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mTORC signaling in hematopoiesis

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Abstract mTOR is a serine/threonine (Ser/Thr) protein kinase that responds to multiple signals, including growth factors, amino acids, energy status, stress, and oxygen, regulates cell survival, cell growth, the cell cycle, and cell metabolism, and maintains homeostasis [1]. Increased or decreased mTORC1 activity can alter HSC function and cause hematological disorders [2, 3]. Therefore, a comprehensive knowledge of mTOR is critical to understanding how HSCs function and maintain homeostasis in the hematopoietic system. In this review, we summarize recent advances in the understanding of the mTOR signaling pathway and its roles in hematopoiesis and leukemia. We also discuss pharmacological approaches to manipulate mTOR activity.

Keywords mTOR · Hematopoiesis · Leukemogenesis · HSC · Leukemia · Targeted therapy

Overview of the mTOR pathway

Rapamycin was first discovered as a new antifungal drug in soil samples from the Polynesian island of Rapa Nui, from which it received its name. In the early 1990s, studies in the budding yeast *Saccharomyces cerevisiae* revealed that a serine/threonine (Ser/Thr) protein kinase is the mediator of the toxic effects of rapamycin in yeast (Target of Rapamycin, TOR) [4, 5]. The mammalian counterpart of TOR was soon afterward purified from mammalian cells and identified as the physiological target of rapamycin [6–8]. mTOR belongs to the phosphatidylinositol-3 kinase related-kinase (PI3KK) family and works as a sensor of cellular growth and metabolism in response to nutrient and hormonal cues (Fig. 1) [9]. mTOR forms two complexes, mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2). They share the same catalytic mTOR subunit and another three known complex components, mLST8, DEPTOR, and Tti1/Tel2 [10–13]. Additionally, mTORC1 has unique subunits of regulatory-associated protein of mammalian target of rapamycin (raptor) and PRAS40; mTORC2 has rapamycin-insensitive companion of mTOR (rictor), mSin1, and protor1/2 as its specific components [14–17].

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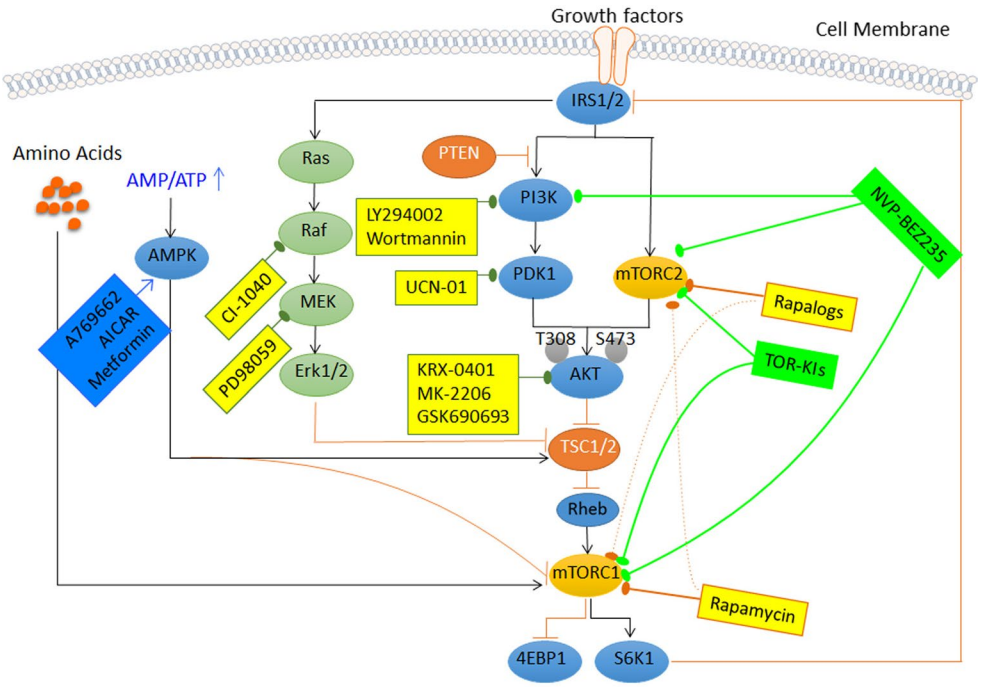
mTOR complex 1

