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REVIEW

Targeting mTOR in Systemic Lupus Erythematosus: From Immune Cell Dysfunction to Clinical Translation

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Abstract: Systemic lupus erythematosus (SLE) is an autoimmune disease mainly characterized by the production of autoantibodies and the deposition of immune complexes, leading to damage to multiple organs and tissues. The mammalian target of rapamycin (mTOR), a serine/threonine kinase, regulates cell growth, proliferation, and survival. The dysfunction of immune cells, such as T cells, B cells, macrophages, and dendritic cells, plays a crucial role in the pathogenesis of systemic lupus erythematosus (SLE) by leading to the overproduction of autoantibodies, deposition of immune complexes, and subsequent tissue damage. The mTOR signaling plays an important role in SLE pathogenesis by affecting the proliferation and differentiation of immune cells and the secretion of inflammatory cytokines. Numerous studies have confirmed that mTOR inhibition can significantly relieve the clinical symptoms and delay disease progression in patients with SLE. Treatment with mTOR inhibitors effectively reduces disease activity and enables glucocorticoid-sparing. However, its therapeutic efficacy in lupus nephritis remains to be investigated. Furthermore, some studies have reported limited efficacy or adverse effects of mTOR inhibitors in certain SLE subsets. Given that mTOR-independent pathways (e.g. JAK-STAT, NF-κB) are also implicated in SLE pathogenesis, combination therapeutic strategies may be necessary. Consequently, further research into the role of mTOR in SLE and the potential of mTOR-targeted therapy is warranted. In this Review, we summarized the biological functions of mTOR, its effects on various immune cells populations, and the therapeutic effects of mTOR inhibitors in SLE, with the aim of providing a reference for the further exploration of therapeutic targets in SLE treatment.

Keywords: systemic lupus erythematosus, SLE, mTOR, treatment, immunometabolism

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by widespread inflammation and tissue damage.[1] It predominantly affects women, especially those of reproductive age.[2] Clinical manifestations are highly variable, ranging from mild fatigue and joint pain to potentially severe, persistent organ damage, including skin rashes, joint pain, renal involvement, and neurological manifestations, all of which contributes to its severity and unpredictability.[3]

mTOR is a serine/threonine protein kinase belonging to the PI3K-related kinase family. It forms two functionally distinct complexes in cells—mTORC1 and mTORC2—and serves as a central regulatory hub for cell growth, metabolism, and immune responses. Its activity is precisely regulated by multiple upstream signals, including growth factors, energy status, oxygen levels, and amino acids. The physiological functions primarily mediated by mTOR include protein synthesis, cellular metabolism, autophagy regulation, and cytoskeleton remodeling.

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The underlying pathogenesis of SLE is the breakdown of immune tolerance to self-antigens.[4] Within this process, the mammalian target of rapamycin (mTOR) plays a key regulatory role in immune cell function. It influences the activation, differentiation, and survival of various immune cells, including T cells, B cells, and macrophages,[5] thereby positioning it a central factor in immune responses and the development of autoimmune diseases such as SLE. Furthermore, dysregulated mTOR signaling can promote aberrations in multiple cellular processes, including growth factor receptor signaling, glycolytic and lipid metabolism, and autophagy.[6]

Understanding how mTOR dysregulation contributes to these immune and inflammatory processes is crucial for developing targeted therapies aimed at modulating its activity in SLE patients. Therefore, this review describes the structure and key processes of the mTOR pathway, highlighting its role in SLE pathogenesis and the mechanisms by which mTOR inhibitors may contribute to disease treatment. By synthesizing these findings, this review aims to explore the potential of harnessing mTOR-targeted therapies to improve clinical outcomes for patients with SLE, as well as to discuss the potential challenges in its clinical translation.

The Biology of mTOR

In 1975, Sehgal et al identified an antifungal macrolide antibiotic from soil samples on Easter Island, which was subsequently named Rapamycin according to its site of origin.[7] Rapamycin associates with the intracellular receptor FK 506-binding protein of 12 kDa (FKBP12), and this complex then binds to and inhibits mTOR.[8,9] mTOR is a member of an evolutionarily conserved family of serine/threonine kinases that serves as a central regulator of cellular growth, metabolism, and homeostasis by integrating various extracellular and intracellular signals.[5] It is essential for numerous biological processes, including cellular metabolism, immune responses, autophagy, survival, proliferation, and migration.[6,10]

mTOR participates in the formation of two different functional complexes, mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2).[11] These complexes process different upstream regulators and downstream effectors, thereby eliciting unique signaling events to govern specific cellular processes.

