enabling further phosphorylation of nearby residues like Ser859 and Ser855, thereby facilitating multisite phosphorylation of RAPTOR to upregulate mTORC1 activity	[96]
	Ser863	Insulin, JNK, ERK1/2 and Nemo-like kinase (NLK) stimulate phosphorylation at Ser863 on RAPTOR, which disrupt its interaction with the Rag GTPase, which is important for mTORC1 lysosomal recruitment	[97–99,102]
	Ser696 and Thr706	Phosphorylation of RAPTOR at Ser-696 and Thr-706 by JNK is essential for the activation of mTORC1 in response to osmotic stress	[102]
	Ser791	Ser791 phosphorylation of RAPTOR by PKA inhibits mTORC1 activity, revealing a key signaling pathway that links GPCR activation with mTORC1 regulation and offering potential therapeutic implications for conditions involving excessive mTORC1 activation	[100,101]
	Ser877	TBK1-mediated phosphorylation of RAPTOR at Ser877 acts as a critical mechanism for limiting mTORC1 activity, thus regulating cellular processes such as growth and autophagy	[103]
	Ser859	Ser859 phosphorylation of RAPTOR by GSK3 is critical for sustaining mTORC1 signaling and regulating cellular growth and proliferation	[104]
	Ser606	Ser606 phosphorylation of RAPTOR by LATS1/2 inhibits mTORC1 activation, highlighting a key intersection between the Hippo and mTORC1 pathways in regulating cell and organ growth	[106]
	Thr908	Thr-908 phosphorylation of RAPTOR by ICK is a key regulatory step for mTORC1 activation	[75]
	Ser719, Ser721 and Ser722	Ser719, Ser721 and Ser722 phosphorylation of RAPTOR by RSK plays a significant role in modulating mTORC1 activity and helps integrate upstream signals to fine-tune mTORC1 activity and, consequently, cellular growth and metabolism	[108]
Acetylation	Lys840	HDAC5 regulates Lys840 acetylation of RAPTOR, which suppresses mTORC1 activity by promoting Ser792 phosphorylation	[117]
O-GlcNAcylation	Thr700	O-GlcNAcylation of RAPTOR at threonine 700 is essential for glucose-dependent activation of mTORC1, facilitating its interaction with Rag GTPases and translocation to the lysosome	[119]

4. Hyperactivation of mTORC1 in Cancer and Disease and the Central Role of RAPTOR

mTORC1 is a master regulator of cell growth, metabolism and survival, integrating signals from growth factors, nutrients and energy status [121]. In many cancers, mutations in upstream regulators of mTORC1, such as the PI3K/AKT and Ras pathways, result in its continuous activation [29,122]. For instance, loss of PTEN (a negative regulator of the PI3K/AKT pathway) or mutations in oncogenes like KRAS result in sustained activation of mTORC1, promoting unchecked cellular growth and tumorigenesis [123–126]. Cancers where mTORC1 hyperactivation is particularly prominent include breast cancer, prostate

cancer, renal cell carcinoma, hepatocellular carcinoma and pancreatic cancer. For example, in breast cancer, mTORC1 activation is often driven by mutations in PIK3CA or loss of PTEN, which accelerates tumor growth and survival [127]. In renal cell carcinoma, mutations in the tumor suppressor VHL lead to increased mTORC1 activity through aberrant hypoxia signaling [71]. Similarly, in pancreatic cancer, KRAS mutations hyperactivate mTORC1, contributing to the aggressive nature of the disease [128,129]. mTORC1-driven tumorigenesis is characterized by enhanced protein synthesis and metabolic reprogramming, which allows cancer cells to meet the high biosynthetic demands required for rapid growth and survival under stress conditions [130,131]. Beyond cancer, mTORC1 hyperactivation is implicated in other diseases, including metabolic disorders like type 2 diabetes and neurodegenerative diseases such as Alzheimer's disease [17,132]. In these conditions, aberrant mTORC1 signaling disrupts normal cellular homeostasis, leading to insulin resistance, increased lipid accumulation or impaired autophagy. Thus, given mTOR's pivotal role in various pathologies, understanding its regulatory components is crucial. In particular, discussing cell signaling mediated by mTORC1 components, such as RAPTOR, is of critical importance due to RAPTOR's central function in modulating mTORC1 activity and its broad implications in cancer and other pathologies. As a scaffolding protein in mTORC1, RAPTOR recruits substrates like S6K and 4E-BP1, driving protein synthesis and lipid metabolism. Aberrant RAPTOR signaling, often due to PI3K/AKT mutations, leads to mTORC1 hyperactivation, promoting unchecked cell growth and metabolic shifts linked to cancers like breast, prostate and pancreatic. RAPTOR also regulates anabolic processes and autophagy, a balance disrupted in tumors, aiding survival under stress. Beyond cancer, its overactivation contributes to metabolic diseases like diabetes and neurodegenerative disorders by impairing insulin sensitivity and autophagy, highlighting its therapeutic significance.

In the subsequent sections, we will examine the signaling cascades regulated by RAPTOR, its modulation of mTORC1 activity and its interactions with other crucial cellular pathways (also outlined in Figure 4) that are essential for maintaining cellular homeostasis and contributing to disease development.

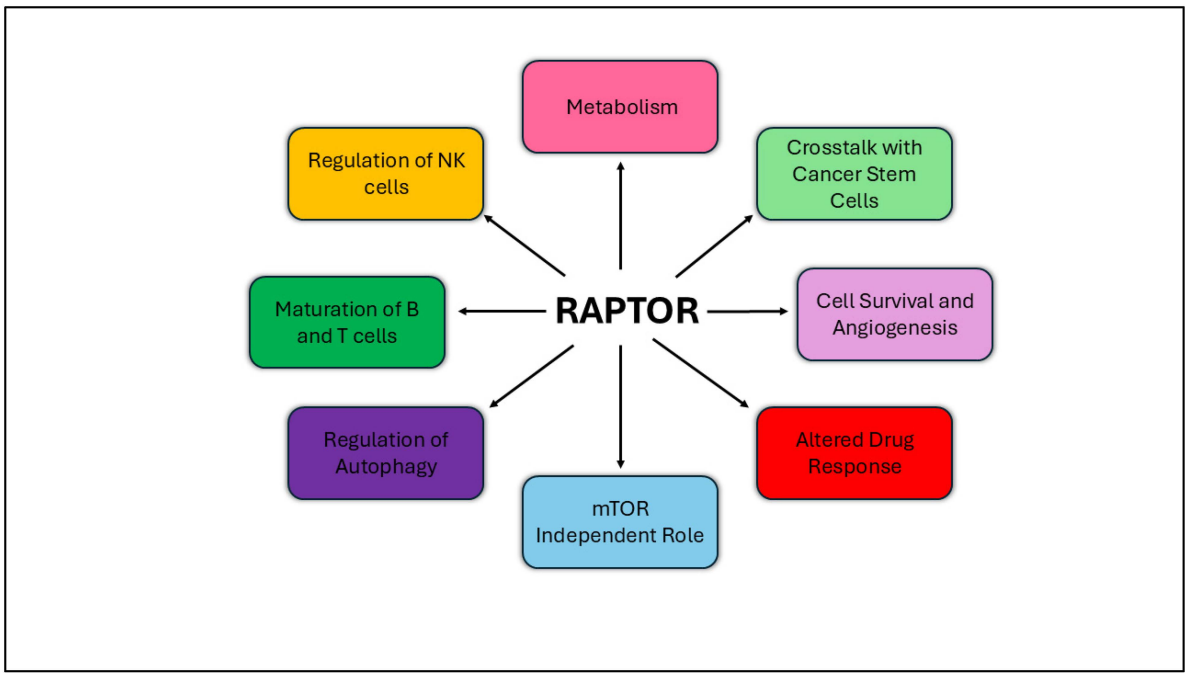


Figure 4. Multifaced role of RAPTOR. RAPTOR plays a multifaceted role in cellular metabolism and immune regulation, influencing several physiological processes through its association with mTORC1. It regulates metabolism by promoting lipid metabolism and energy homeostasis, while also orchestrating angiogenesis and crosstalk with other signaling pathways, such as insulin and

AMPK. Beyond its metabolic roles, RAPTOR is essential for autophagy and cell survival, ensuring cellular resilience under stress. In immune modulation, RAPTOR impacts natural killer (NK) cell activity and maturation, while also playing critical roles in B- and T-cell development, thereby shaping adaptive immunity. Moreover, RAPTOR's influence extends to tumor microenvironments, particularly through interactions with cancer-associated fibroblasts (CAFs) and regulation of cancer stemness, supporting tumor progression. Furthermore, RAPTOR also exhibits mTOR-independent functions, suggesting its broader regulatory capacity beyond mTORC1.