The regulatory pathway of mTORC1 is complicated because it responds to multiple signals such as amino acids, energy, and oxygen. It coordinates diverse signaling to regulate cell metabolism and growth. Additionally, mTORC1 is sensitive to rapamycin. The effects of rapamycin on mTOR signaling are even more complicated. First, rapamycin forms a gain-of-function complex with FK506-binding protein (FKBP12) [6]. Then, this complex directly interacts with mTOR and inhibits its activity as a part of mTORC1 but not mTORC2 [10]. Rapamycin has additional effects that cannot be attributed to mTORs.

A key upstream regulator of mTORC1 is TSC1/TSC2, a heterodimer with GTPase activity consisting of tuberous sclerosis 1 (TSC1) and tuberous sclerosis 2 (TSC2), and this complex negatively controls the activity of mTORC1 [18]. Mutations in either TSC1 or TSC2 cause the hamartomatous syndrome tuberous sclerosis complex (TSC). TSC1/2



The activating (blue arrows) or inhibiting (orange or green line with dots) effects of the different drugs are also shown.

Fig. 1 mTOR signaling pathway and chemicals targeting the associated pathway. The activating (*blue arrows*) or inhibitory (*orange* or *green line with dots*) effects of the various drugs are shown

is conduit through which many intracellular and extracellular signals affect mTORC1. The effectors of these signaling pathways, including protein kinase B (PKB/AKT) and extracellular-signal-regulated kinase (ERK1/2), phosphorylate the TSC1/TSC2 complex to inactive TSC1/2 and thus promote Ras-like GTPase (Rheb) to activate mTORC1 [19, 20]. Like other small GTPases, Rheb alternates between the active GTP-bound form and the inactive GDP-bound form, and its function is determined by its GTP-/GDP- status [21]. For mTORC1 to be active, it needs to bind to GTP-bound Rheb [22]. TSC1/2 works as a GTPase-activating protein (GAP) for Rheb. TSC1/2 can reduce the level of GTP-bound Rheb and inhibit Rheb-mediated mTORC1 signaling. AKT phosphorylates PRAS40, an inhibitory component of mTORC1, diminishing its binding ability, releasing mTOR from PRAS40 repression, and promoting Rheb to activate mTORC1 [17]. In contrast to the AKT-driven activation of mTORC1, LKB1-AMPK signals can promote TSC1/TSC2 activity to inhibit the mTORC1 pathway [23]. It can also inhibit mTORC1 directly.

Amino acids have long been shown to activate mTORC1 [24], most likely independent of TSC1/TSC2. Amino acid deprivation may actually activate TSC1/2 [25]. Recently, members of the Rag GTPase family were shown to be amino acid-specific regulators of the mTORC1 pathway. Amino acids promote the loading of RagA/B GTP, which enables it to interact with Raptor in mTORC1 and thus translocate RagA/B-Raptor-mTORC1 from the cytoplasm to the lysosomal surface [26]. Rheb is found throughout the endomembrane system, and when amino acid-sensitive Rag brings mTORC1 onto the lysosomal membrane surface, Rheb activates mTORC1 [26].

As a key sensor of nutritional status, mTORC1 regulates protein production and cell metabolism. mTORC1 directly phosphorylates eIF4E-binding protein 1 (4E-BP1) and ribosomal S6 kinase (S6K) and promotes protein synthesis [27–29]. The phosphorylation of 4E-BP1 prevents its binding to cap-binding protein eIF4E complex, which is required for the initiation of cap-dependent translation. S6K controls the translation of several mRNAs that encode most of the protein components. mTORC1 also up-regulates glycolytic flux by activating the transcription and translation of hypoxia inducible factor 1α (HIFα), a positive regulator of many glycolytic genes [30]. Furthermore, mTORC1 negative regulates the lysosomal function through transcription factor EB (TFEB), which controls the expression of many genes that have key roles in lysosomal biogenesis [31]. In summary, mTORC1 is a key regulatory nexus that modulates the balance between anabolic processes and catabolic processes in response to nutrients, growth cues, and the cellular energy status (Fig. 1).