mTORC1 is composed of three core components and two inhibitory components. The core components include mTOR, mammalian lethal with Sec13 protein 8 (mLST8), and Raptor (regulatory associated protein of mTOR complex 1).[12] mLST8 associates with the catalytic domain of mTORC1 and stabilizes its kinase domain.[13] Raptor is vital for recruiting substrates to mTORC1 and ensuring its proper subcellular localization.[14] The two inhibitory components of mTORC1 are DEP-domain-containing mTOR-interacting protein (DEPTOR) and proline-rich AKT substrate 40 kDa (PRAS40).[15,16] The primary function of mTORC1 is to promote anabolic processes by phosphorylating substrates that drive the production of macromolecules, including proteins, lipids, and nucleotides, and by stimulating ATP production.[17] Additionally, mTORC1 inhibits catabolic processes such as autophagy.[18] In proliferating cells, mTORC1 drives the synthesis of macromolecules required for growth. In metabolic tissues such as the liver, mTORC1 enhances nutrient storage and inhibits catabolic metabolism.[19] These functions collectively ensure an adequate supply of energy and building blocks for cell growth and proliferation.

The core components of mTORC2 also include mTOR and mLST8, both of which are essential for its stability and function.[20] In contrast to mTORC1, mTORC2 consists of rapamycin-insensitive companion of mTOR (Rictor), which, together with DEPTOR and the regulatory subunits mSin1 and Protor1/2, forms the functional complex.[17] The presence of Rictor and mSin1 physically blocks the binding of the FKBP12-rapamycin complex to mTOR, rendering mTORC2 acutely insensitive to rapamycin. Regarding its biological functions, mTORC2 phosphorylates members of the AGC kinases family including AKT, to modulate cell survival, proliferation, and cytoskeletal organization.[19]

Upstream Regulators of mTOR

mTORC1 activity is tightly regulated by various environmental cues, including growth factors, energy status, oxygen levels, and amino acid availability. Growth factors primarily signal through the phosphatidylinositol 3-kinase (PI3K) – phosphoinositide-dependent kinase-1 (PDK1) –protein kinase B (AKT) axis, while energy stress and hypoxia act through the LKB1 liver kinase B1 (AKT)/ AMP-activated protein kinase (AMPK) pathway.[5,6]

The PI3K/AKT/TSC signaling cascade constitutes the major regulatory mechanism for mTORC1 in response to growth factors. Ligand binding to cell surface receptors initiates the recruitment and phosphorylation of PI3K, which

generates phosphatidylinositol 3,4,5-trisphosphate (PIP3). This facilitates the membrane recruitment and activation of PDK1 and AKT. Subsequently, activated AKT phosphorylates the tuberous sclerosis complex 1/2 (TSC1/TSC2) complex, thereby inhibiting its GAP (GTPase-activating protein) activity toward RHEB (Ras homolog enriched in brain).[21] Maintaining RHEB in the GTP-bound active state enables the activated RHEB to directly bind to mTORC1 and activate it. Conversely, phosphatase and tensin homolog negatively (PTEN) regulates this pathway by dephosphorylating PIP3, thereby antagonizing PI3K signaling and suppressing mTORC1 activation.[5]

Under hypoxic conditions, regulated in development and DNA damage responses 1 (REDD1) is induced and promotes TSC2 function, leading to mTORC1 inhibition.[5] DNA damage can also suppress mTORC1 through multiple mechanisms, including transcriptional upregulation of TSC2 and PTEN.[5] Additionally, both hypoxia and energy depletion activate LKB1-dependent AMPK. Activated AMPK inhibits mTORC1 through two parallel pathways: one is to phosphorylate and activate TSC2, promoting the formation of the inhibitory TSC1/TSC2 complex; the other is to directly phosphorylate Raptor, leading to the conformational inhibition of mTORC1.[22] This dual mechanism ensures robust suppression of mTORC1 under conditions of energetic stress.

Beyond growth factor and energy sensing, mTORC1 activation is uniquely dependent on amino acid availability, particularly leucine and arginine, and this signaling occurs at the lysosomal membrane surface.[5] Unlike growth factor signaling, the amino acid sensing mechanism does not rely on the TSC1/2 complex but is mediated by a specific protein.[5] The Rag family of GTPases serves as a critical relay for amino acid sufficiency. Mammalian cells express four Rag isoforms: RagA, RagB, RagC, and RagD. These proteins form obligate heterodimers consisting of either RagA or RagB with either RagC or RagD.[23] In the presence of sufficient amino acids, RagA/B is loaded with GTP while RagC/D binds GDP. The Rag GTPases, together with their regulator, the Ragulator complex, are anchored to the lysosomal surface. By recruiting mTORC1 to the lysosomal membrane, they achieve amino acid-dependent activation of mTORC1.[5] Specifically, sufficient amino acids promote the GTP-bound state of RagA/B, enabling the recruitment of mTORC1 via interaction with Raptor. This transfer brings mTORC1 close to the direct activator RHEB, which is also located on the lysosomal membrane, thereby completing the activation.[24]

The cells' perception of sufficient amino acids depends on the accumulation of amino acids within the lysosomal cavity. This process requires the participation of vacuolar H+-adenosine triphosphatase (v-ATPase). This proton pump, situated on the lysosomal membrane, acidifies the lysosomal lumen and initiates a signaling cascade that promotes Rag GTPase interaction with RHEB, thereby facilitating mTORC1 activation.[25] A feedback loop exists between mTORC1 and v-ATPase, allowing for coordinated regulation of lysosomal function and mTORC1 signaling[25] (Figure 1).