4.1. Regulation of Metabolism Through RAPTOR

RAPTOR plays significant roles beyond its canonical function as a scaffolding protein in regulating metabolism. AMPK directly phosphorylates RAPTOR at Ser722 and Ser 792, which is crucial for inhibiting mTORC1 and enforcing cell cycle arrest under energy stress [95]. Additionally, RAPTOR's O-GlcNAcylation at Thr700 modulates mTORC1 activation in response to glucose levels by facilitating RAPTOR's interaction with Rag GTPases and mTOR translocation to the lysosomal surface [119]. AMPK-mediated phosphorylation of RAPTOR inhibits this O-GlcNAcylation and dampens glucose-induced mTORC1 activation, demonstrating a sophisticated mechanism of metabolic regulation. In liver tissues, RAPTOR stabilizes the Akt phosphatase PHLPP2, preventing excessive fatty liver development [133]. In contrast, loss of RAPTOR due to aging or obesity results in increased mTOR–RAPTOR association, reduced PHLPP2 levels and subsequent hepatic triglyceride accumulation. Notably, the interaction between RAPTOR and Bcl-3, an atypical IκB family member that affects Th17 cell metabolism and autoimmunity. Bcl-3's role in regulating Th17 pathogenicity through RAPTOR highlights its impact on energy metabolism [134]. RAPTOR's function in metabolic regulation is also evident in its role in hepatic lipid metabolism, where the balance between mTORC1-associated and free RAPTOR influences lipid accumulation and insulin resistance. Adipose-specific RAPTOR knockout mice (RAPTOR(ad-/-)) demonstrate significant metabolic changes such as reduced adipose mass, protection against diet-induced obesity and hypercholesterolemia and improved insulin sensitivity, despite lower physical activity and unchanged caloric intake [135]. Additionally, RAPTOR(ad-/-) mice exhibit elevated expression of genes related to mitochondrial uncoupling proteins, indicating increased energy expenditure through mitochondrial uncoupling. One in vivo study using mice deficient in RAPTOR, Rictor or mLST8 has shown that RAPTOR is crucial for early development, as RAPTOR-null embryos, similar to mTOR-null embryos, show embryonic lethality [136]. Additionally, in muscle tissues, RAPTOR-deficient mice exhibit progressive dystrophy and impaired oxidative capacity, alongside increased glycogen stores. This metabolic disruption is linked to diminished activation of mTORC1 downstream targets, reduced mitochondrial biogenesis and hyperactivation of PKB/Akt, which does not require mTORC2 [61]. Similarly, in cardiac tissues, the ablation of RAPTOR in adulthood leads to severe dilated cardiomyopathy, with early onset under pathological conditions such as aortic banding [137]. Interestingly, the metabolic profiles of young and aged mice with targeted deletions of RAPTOR (RAmKO) and TSC1 (TSCmKO) in muslces reveal distinct regulatory roles of mTORC1 [138]. At ten weeks of age, RAmKO mice are notably lean, insulin-resistant and exhibit heightened energy expenditure. They show increased expression of histone deacetylases (HDACs) and downregulation of genes involved in glucose and fatty acid metabolism, while also resisting a high-fat diet (HFD). RAmKO mice eventually develop age-related myopathy, characterized by decreased fat and lean mass, which ultimately leads to insulin resistance and an increased intramyocellular lipid content.

Thus, RAPTOR is a key player in orchestrating metabolic processes, with implications for metabolic diseases, cancers and aging. Figure 5 summarizes the contribution of RAPTOR in the regulation of metabolism.

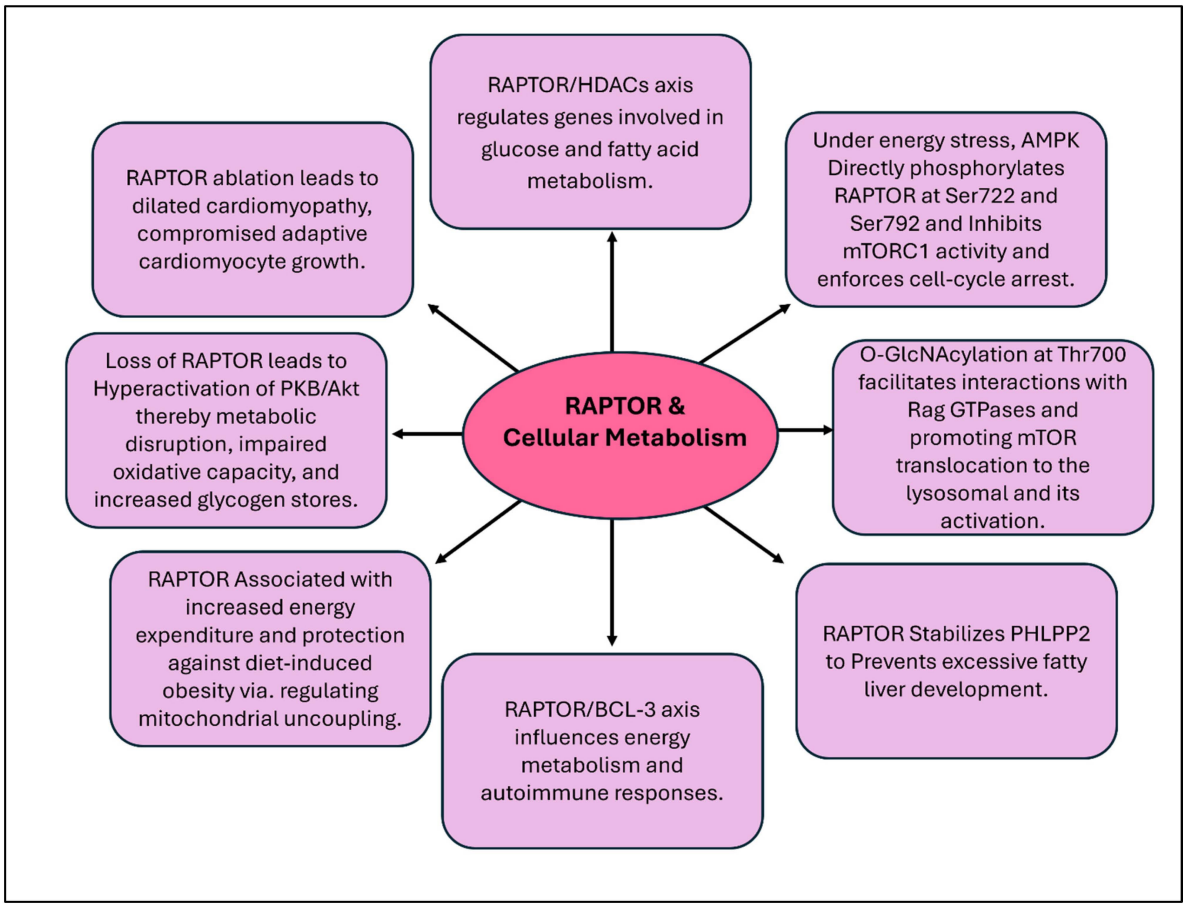


Figure 5. RAPTOR-mediated regulation of cellular metabolism. RAPTOR is crucial for metabolic regulation, influencing energy homeostasis through multiple pathways. Its loss leads to severe cardiac dysfunction, impaired metabolism and excessive fatty liver development. RAPTOR stabilizes PHLPP2 and regulates genes involved in glucose and fatty acid metabolism via its interaction with HDACs. O-GlcNAcylation at Thr700 enhances its activation of mTOR, while its interaction with BCL-3 affects energy expenditure and immune responses. RAPTOR also protects against diet-induced obesity by promoting mitochondrial uncoupling. Under energy stress, AMPK inhibits mTORC1 by phosphorylating RAPTOR, enforcing cell cycle arrest and maintaining the metabolic balance.