mTOR complex 2

Compared to mTORC1, less is known about the regulatory mechanism of mTORC2. mTORC2 is important developmentally because the deletion of Rictor is embryonic lethal. Interestingly, mTORC2 is insensitive to rapamycin but

Table 1 Genetic murine models associated with the mTOR pathway and their phenotypes

Gene	Type of mouse	Target cells	Comments
mTOR	cKO (Mx-Cre)	BM	KO results in the loss of quiescence of HSCs [39]
	cKO (CD4-Cre)	T cells	mTOR-deficient T cells failed to differentiate into Th1, Th2, or Th17 effector cells [50]
TSC1	cKO (Mx-Cre)	BM	KO reduces the self-renewal of HSCs [41]
Rictor	cKO (Mx-Cre/Vav-Cre)	BM	Rictor-NULL BM contributed to lower levels of the lymphoid lineages [44, 45]
	cKO (Lck-Cre)	T cells	Deletion of Rictor impaired Notch-driven proliferation and differentiation of pre-T cells [49]
Raptor	cKO (Mx-Cre)	BM	Raptor KO BM cells cannot reconstitute the recipients [44]
	cKO (Lck-Cre)	T cells	Deletion of Raptor resulted in cell cycle abnormalities in early T cell progenitors [47]
	cKO (Vav-Cre)	RBCs	Raptor-deficient mice acquired anemia [57]
RHEB	cKO (CD4-Cre)	T cells	Rheb-deficient $CD8^+$ T cells failed to differentiate into effector cells but retained memory characteristics [54]
PTEN	cKO (Mx-Cre)	BM	Pten-deficient adult HSCs gave only transient multi-lineage reconstitution that lasted less than 16 weeks after transplantation in all recipient mice [45]
Sin1	KO	T cells	Sin1 deficiency results in an increased proportion of Foxp3(+) natural T-regulatory (nTreg) cells in the thymus [97]

responds to growth factor and regulates cell metabolism, most likely through PI3K and other signaling pathways. Its substrates include the Ser/Thr protein kinase AKT, SGK, and PKC, which share the hydrophobic motif at their phosphorylation site [32]. Akt regulates cellular processes such as apoptosis, growth, and metabolism by phosphorylating many downstream effectors. mTORC2 directly phosphorylates Akt at S473 site and activates it (Fig. 1) [33]. Defective Akt phosphorylation inhibits mTORC2 activity and thereby reduces the function of some Akt targets such as FoxO1/2 [34]. mTORC2 also activates SGK1, a kinase controlling ion transport and growth. mTORC2 deletion blocks the activity of SGK1 [35]. Although we now know much about mTORC2, the exact biological role of mTORC2 still needs to be fully investigated.

mTOR in hematopoiesis

Hematopoietic stem cells (HSCs) need to coordinate proliferation and differentiation with their available essential nutrients and metabolic demands. Mammalian target of rapamycin (mTOR) signaling acts as an important integrator of nutrient-sensing pathways for metabolism and plays essential roles in regulating hematopoiesis during embryonic development and adulthood [34]. Table 1 is a summary of several mTOR-related genetic mouse models and the main conclusions of the individual studies.

The role of mTORC1 and mTORC2 in HSCs

mTOR and its complex components such as Raptor, Rictor, and mSin1 play important roles during embryonic development. Mice lacking mTOR, Rictor, or Raptor die early in development and display functional abnormality in various organs [34, 36–38]. In addition, genetic studies of important regulatory molecules associated with mTOR signaling demonstrate the central role of the mTOR pathway in both embryonic and adult hematopoiesis. Conditional mTOR deletion results in the loss of quiescence for hematopoietic stem cells, leading to a transient increase but a long-term exhaustion of HSCs and the defective engraftment of HSCs in lethally irradiated recipient mice [39]. These results demonstrate that mTOR is essential for hematopoietic stem cell engraftment and multi-lineage hematopoiesis. Interestingly, the over-activation of mTOR also drives the HSCs from quiescence into more active cell cycling. Chen et al. showed that mTOR over-activation increased mitochondrial biogenesis and caused the accumulation of a much higher level of reactive oxygen species (ROS). The removal of ROS rescued HSC defects associated with hyper-activated mTOR [40]. Moreover, the hematopoietic lineage deletion of TSC1 reduced the self-renewal of HSCs, as revealed by serial and competitive bone marrow transplantation. In vivo treatment with an ROS antagonist restored HSC numbers and functions. These data demonstrated that the TSC-mTOR pathway is key to HSC quiescence and maintains the quiescence of HSCs by repressing ROS production [41, 42]. Additionally, Chen et al. showed increased mTOR activity in HSCs from older mice compared with those from young mice. Conditional TSC1 deletion reduced mTORC1 activity and impaired HSCs' regenerative capacity. The phenotypes of TSC1-deficient HSCs are similar in several ways to those of HSCs derived from wild type aged mice. The data indicate that mTOR signaling is important for HSC aging [43].