4.2. Regulation of Angiogenesis via RAPTOR

RAPTOR exerts a profound influence on angiogenesis and various signaling cascades, particularly within the contexts of oncogenesis and vascular remodeling. In one study, it was elucidated that RAPTOR significantly modulates the angiogenic response through its interaction with hypoxia-inducible factors (HIFs) and vascular endothelial growth factor (VEGF) [139]. Notably, RAPTOR expression exhibits a positive correlation with HIF-1α and VEGF levels in CRC, underscoring its role in fostering angiogenesis. In pulmonary arterial hypertension, a disease associated with dysfunctional angiogenesis, D prostanoid receptor subtype 1 (DP1) activation triggers the phosphorylation of RAPTOR, which subsequently inhibits mTORC1 activity and mitigates the adverse vascular remodeling induced by hypoxic conditions [140]. This interaction highlights the broader implications of RAPTOR in vascular pathophysiology and its potential as a therapeutic target in both cancer and vascular diseases.

In summary, while there are limited reports that specifically address the direct role of RAPTOR in angiogenesis, existing studies suggest that RAPTOR significantly influences angiogenesis and vascular remodeling through its regulation of mTORC1 signaling. Therefore, further research in this area is warranted.

4.3. Interaction of RAPTOR with Autophagy and Cell Survival Pathways

RAPTOR primarily regulates autophagy by modulating mTORC1 activity, playing a key role in cancer cell survival [141]. However, reports directly linking RAPTOR as a component of mTOR in autophagy regulation remain limited. A recent study shows that leucine supplementation triggers EP300-mediated acetylation of RAPTOR, enhancing mTORC1 activation and inhibiting autophagosome formation [116]. Similarly, another study found that RBM3 is upregulated during ischemia–reperfusion injury, exerting protective effects by regulating autophagy through its interaction with RAPTOR [142]. In granular corneal dystrophy type 2 (GCD2), RAPTOR plays a key role in autophagy, critical for clearing mutant-TGFBIp, a pathogenic protein [77]. In GCD2 corneal fibroblasts, mutant-TGFBIp accumulates despite active autophagy due to reduced RAPTOR levels, impairing autophagic clearance. Although depleting RAPTOR increased LC3-II, indicating more autophagy, mutant-TGFBIp still built up, showing that RAPTOR is crucial for proper autophagic function. A mechanistic study shows that SHOC2, a RAS activator, interacts with RAPTOR, disrupting its binding to mTORC1 and promoting autophagy. [143]. In contrast, when RAPTOR binds to SHOC2, it prevents SHOC2 from activating RAS, blocking MAPK signaling.

Interestingly, a study found that RNA interference (RNAi) targeting RAPTOR and mTORC1 inhibition with rapamycin enhanced autophagy, as shown by increased LC3-II and decreased p62/SQSTM1 levels [144]. This was linked to reduced apoptosis and senescence, indicated by fewer TUNEL-positive cells, decreased PARP and caspase-9 cleavage and lower levels of senescence-associated beta-galactosidase (SA-β-gal) and p16/INK4A expression. Additionally, RAPTOR interference improved matrix metabolism by lowering IL-1β-induced catabolic matrix metalloproteinase (MMP) activity and increasing anabolic gene expression. Moreover, a recent study highlighted RAPTOR's critical role in mTORC1 signaling and autophagy regulation during hepatic lipid homeostasis. Liver-specific deletion of ACOX1, an enzyme that breaks down very long-chain fatty acids (VLCFAs) in the peroxisomal fatty acid beta-oxidation pathway, protected against fasting- or high-fat diet-induced hepatic steatosis by promoting lipophagy [115]. Mechanistically, a lack of ACOX1 decreased cytosolic acetyl-CoA levels, reducing RAPTOR acetylation and impairing mTORC1 activation, which enhanced autophagy. This dysregulation of peroxisomal β-oxidation affects RAPTOR-mediated mTORC1 signaling, identifying peroxisome-derived acetyl-CoA as a key metabolic regulator of autophagy and hepatic lipid homeostasis.

In summary, RAPTOR modulates mTORC1 activity to balance autophagy and cellular growth, impacting various metabolic processes and stress responses. This function is crucial during metabolic stress, where RAPTOR can either inhibit or promote autophagy based on cellular needs. Its ability to integrate signals from different metabolic pathways underscores its central role in maintaining cellular homeostasis. Figure 6 summarizes the multifaceted roles of RAPTOR in the regulation of angiogenesis, autophagy and cell survival.

4.4. Role of RAPTOR in Immune Modulation

Beyond its previously discussed functions, RAPTOR is also a key modulator of immunity, affecting various leukocyte types and influencing their development and the overall immune response [145]. Through mTORC1 signaling, RAPTOR regulates cellular metabolism and immune cell differentiation, thereby shaping immune outcomes [146,147]. The upcoming sections underscore RAPTOR's importance in fine-tuning immune functions and maintaining immune homeostasis.

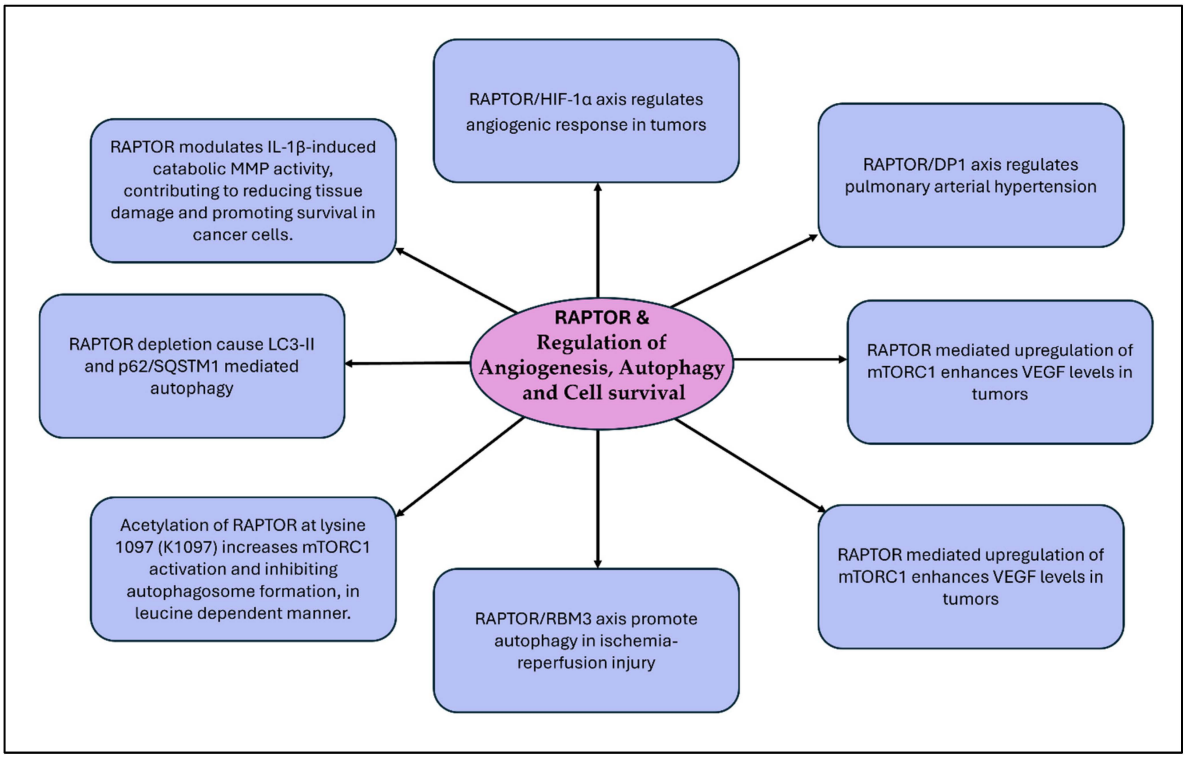


Figure 6. Role of RAPTOR in regulation of angiogenesis, autophagy and cell survival. The RAPTOR/HIF-1α axis facilitates angiogenic responses in tumors, while the RAPTOR/DP1 axis is linked to pulmonary arterial hypertension. By enhancing mTORC1 activation, RAPTOR increases VEGF levels in tumors, promoting angiogenesis. It also promotes autophagy during ischemia–reperfusion injury via the RBM3 axis. However, acetylation of RAPTOR at lysine 1097 inhibits autophagosome formation in a leucine-dependent manner. RAPTOR depletion leads to increased autophagic markers like LC3-II and p62/SQSTM1 and it modulates IL-1β-induced catabolic MMP activity, supporting tissue protection and cancer cell survival.

4.4.1. Role of RAPTOR in Regulation of Macrophages

RAPTOR is reported in regulation of the differentiation and function of macrophages, particularly in response to 1,25-Dihydroxyvitamin D3 (1,25(OH)2D3)-induced signals [148]. In human myeloid cell lines like THP-1, 1,25(OH)2D3 activates the mTOR pathway, upregulating differentiation markers such as CD14. This process involves both mTORC1 and mTORC2; silencing RAPTOR or Rictor significantly impairs differentiation, including morphological changes and CD14 expression. Inhibiting mTOR activity through inhibitors or disrupting phosphatidic acid production further confirms the essential role of the RAPTOR-containing mTORC1 complex in macrophage differentiation. Moreover, RAPTOR's role extends beyond myeloid differentiation, as it has been shown to be essential in inflammation-mediated responses [149].

A recent study found that syntenin-1, an endogenous ligand enriched in rheumatoid arthritis (RA) specimens, interacts with syndecan-1 (SDC-1) on macrophages and endothelial cells in synovial tissue. This interaction influences the inflammatory and metabolic landscape in RA by modulating macrophage behavior through the mTOR signaling pathway, with RAPTOR being essential for syntenin-1-induced macrophage reprogramming, leading to altered inflammation and glycolytic activity [150]. This modulation is crucial for amplifying inflammatory and glycolytic networks in RA, which are disrupted in SDC-1-deficient models. Another study found that deleting RAPTOR in osteoclasts increases bone mass and reduces bone resorption. This study reveals that RAPTOR-deficient bonemarrow-derived macrophages show decreased mTORC1-S6K1 signaling and impaired osteoclastogenesis, which can be rescued by reintroducing active S6K1 [151]. Targeted

deletion of RAPTOR in osteoclast precursors led to increased osteoclast formation and osteopenia in RAPTOR-deficient mice [152]. In contrast, deletion of Tsc1, a negative regulator of mTORC1, impaired osteoclast-like differentiation, which was restored by rapamycin. Notably, mTORC1 negatively regulates critical osteoclast differentiation transcription factors NF-κB and NFATc1, limiting osteoclast differentiation. Transplanting bone marrow from RAPTOR-deficient mice into Ldlr(-/-) mice resulted in reduced macrophage infiltration, a smaller lesion size and lower chemokine gene expression in atherosclerotic lesions [153]. This was associated with decreased phosphorylation of STAT3 and diminished Ccl2 promoter binding in RAPTOR-deficient macrophages, highlighting mTORC1's regulatory role in macrophage-mediated inflammation. Additionally, mice with macrophage-specific RAPTOR deficiency demonstrate improved insulin sensitivity and reduced inflammatory responses to high-fat diets, linked to decreased activation of inflammatory pathways like IRE1α/JNK/NFκB [154]. Additionally, excessive dietary protein stimulates macrophage mTOR signaling and exacerbates atherosclerosis through mitochondrial dysfunction and apoptosis. RAPTOR-null mice show a diminished response to high-protein diets, highlighting RAPTOR's role in mediating the adverse effects of dietary protein on macrophage function and atherosclerosis progression.

4.4.2. Role of RAPTOR in Regulation of Natural Killer Cells

Natural killer (NK) cells are vital components of the immune system, playing a critical role in antiviral defense, tumor elimination, hypersensitivity reactions and autoimmune diseases. The differentiation process of NK cells involves several stages, from common lymphoid progenitors to mature NK cells. These stages are marked by distinct surface markers, such as CD27 and CD11b, which reflect the cells' maturation state [155]. RAPTOR deficiency halts the progression from the CD27 + CD11b− immature NK stage to the more mature CD27 + CD11b+ stage, indicating that RAPTOR is essential for late-stage NK-cell differentiation. Both mTORC1 and mTORC2 complexes are involved in regulating NK-cell development, with RAPTOR being primarily responsible for the maturation of CD27 + CD11b− cells, while Rictor (a component of mTORC2) affects early immature NK-cell development [156]. Notably, during development, NK cells transition from the bone marrow to the bloodstream, a process intricately regulated by CXCR4 and sphingosine-1 phosphate receptor 5 (S1P5), with RAPTOR playing a crucial role in modulating this transition [157]. CXCR4 retains NK cells in bone marrow, while S1P5 facilitates their exit. During differentiation, CXCR4 expression decreases and S1P5 expression increases, promoting mature cell egress. The research further shows that cell egress relies on both CXCR4 desensitization and S1P5 activation, with RAPTOR deficiency impairing this signaling and disrupting their interactions. After entering the bloodstream, S1P5 responsiveness decreases but recovers in lymph nodes, allowing further egress via lymphatics independent of CXCR4. Thus, RAPTOR modulates CXCR4 and S1P5 to regulate cell trafficking.

RAPTOR is crucial for the development of invariant natural killer T (iNKT) cells, which connect innate and adaptive immunity. These cells are classified into NKT1, NKT2 and NKT17 lineages, each with distinct transcription factors and cytokine profiles, though the mechanisms driving lineage decisions remain unclear. One of the studies highlights the necessity of RAPTOR in iNKT-cell differentiation, particularly for NKT17 cells [158]. RAPTOR deficiency impairs the maturation of iNKT cells, significantly reducing their numbers in both thymic and peripheral compartments. T-cell-specific deletion of RAPTOR leads to a block in early thymic iNKT-cell stages and decreased mature iNKT-cell counts [159]. These cells also show impaired cytokine production upon stimulation with αGalCer. Bone marrow chimeras further confirm that mTORC1's role in iNKT-cell differentiation is cell-intrinsic. Conditional deletion of RAPTOR disrupts mTORC1 signaling, resulting in severe developmental defects in iNKT cells and diminished numbers in the thymus and peripheral tissues [160]. This impairment affects both iNKT-cell proliferation and cytokine production in response to α-galactosylceramide, mitigating liver inflammation in a hepatitis model. Additionally,

RAPTOR deficiency and rapamycin treatment lead to improper localization and dysfunction of the PLZF transcription factor, essential for iNKT-cell development and function.