Deficiency in *Raptor*, an essential component of mTORC1, leads to the expansion of $CD48^+CD150^-$ and $CD48^+CD150^+$ LSK populations and promotes more ST-HSCs to transition from G0 phase to G1 phase. Furthermore, Raptor-deficient BM cells cannot reconstitute hematopoiesis in lethally irradiated recipient mice [44]. Interestingly, the deletion of Rictor, the regulatory-associated protein of mTORC2 in the hematopoietic system, did not affect HSC number or its function. Rictor-deficient bone marrow cells achieved long-term multi-lineage reconstitution of all recipient mice for at least 16 weeks after transplantation although there was reduced B cell development due to the blocking of B cell development at an immature stage [3, 45, 46].

The role of mTORC1 and mTORC2 in T cells

The evolutionarily conserved kinase mTOR couples cell growth and metabolism to environmental inputs in eukaryotes. T cells depend on mTOR signaling to integrate immune signals and metabolic cues for their proper maintenance and activation. Evidence has shown that mTORC1 plays a more prominent role than mTORC2 in the development of early T cell progenitors. The deletion of Raptor, but not Rictor, resulted in cell cycle abnormalities in early T cell progenitors and generated defective T cell progenitors during the early T cell development in vivo and in vitro [47]. Under steady-state conditions, mTOR activity is kept low to allow normal T cell homeostasis. Under the antigen recognition conditions in naive $CD4^+$ and $CD8^+$ T cells, mTOR is activated and promotes T cell differentiation to functionally distinct lineages [48]. Lee et al. found that both mTOR-PKC and mTOR-Akt participate in T cell differentiation, whereas mTORC2 regulates the development of T helper 1 (Th1) and T helper 2 (Th2) cells by distinct pathways [49]. Furthermore, Delgoffe et al. showed that mTOR-deficient T cells failed to differentiate into Th1, Th2, or Th17 effector cells [50]. In addition, they found that the deletion of Rictor impaired Notch-driven proliferation and the differentiation of pre-T cells [51]. Rictor-deleted thymus has drastically reduced thymic cellularity, primarily due to reduced proliferation of the immature thymocytes [52]. Because NF-κB activity is dependent on the integrity of mTORC2 in thymocytes, activating Akt in Rictor-deficient pre-T cells maintained their NF-κB activation, proliferation, and differentiation [51].

mTORC1 and mTORC2 regulate the $CD8^+$ T cell effector and memory state. TSC1 deletion enhanced the generation of potent $CD8^+$ T cells by activating mTORC1, whereas Rheb deficiency reduced mTORC1 activity and inhibited $CD8^+$ T cells to differentiate into effector cells that retained memory characteristics. mTORC2 activity regulates $CD8^+$ T cell memory. The inhibition of mTORC2 activity increased the absolute number of $CD8^+$ memory cells [50, 53, 54].

In contrast to the requirement for mTORC1 in programming Treg cells, mTORC2 most likely contributes to Treg maintenance. Zeng et al. used a model of colitis induced by the transfer of pathogenic effector T cells into $Rag1^{-/-}$ hosts, which could be prevented by co-transfer with wild-type Treg cells. However, co-transfer with Raptor-deficient Treg cells failed to inhibit colitis or the expansion of and IFN-γ production by effector T cells. Therefore, Raptor is required for the suppressive function of Treg cells in vivo. However, the Treg-specific deletion of Rictor, the defining component of mTORC2, only resulted in a small reduction of Treg cells in the periphery, indicating a non-essential role in Treg regulation [55].