Overall, these findings establish RAPTOR as a critical regulator of iNKT-cell development and activity through mTORC1 signaling, underscoring its fundamental importance in immune cell regulation.

4.4.3. Role of RAPTOR in B-Cell Maturation

The development of B cells is a highly regulated process that involves multiple checkpoints during gene rearrangement, positive selection and negative selection. This intricate process can be categorized into several stages: the pre–pro B-cell, pro-B-cell, early and late pre-B-cell, immature B-cell and mature B-cell stages, each characterized by specific immunoglobulin expression and cell surface proteins. Any errors in differentiation can lead to clonal deletion, emphasizing the importance of tight control over B-cell maturation. In studies focused on the role of RAPTOR-mTORC1, strategic knockout of the RAPTOR gene at various stages of B-cell development revealed that RAPTOR-mTORC1 plays a critical role not only in early differentiation stages but also in the regulation of B cells beyond the pre-B-cell stage [161]. Specifically, RAPTOR was found to promote the production of the Ig H chain (IgH), maintain pre-B-cell homeostasis and survival and regulate intracellular respiration and glycolysis, all of which are essential for antibody production. One of the key findings was that RAPTOR deficiency leads to a significant reduction in interleukin-7 (IL-7), a cytokine essential for B-cell maturation [162]. IL-7 is critical during the transition from pro-B- to pre-B-cell stages, and its depletion causes a developmental block at the pre-B-cell stage, resulting in a significant decline in peripheral B cells and Ag-specific antibody production. Furthermore, RAPTOR-deficient pre-B cells exhibit severe reductions in oxidative phosphorylation and glycolysis, highlighting the role of mTOR signaling in maintaining cellular metabolic capacity.

In addition to directly affecting B-cell development, RAPTOR-mTORC1 signaling plays a pivotal role in the bone marrow microenvironment, which supports B-cell commitment and maturation. Osteoblasts, essential for B-cell development, depend on mTORC1 for their expansion and differentiation. Deleting RAPTOR in osteoblast-lineage cells significantly reduces IL-7 expression, resulting in abnormal IL-7/Stat5 signaling in early B lymphocytes and increased apoptosis of pre-B and immature B cells [163]. This highlights the systemic role of RAPTOR-mTORC1 in B-cell development, as restoring IL-7 partially rescues differentiation. RAPTOR is vital for regulating B-cell development through mTORC1, which activates IL-7 to drive early B lymphopoiesis [164]. These findings collectively demonstrate that RAPTOR, through mTORC1, not only regulates the intrinsic development of B cells but also ensures that the surrounding bone marrow environment is conducive to proper B-cell maturation.

4.4.4. Role of RAPTOR in T-Cell Maturation

T cells originating from the bone marrow and maturing in the thymus are integral to the adaptive immune system, giving rise to diverse subsets such as helper, cytotoxic, regulatory and memory T cells. Their development and function are critically modulated by various signals, including immune, nutritional and environmental cues, which converge on the RAPTOR-mediated mTOR signaling pathway. RAPTOR is crucial for T-cell differentiation and function, with T cells showing greater dependency on RAPTOR than B cells. Both CD4+ (helper) and CD8+ (cytotoxic) T cells, as well as $\gamma\delta$ and $\alpha\beta$ subsets, rely on RAPTOR-mediated signaling for metabolic programming, membrane molecule expression and macromolecule synthesis. In CD4+ T cells, mTORC1 signaling regulates glycolytic enzyme expression, essential for cytokine production and immune responses. The RAPTOR-mTORC1 pathway is vital for transforming naïve T cells into effector subsets like Th1, Th2 and Th17 upon antigen stimulation [165,166]. RAPTOR facilitates the metabolic transitions needed for T cells to exit quiescence and undergo clonal expansion by integrating glycolysis, lipid biosynthesis and oxidative phosphorylation with antigen receptor signaling and cytokine responsiveness. Loss of RAPTOR disrupts T-cell priming

and Th2 differentiation, highlighting its essential role in regulating T-cell fate. Further, in CD8+ memory T cells, RAPTOR-mTORC1 signaling drives the initial expansion of memory precursors and accelerates their transition from effector to memory cells [167]. Interestingly, inhibiting mTORC1 with rapamycin enhances both the quality and quantity of memory CD8+ T cells, highlighting RAPTOR's complex role in balancing immune activation and suppression. In regulatory T cells (Tregs), which maintain immune homeostasis, RAPTOR-mTORC1 signaling is also critical. Tregs exhibit higher mTORC1 activity than naive T cells, integrating signals from the T-cell antigen receptor (TCR) and interleukin-2 (IL-2) to regulate metabolism and suppressive function. RAPTOR deficiency in Tregs severely impairs their suppressive capacity, leading to fatal inflammatory conditions [168]. Unlike other T cells, RAPTOR-mTORC1 does not directly affect cytokine expression in Tregs; instead, it promotes cholesterol and lipid metabolism via the mevalonate pathway, essential for upregulating suppressive molecules like CTLA4 and ICOS. This underscores RAPTOR's unique role in linking metabolic reprogramming to immune tolerance.

Overall, RAPTOR plays a critical role in immune regulation by influencing various aspects of immune cell differentiation and function. It regulates macrophage differentiation in response to 1,25-Dihydroxyvitamin D3 through mTOR signaling and is involved in osteoclast differentiation, which affects bone mass and resorption. In the context of atherosclerosis, RAPTOR deficiency leads to decreased macrophage infiltration and reduced inflammatory chemokine expression in lesions. Additionally, RAPTOR is essential for the late-stage differentiation of natural killer (NK) cells, particularly in their maturation and trafficking via the RAPTOR/CXCR4/S1P5 axis. It also plays a pivotal role in invariant natural killer T (iNKT)-cell development into various lineages and is crucial for B-cell development and bioenergetics. Furthermore, RAPTOR is vital for the differentiation of CD4+ and CD8+ T cells and is critical for the function of regulatory T cells (Tregs) through mTORC1 signaling, highlighting its integral role in orchestrating immune responses. Figure 7 illustrates various aspects of immune pathways regulated by RAPTOR.

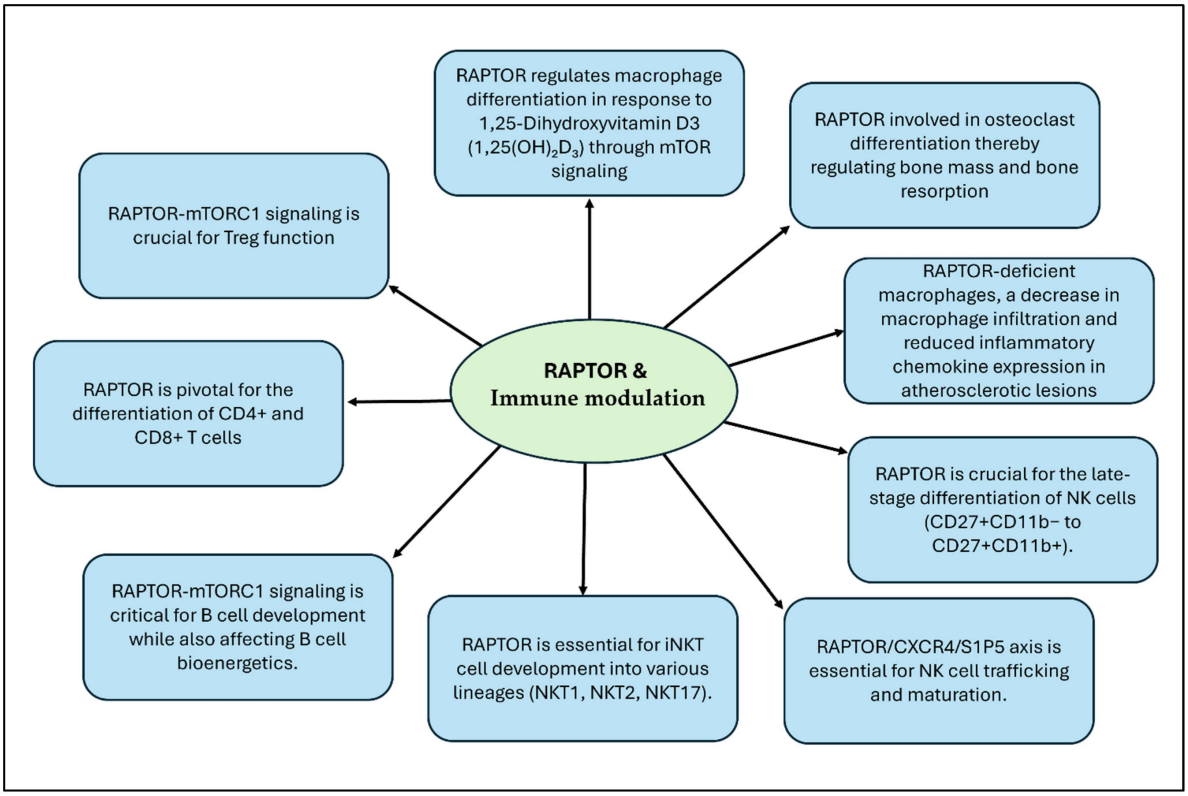


Figure 7. Illustration of the diverse immune pathways regulated by RAPTOR. RAPTOR modulates macrophage differentiation in response to 1,25-Dihydroxyvitamin D3 via mTOR signaling and is

involved in osteoclast differentiation, affecting bone mass and resorption. In atherosclerosis, RAPTOR deficiency leads to reduced macrophage infiltration and lower inflammatory chemokine expression. Additionally, RAPTOR is essential for the late-stage differentiation and trafficking of natural killer (NK) cells through the RAPTOR/CXCR4/S1P5 axis and it supports the development of invariant natural killer T (iNKT) cells and B cells. Furthermore, RAPTOR plays a significant role in the differentiation of CD4+ and CD8+ T cells and is vital for the function of regulatory T cells (Tregs), highlighting its importance in immune responses.

4.5. Interplay Between RAPTOR and Cancer Stem Cells in Tumorigenesis

The crosstalk between mTORC1 via RAPTOR and cancer stem cell (CSC) pathways underscores a complex network of regulatory interactions that are crucial to both tumorigenesis and stem cell function. While much of the current literature emphasizes the role of mTORC1 in the regulation of CSCs [2,169,170], direct studies specifically addressing RAPTOR's involvement in CSC dynamics remain limited. However, emerging evidence suggests that RAPTOR, as a core component of mTORC1, may indeed play a direct role in CSC regulation, positioning it as a potentially significant area for future scientific investigation. One study in this context suggests that activation of mTORC1 enhances CSC differentiation into more mature cancer cells, paradoxically increasing their sensitivity to chemotherapy. This dynamic is exemplified in hepatocellular carcinoma (HCC), where branched-chain amino acids (BCAAs), acting as mTORC1 activators, reduce the population of EpCAM-positive CSCs and sensitize them to chemotherapeutic agents like 5-fluorouracil (5-FU). The knockdown of RAPTOR in these models demonstrates that targeting mTORC1 can disrupt the regenerative potential of CSCs [171]. Interestingly, a study reports that dual inhibition of mTORC1 and AR by CSC inhibitors leads to autophagy and reduced prostate cancer cell survival [172]. Further, inhibition of RAPTOR-mediated mTORC1 via the inhibitory component PRAS40 disrupts epithelial-to-mesenchymal transition (EMT) and migration, both crucial for CSC-driven metastasis and wound healing [173]. By modulating EMT markers and Smad signaling, RAPTOR-mediated mTORC1 activity regulates the migration and invasive properties of epithelial CSCs.

In summary, by attuning mTORC1 activity, RAPTOR modulates key oncogenic and stemness properties among multiple cancer types. Moreover, the exploration of RAPTOR's direct roles in CSC regulation remains a compelling area for further scientific investigation, with the potential to reveal new insights into its complex biology.

4.6. Crosstalk with Other Signaling Pathways

Accumulating evidence suggests that RAPTOR is actively involved in mediating interactions among signaling pathways that influence cellular growth and tumor development. In clear cell renal cell carcinoma, VHL normally represses RAPTOR by promoting its degradation through ubiquitination, thereby inhibiting mTORC1 signaling [71]. This repression is lost in VHL-deficient tumors, leading to hyperactivation of mTORC1 and contributing to tumor progression. This mechanism highlights how VHL's control over RAPTOR and mTORC1 impacts tumor behavior and organ integrity. Another study reports that RAPTOR's interaction with mTORC1 promotes CRC-cell proliferation, migration and cell cycle progression through upregulation of Urb1 and cyclin A2 [174]. Another study utilized an inducible muscle-specific RAPTOR knockout (RAPTOR ko) mice model to examine RAPTOR's role in interacting with other cellular pathways during cancer cachexia and oxidative stress [175]. The study investigated the impact of reduced mTORC1 signaling in cancer cachexia, revealing a significant impairment that resulted in a 57% decrease in the protein synthesis rate. In RAPTOR knockout mice, diminished mTORC1 activity leads to increased autophagic flux without worsening muscle wasting. Conversely, activating Akt-mTORC1 signaling in cachectic mice reverses 15–20% of muscle mass loss, restores normal transcriptional regulation and reduces protein degradation in muscle tissue, without affecting tumor size or spleen mass.

Interestingly, mutations in RAPTOR, as observed in the naked mole-rat (NMR) *Heterocephalus glaber*, suggest a protective mechanism against tumorigenesis, highlighting its dual role in cancer progression and potential resistance mechanisms [176]. These mutations disrupt the usual overactivation of mTORC1, dampening translation and promoting cellular adaptation to stress conditions like hypoxia, a state frequently exploited by tumors for survival. Further, RAPTOR's regulatory functions extend into other pathological conditions, including pulmonary arterial hypertension (PAH) and cardiometabolic diseases. In PAH, the dysregulation of RAPTOR and mTORC1 signaling contributes to aberrant vascular remodeling and sustained vasoconstriction, exacerbating the disease's progression [177]. By driving proliferation, migration and phenotypic switching in pulmonary artery smooth muscle cells, RAPTOR facilitates the pathological changes that underlie PAH. Similarly, in metabolic disorders such as obesity and non-alcoholic fatty liver disease, RAPTOR deletion in murine models reveals its role in cardiac remodeling and metabolic reprogramming, underscoring the importance of tightly regulated mTORC1 activity for maintaining cellular homeostasis [178]. Furthermore, the effect of RAPTOR on redox homeostasis in ovarian cancer cells treated with cardamonin was examined [179]. Cardamonin inhibited cell growth by promoting ROS accumulation and decreasing RAPTOR expression. Proteomic analysis revealed that cardamonin disrupts RAPTOR expression and mTORC1 activity, as well as ERK1/2 signaling.

In summary, RAPTOR influences tumor progression and cellular responses in various pathological conditions, including cancer and metabolic disorders, through its complex interactions with multiple signaling pathways (Figure 8).