The role of mTORC1 and mTORC2 in B cells

Interestingly, the loss of Raptor does not seem to influence the number of B cells in BM and spleen, whereas Rictor deficiency reduced the frequencies and absolute numbers of mature B lymphocytes, including follicular and MZ B cells. Furthermore, Rictor-deficient BM cells showed a competitive disadvantage in the generation of mature splenic B cells compared with WT controls, indicating a cell-autonomous role of Rictor in the establishment of mature B cell populations [56]. More detailed work is needed to determine the role of mTORC1 during B cell development.

The role of mTORC1 and mTORC2 in RBCs

mTORC1 is a critical regulator of RBC proliferation. Knight et al. found that mTORC1 activity is regulated by dietary iron in RBCs, and the genetic activation or inhibition of mTORC1 resulted in macrocytic or microcytic anemia, respectively [57]. Furthermore, Gan et al. demonstrated that TSC1 deficiency causes severe multi-lineage defects characterized by anemia, myeloid expansion, and the suppression of lymphoid lineage development [42].

The role of mTORC1 and mTORC2 in homeostasis

Recent evidence indicates that HSCs reside in a low-perfusion and low-nutrient niche. However, how cellular metabolism regulates stem cell function is poorly understood. Several new studies demonstrated that several nutrient-sensing pathways contribute to HSC homeostasis, and the field is now under intensive investigation. Huang et al.

reported that the suppression of the mTOR pathway, an established nutrient sensor, combined with the activation of canonical Wnt-β-catenin signaling, allows for the ex vivo maintenance of human and mouse long-term HSCs under cytokine-free conditions. They also showed that the combination of CHIR99021 (GSK-3 inhibitor) and rapamycin (mTOR inhibitor) activates Wnt-β-catenin, inhibits mTOR signaling, and increases the absolute number of long-term HSCs in vivo [58]. In addition, GSK-3 regulates both HSC Wnt and mTOR signaling in mice and thus promotes HSC self-renewal and lineage commitment. GSK-3 inhibition in the presence of rapamycin expanded the HSC pool in vivo [59]. Furthermore, mTOR and p38 mitogen-activated protein kinase (MAPK) signaling pathways were always activated in the HSC population with higher ROS levels. However, this population was exhausted more quickly than the HSC population with lower ROS levels. Treatment with an mTOR inhibitor or a p38 inhibitor can restore HSC function in vivo [60].

mTOR signaling in leukemia

Many components of leukemia-associated signaling pathways are upstream of mTOR and are dysregulated or mutated in human leukemia. For example, PTEN mutation, a common loss of function event in leukemia, promotes mTOR activation [61, 62]. In addition, several familial leukemia syndromes arise from the up-regulation of oncogenes that lie upstream of mTOR, including PI3K and NF1 [63, 64]. Oncogenic mTOR signaling activation facilitates several processes required for leukemic cell growth and survival. In this section, we will summarize the effects of mTOR in leukemogenesis and leukemia therapy.

AML (acute myeloid leukemia)

AML is initiated by a blockage in the differentiation of hematopoietic stem cells, which results in the growth of a clonal population of neoplasm cells accompanied by the dysregulation of key signaling transduction pathways. Constitutive PI3K/Akt/mTOR pathway activation is detectable in 50–80 % of AML patients and is associated with very poor prognosis [63, 65]. A growing body of evidence indicates that the dysregulation of components of mTOR plays a central role in leukemia formation. In the MLL-AF9 AML mouse model, Raptor deficiency significantly suppresses leukemia progression by reducing the cellularity of peripheral leukemia cells, mainly by increasing apoptosis and decreasing leukemic cell proliferation, thereby prolonging the survival of AML mice [2]. Interestingly, the leukemia stem cells (LSCs, $cKit^{+}Gr\text{-}1^{-}$ cells) [66] were largely unaffected, as demonstrated by the comparable cell numbers and the similar cell cycle and apoptosis rates between Raptor-deficient and control LSCs. However, the leukemia initiating ability of LSCs was impaired in the absence of Raptor, indicating that mTORC1 plays an important role in modulating LSC function [2]. The phosphorylation of the mTORC1 substrates p70S6K and 4E-BP1 in AML cells was also significantly reduced with Raptor deletion, indicating reduced mTORC1 activity. Interestingly, the phosphorylation of AKT S473 was also significantly decreased, which is different to the mTORC1-IRS1 negative feedback regulation found in some cell type studies, suggesting a different feedback loop for AKT inhibition through mTORC1 in leukemia cells [2].