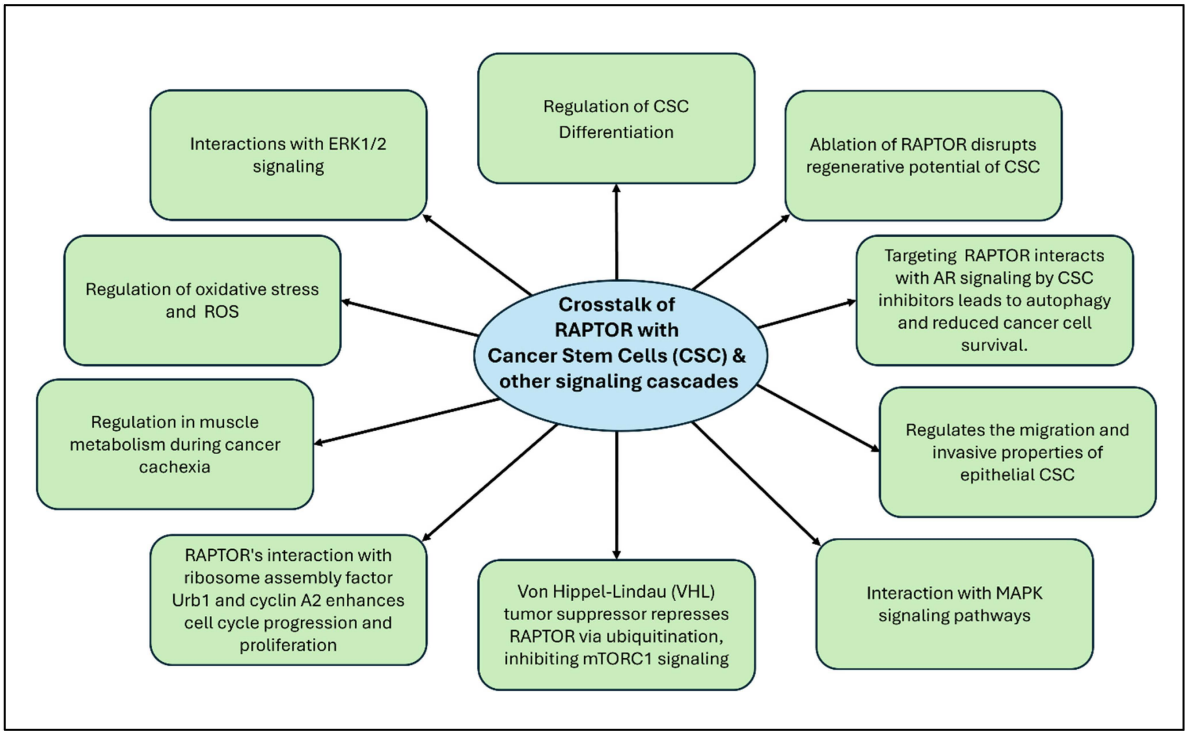


Figure 8. The role of RAPTOR in cancer stem cells and signaling pathways. RAPTOR governs cancer stem cell (CSC) differentiation, with RAPTOR ablation disrupting their regenerative potential. Targeting RAPTOR alongside androgen receptor (AR) signaling through CSC inhibitors promotes autophagy and reduces cancer cell survival, while also affecting the migration and invasive properties of epithelial CSCs. Additionally, RAPTOR interacts with MAPK signaling pathways, and its repression by the Von Hippe–Lindau (VHL) tumor suppressor inhibits mTORC1 signaling, impacting tumor growth. RAPTOR also enhances cell cycle progression through interactions with ribosome assembly factor Urb1 and cyclin A2, regulates muscle metabolism during cancer cachexia and modulates oxidative stress and reactive oxygen species (ROS) levels, underscoring its critical role in cancer biology.

4.7. mTOR-Independent Role of RAPTOR

RAPTOR is primarily known for its role in the mTORC1 pathway, where it facilitates nutrient and growth factor sensing, as well as protein synthesis. Emerging research indicates that RAPTOR has mTOR-independent functions, suggesting roles beyond its involvement in mTORC1 signaling. Recent research shows that RAPTOR regulates hepatic Akt activity and lipid metabolism independently of the mTORC1 pathway. This "free" RAPTOR negatively impacts Akt signaling and reduces lipogenesis in the liver [180]. Notably, free RAPTOR levels decline with age and obesity, correlating with increased lipid accumulation in the liver. Restoring free RAPTOR levels reduces the hepatic triglyceride content by inhibiting the degradation of PHLPP2, an Akt phosphatase, via the ubiquitin ligase β-TrCP. This highlights the crucial balance between mTORC1-associated and free RAPTOR in lipid metabolism regulation. Additionally, forced expression of PHLPP2 alleviates hepatic steatosis in obese mice.

Similarly, other findings have unveiled novel mTOR-independent roles of RAPTOR in Sertoli cells (SCs), which are essential for testis development and spermatogenesis [181]. While the canonical TSC-mTORC1 pathway is vital for SC functions, this study reveals that RAPTOR has significant roles outside of mTORC1 signaling, particularly in cytoskeletal organization and cell polarity. SC-specific deletion of RAPTOR, unlike deletion of the upstream mTORC1 activator Rheb, leads to severe testicular tubular degeneration and azoospermia, indicating RAPTOR's essential functions beyond mTORC1. Transcriptome analysis showed reduced expression of cingulin, a tight junction protein crucial for cytoskeletal regulation, in RAPTOR-deficient SCs, which correlated with cytoskeletal disorganization. Additionally, RAPTOR depletion impaired Rac1 activity by downregulating Asef, a guanine exchange factor for Rac1. These findings underscore RAPTOR's independent role in maintaining cytoskeletal homeostasis and cell polarity. Emerging evidence further suggests that RAPTOR regulates hepatic lipid metabolism and cellular organization, emphasizing its versatile regulatory role across various tissues.

In summary, RAPTOR exhibits significant mTORC1-independent functions, regulating hepatic Akt activity and lipid metabolism by negatively impacting lipogenesis and promoting the degradation of PHLPP2, an Akt phosphatase. Additionally, in Sertoli cells, RAPTOR is crucial for maintaining cytoskeletal organization and cell polarity, with its absence leading to severe reproductive impairment.

5. Role of RAPTOR in Chemoresistance and Recent Therapeutic Intervention

Pharmaceutical intervention targeting the mTOR pathway [182], specifically through modulation of RAPTOR, has emerged as a promising approach in cancer therapy due to the pathway's critical role in regulating cell growth, metabolism and survival. The first-generation mTOR inhibitors, such as rapamycin (sirolimus) and its analogs (rapalogs) like everolimus [183], primarily target mTORC1 by disrupting its interaction with RAPTOR [184,185]. These drugs have demonstrated efficacy in treating certain cancers, such as renal cell carcinoma, by inhibiting cell proliferation and inducing apoptosis. However, their effectiveness is limited by feedback activation of alternative survival pathways and their inability to inhibit mTORC2, which is also influenced by RAPTOR. To address these limitations, second-generation mTOR inhibitors, like AZD8055 and [186], have been developed to target both mTORC1 and mTORC2, providing a more comprehensive blockade of the mTOR pathway and potentially leading to better therapeutic outcomes [187]. However, among this pool of first- and second-generation mTOR inhibitors, drugs directly targeting RAPTOR remains an underexplored area and require further scientific investigation and development. In one such attempt, a study specifically explores how cardamonin, a flavonoid derived from *Alpinia katsumadi*, mediates its effects through the RAPTOR protein [188]. This study revealed that while rapamycin and AZD8055 inhibit mTORC1 activity, cardamonin uniquely suppresses both the phosphorylation and protein expression of RAPTOR. This suppression leads to decreased mTOR activation and reduced cell proliferation. Furthermore, cardamonin disrupts the lysosomal colocalization of mTOR with

lysosomal-associated membrane protein 2 (LAMP2), an effect that is amplified in cells with reduced RAPTOR expression. Very recently, a natural diterpenoid derivative, 1c, has been identified as demonstrating exceptional lipid-lowering efficacy in a RAPTOR-dependent manner, effectively mitigating obesity and associated metabolic disorders without notable toxicity [189]. Mechanistically, 1c inhibits the formation of the mTORC1 complex by targeting RAPTOR, which in turn suppresses downstream C/EBPs/PPARγ signaling and retards early-stage adipocyte differentiation. These findings highlight 1c as the first RAPTOR inhibitor and underscore its potential as a groundbreaking agent in the development of new treatments for obesity and related metabolic conditions.