T-ALL

Physiological Notch signaling determines the developmental fates of organisms. However, gain-of-function Notch1 mutations are commonly seen in leukemia. More than 50 % of human T-ALL cell development depends on ongoing Notch-initiating signals for their growth or viability [67]. mTORC1 can be activated by the Notch1-induced transcription of c-Myc. The hyper-activation of mTORC1 has been observed and can be inhibited by γ-secretase inhibitors (GSIs), which would abolish Notch1 signaling transduction, in T-ALLs induced by mutant Notch [68–70]. Furthermore, the deletion of Raptor in a NOTCH1-driven T-ALL mouse model prolonged the survival of mice, indicating that mTORC1 is required for lymphomagenesis [47]. In addition, the transformation of $Rictor^{-/-}$ hematopoietic bone marrow precursors by Notch cleaved intracellular polypeptide (ICN1) was also significantly repressed compared with control cells, as evidenced by prolonged survival in the $Rictor^{-/-}$ group. Without affecting the circulating number of $Thy^{+}CD4^{+}CD8^{+}$ cells, the tissue infiltration was strikingly decreased by Rictor depletion. Mechanistically, the expression of the NF-κB-dependent chemokine receptor CCR7, which was reported as an important factor of Notch-induced T-ALL, was greatly reduced in $Rictor^{-/-}$ cells. However, the expression of the FoxO target genes Il7ra, Sell, and S1P1 was largely unchanged [51]. In a similar model, by deleting Rictor in T-ALL, Hua et al. found that leukemia progression was significantly suppressed by arresting a greater proportion of $Rictor^{f/f}$ leukemic cells at the G0 phase of the cell cycle. More importantly, they established that FoxO3 is the downstream target for mTORC2 inactivation in Notch-induced murine T-ALL model [71].

Pten mutation was mostly found in adult leukemia and rarely occurs in pediatric leukemia. It was reported that the loss of Pten will induce HSC proliferation and depletion,

and lead to the progression to T cell acute lymphoblastic leukemia (T-ALL) [3, 72, 73]. Using a Pten-loss-induced T-ALL mouse model, Magee et al. found that Rictor deletion largely decreased the elevated phosphorylation level of AKT and suppressed the leukemogenesis induced by Pten deletion. Furthermore, additive rapamycin treatment with other drugs could improve the outcome of myeloproliferative disorder caused by Pten deletion, suggesting that both mTORC1 and mTORC2 contribute to Pten-loss-induced leukemogenesis, consistent with the phenotype of Raptor knockout mice [45]. The ablation of Raptor did not affect the numbers of Pten-loss-induced changes of BM or splenic $LSK^{-}CD48^{-}CD150^{+}$ cells, but it significantly extended the survival of mice in Pten-loss-induced leukemogenesis, indicating that Raptor/mTORC1 is required for PTEN-loss-induced T-ALL [3, 44]. Higher levels of AKT phosphorylation at Ser473 in Raptor/Pten double knockout LSK cells were observed, suggesting that the impaired leukemogenesis may be due to diminished Foxo activity [74].

Consistently, in another T-ALL mouse model with an oncogenic Kras mutation (KrasG12D), the inhibition of mTORC1 by Raptor deficiency dramatically suppressed the development of oncogenic Kras-induced T-ALL. The mechanism by which mTORC1 prevents T-ALL was most likely via the inhibition of the cell cycle rather than affecting cell differentiation and apoptosis. The role of Raptor in three different T-ALL murine models was consistent, indicating the important role of mTOR in the progress of lymphomagenesis.