Additionally, the intricate interplay between the PI3K and mTOR pathways has led to the development of dual inhibitors such as BEZ235 and GDC-0980. These compounds target both PI3K and mTOR to inhibit RAPTOR-mediated signaling, thereby reducing resistance and enhancing anti-cancer efficacy [69]. This study underscores the pivotal role of RAPTOR in driving resistance to mTOR kinase inhibitors, particularly in the context of renal cell carcinoma, highlighting its importance in targeted drug therapy. Upregulation of RAPTOR was identified as a key factor contributing to BEZ235 resistance, a dual PI3K-mTOR inhibitor, by maintaining mTORC1 activity despite drug treatment. This resistance was linked to the persistent phosphorylation of 4E-BP1, a downstream target of mTORC1. Knockdown of RAPTOR or the use of rapamycin to inhibit mTORC1 partially reversed resistance, suggesting that RAPTOR is not only essential in regulating mTORC1 signaling but also plays a crucial role in acquired drug resistance. Another report highlights the role of RAPTOR in mediating resistance to mTOR inhibitors, particularly in breast cancer cells resistant to rapamycin and metformin [190]. Both resistant sublines exhibited increased RAPTOR expression, enhanced Akt phosphorylation and activation of the AP-1 transcription factor, which contributed to reduced drug efficacy. The resistance was partially reversed with the PI3K inhibitor wortmannin, linking Akt activation to a poor drug response. Additionally, transfection with mir-181c, which regulates Akt and mTOR, further increased resistance through RAPTOR overexpression. Similarly, another study underscores the pivotal role of RAPTOR in targeted drug therapy for colorectal cancer (CRC), particularly in relation to multidrug resistance (MDR) [191]. The investigation revealed that expression levels of autophagy-related genes, including RAPTOR, Beclin1 and Rictor, were significantly elevated in CRC tissues compared to adjacent healthy tissues. Notably, RAPTOR expression was inversely correlated with both Rictor and MDR-1, while it was also negatively associated with patient survival, indicating its role in promoting drug resistance. The negative correlation between RAPTOR and autophagy markers like LC3 suggests that RAPTOR may suppress autophagy, contributing to cancer progression and resistance to therapy. Interestingly, a signaling-based study reveals that nuclear localization of RAPTOR is notably higher in ERα-positive, luminal A subtype tumors compared to other breast cancer subtypes. This nuclear RAPTOR presence correlates with increased phosphorylation of ERα and higher expression of ERα-activated gene products [192]. Moreover, nuclear RAPTOR is observed even in tamoxifen-resistant MCF7 cells, linking its presence to a reduced clinical benefit from tamoxifen. The study suggests that nuclear RAPTOR might inhibit mTORC1 activity by relocating from the cytoplasm to the nucleus, potentially leading to decreased mTORC1-driven oncogenic activity. This relocation could reflect a mechanism by which tumors adapt to low estradiol levels or increased dependence on growth factor signaling. Collectively, these reports suggest the necessity for combination therapies targeting RAPTOR to overcome resistance in cancer treatment, potentially enhancing the efficacy of mTOR inhibitors in clinical settings. Table 2 summarizes the key drugs targeting RAPTOR/RAPTOR–mTOR interaction and their mechanisms of action.

Table 2. An overview of the principal drugs that target the RAPTOR/mTOR interaction, along with their respective mechanisms of action.

Drug Name	Target	Mechanism of Action	Reference
Rapamycin (Sirolimus)	mTORC1	Disrupts interaction with RAPTOR, inhibiting cell proliferation and inducing apoptosis.	[182,183]
Everolimus	mTORC1	Similar to rapamycin, targets mTORC1 by inhibiting its interaction with RAPTOR.	[183,184]
Cardamonin	RAPTOR	Suppresses phosphorylation and protein expression of RAPTOR, reducing mTOR activation and cell proliferation.	[188]
1c	RAPTOR	Inhibits mTORC1 complex formation by targeting RAPTOR, suppressing adipocyte differentiation.	[189]
BEZ235	PI3K and mTOR	Dual inhibitor that reduces resistance and enhances anti-cancer efficacy by targeting RAPTOR-mediated signaling.	[69]
GDC-0980	PI3K and mTOR	Similar to BEZ235, it inhibits RAPTOR-mediated signaling to combat drug resistance.	[69]
Wortmannin	PI3K	Inhibitor that reverses drug resistance linked to RAPTOR overexpression and Akt activation.	[190]

In summary, targeting RAPTOR in the mTOR pathway has shown promise in cancer therapy due to its role in regulating cellular growth, metabolism and survival. Early pharmaceutical approaches, including AZD8055, rapamycin and rapalogs such as sirolimus and everolimus, initially disrupted RAPTOR's interaction with mTORC1. Also, naturally derived drugs such as cardamonin affect the phosphorylation of RAPTOR. Despite these advances, there is a critical need for RAPTOR-specific inhibitors. The recent discovery of compound 1c, the first selective RAPTOR inhibitor, represents a breakthrough where it modulates mTORC1 activity by blocking RAPTOR incorporation. While other mTORC1 inhibitors continue to emerge with their abilities to disrupt the complex [193–195], the identification of compound 1c is anticipated to pave the way for a new era in RAPTOR-based drug discovery. Furthermore, RAPTOR's role in drug resistance is another area of emerging interest. Studies suggest that RAPTOR overexpression contributes to resistance by sustaining mTORC1 signaling, as seen in resistance to dual PI3K-mTOR inhibitors like BEZ235. These findings underscore RAPTOR's essential role in both promoting cancer progression and mediating resistance to therapies, highlighting the need for combination therapies that target RAPTOR for improved treatment outcomes.

6. Conclusions and Perspectives

In conclusion, RAPTOR is a crucial player in cancer and various diseases, including metabolic disorders like type 2 diabetes and neurodegenerative diseases such as Alzheimer's. By regulating key cellular signaling pathways such as metabolism, immune evasion, angiogenesis, hypoxia, autophagy and extracellular matrix remodeling through the mTORC1 pathway, RAPTOR influences both tumor cells and the tumor microenvironment, driving tumor progression and therapeutic resistance.

Despite RAPTOR's central role as a regulatory component of mTORC1, its therapeutic potential has been underexplored due to the lack of a specific inhibitor. Most of existing drugs impact RAPTOR–mTORC1 complex formation through modulation of upstream effectors or PTMs. However, the recent discovery of compound 1c represents a significant breakthrough as this is the first RAPTOR-specific small-molecule inhibitor, selectively blocking RAPTOR's incorporation into mTORC1. Given RAPTOR's regulatory influence on mTORC1 across a range of physiological and pathological conditions including cancer, metabolic disorders, and neurodegenerative diseases, this compound opens up new research avenues to explore RAPTOR-targeted therapies for conditions involving dysregulated mTORC1 activity.

A promising direction for future research is the discovery and characterization of RAPTOR's PTMs, which may reveal new therapeutic targets in mTOR-dysregulated pathologies. Targeting these PTMs with existing drugs to disrupt RAPTOR–mTORC1 interaction offers an innovative approach to enhance immunotherapy, especially in combination with immune checkpoint inhibitors. By destabilizing the RAPTOR–mTORC1 complex, such treatments could inhibit tumor growth while simultaneously boosting the immune response through enhanced antigen presentation. These combinatorial strategies may significantly improve therapeutic efficacy in cancer and other mTOR-dysregulated diseases, potentially overcoming drug resistance and enhancing patient outcomes.

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