B-ALL and other hematologic malignancies

Elevated mTOR signaling was reported to correlate with poor prognosis in B-ALL patients [75]. However, no knockout mouse disease models for mTORC1 or mTORC2 to study B-ALL in mice was reported. Instead, mTOR inhibitors such as rapamycin were used to investigate the role of mTORC1 in B-ALL [76]. Rapamycin was found to inhibit the growth of pre-B-ALL cell lines in vitro by increasing apoptosis. Using Eμ-ret transgenic mice, a model for pre-B-ALL, rapamycin was shown to prolong the survival of disease models by inhibition of mTOR activity [77]. In addition, mTOR signaling is activated in CRLF2-rearranged B-ALL, indicated by the increased phosphorylation of pS6 and 4EBP1. The mTOR inhibitors rapamycin, PI103, and PP242 inhibited the activated signal transduction of mTORC1 downstream effectors, suggesting a therapeutic potential in this type of B-ALL [78]. When rapamycin was used in xenograft models with pediatric B-ALL samples, it reduced the leukemia burden progression regardless of the presence or absence of CRLF2 and JAK genomic mutations. Although S6 was constitutively phosphorylated in 8 patient samples, only 2 samples treated with rapamycin showed decreased S6 phosphorylation levels. Additionally, Akt phosphorylation level was not changed much in these cases, implying unaffected mTORC2 activities. Thus, the underlying the mechanism behind the effectiveness of rapamycin and its analogs still needs to be explored and fully evaluated [79].

Increased mTORC1 signaling was also observed in Eμ-Myc transgenic mice, a Burkitt lymphoma model caused by deregulated MYC expression [80]. Myc loss leads to a defect in translation initiation control mediated by the mTOR pathway, primarily due to elevated levels of TSC2, suggesting a potential role of mTOCR1 in leukemia driven by Myc [81].

Targeting mTOR signaling for leukemia therapy

The evidence linking activated mTOR signaling to leukemia has generated significant interest in targeting the mTOR pathway for leukemia therapy, and some next-generation mTOR inhibitors are now in pre-clinical investigations and/or clinical trials (Fig. 1). Rapamycin (RAP) and its analogs temsirolimus and everolimus (rapalogs) are the classic mTOR inhibitors. Rapamycin was also reported to inhibit the mTORC2 by long-term exposure, the mechanism mainly by depletion of mTOR from mTORC2, not by directly inhibiting mTORC2 [82]. The in vitro treatment of mantle-cell lymphoma (MCL) cells with rapamycin-induced cell cycle arrest [83]. MCL patients exhibited one of the best clinical responses to rapamycin [84, 85]. Rapamycin was also found to be a potential treatment for AML [86]. The PI3K–AKT–mTOR pathway is hyperactive in patient-derived AML cells. However, rapamycin and its analogs failed to provide a significant improvement of response in leukemia patients [87], most likely due to the negative feedback loops. The elevation of RTK–PI3K–PDK1 activity in response to rapamycin can promote Akt phosphorylation on Thr308, which may be sufficient for cell survival [88].

Another type of inhibitor is the newly developed ATP-competitive mTOR kinase inhibitors (TOR-KIs), including AZD8055, PP242, and Torin-2, which can suppress both mTORC1 and mTORC2 [89, 90]. AZD8055 induced the caspase-dependent apoptosis and autophagy of AML cell lines in vitro [91]. PP242 was shown to suppress B-ALL, T-ALL, and AML cells by inhibiting the PI3K/AKT/mTOR pathway and prolonging survival in AML mouse models [92–94]. Torin-2, an ATP-competitive inhibitor of mTOR, causes both apoptosis and autophagy and suppresses the cell cycle by affecting both mTORC1 and mTORC2 activities [93, 95]. However, no clinical data for TOR-KIs have been reported thus far [87]. The compounds NVP-BEZ235 and XL-765 (Exelixis)

simultaneously inhibit PI3K and mTOR kinases and decrease the phosphorylation of Akt, S6K1, and 4E-BP1. Some studies indicated that such broad inhibition of cellular signaling may also affect normal cells, thus limiting the therapeutic window of these compounds [92]. Nonetheless, these molecules have been used in phase 1 clinical trials and show promising efficacy in patients with various types of cancer [96].

The studies of mTOR in hematopoiesis and leukemogenesis provide us a better understanding of how HSCs function in generating full lineage of blood cells and a potential therapeutic window for treating leukemogenic development arising from PI3K–AKT–mTOR dysfunction.

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Compliance with ethical standards

Conflict of interest No financial interest/relationships with financial interest relating to the topic of this article are declared.

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