Compared to mTORC1, the regulation of mTORC2 is considerably less understood.[5] Current evidence indicates that mTORC2 is primarily responsive to growth factor and hormone signaling, such as insulin, through the PI3K pathway.[26,27] The PI3K product PIP3 promotes mTORC2 activation and facilitates the phosphorylation of AKT at Ser473, a residue commonly used as a marker of mTORC2 activity.[5] PIP3 can also engage the PH domain of the mTORC2 subunit mSin1, relieving autoinhibition and promoting complex activation.[5] Growth factor signaling enhances the association of mTORC2 with ribosomes, and insulin/PI3K signaling may promote AKT translation. Notably, there is a negative feedback loop between mTORC1 and mTORC2. Increased mTORC1 activity elevates ribosomal protein S6 kinase 1 (S6K1) function, which in turn phosphorylates insulin receptor substrate-1 (IRS-1) and growth factor receptor-bound protein 10 (Grb10). Finally, it inhibits the insulin/PI3K signaling pathway, thereby suppressing the activation of mTORC2[26] (Figure 1).

Downstream Targets of mTOR

Protein Synthesis

Ribosomal protein S6 kinase beta-1 (S6K1) and eukaryotic translation initiation factor 4E-binding protein 1 (4E-BP1) are two key downstream effectors through which mTORC1 regulates mRNA translation and protein synthesis. Upon activation, mTORC1 directly phosphorylates both S6K1 and 4E-BP1, thereby promoting cap-dependent translation initiation.[6]

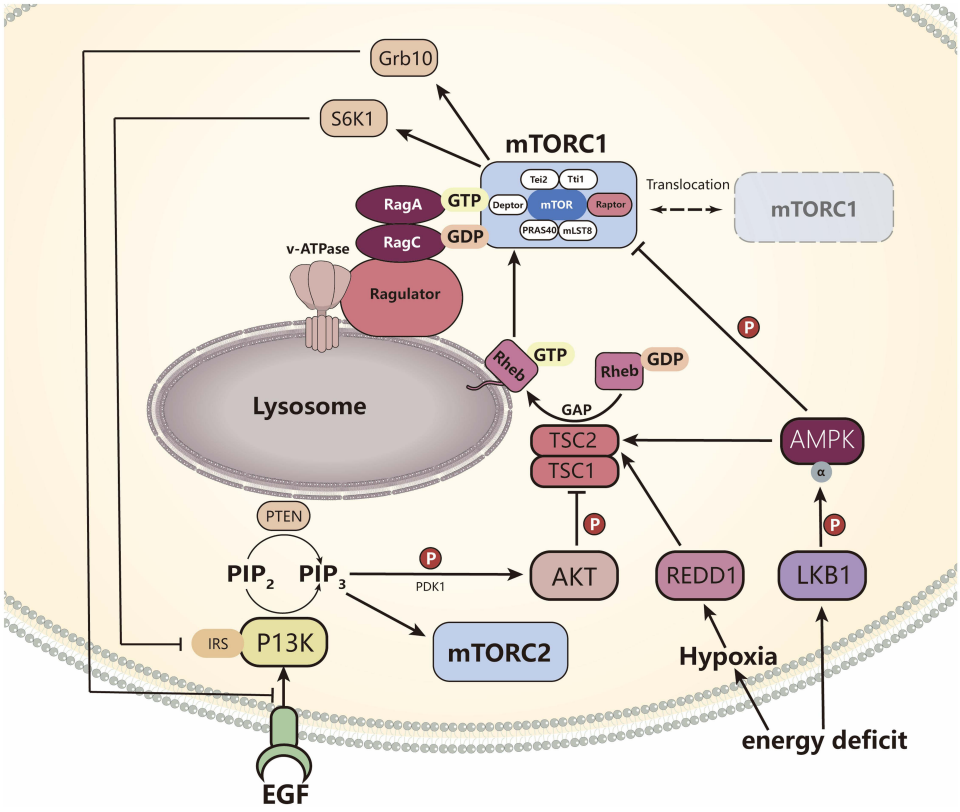

Figure 1 Upstream regulatory pathway of mTOR. Hypoxia and low energy can regulate the TSC1/TSC2 complex by activating the PI3K/Akt and LKB1-AMPK pathways, thereby inhibiting its GAP activity, activating RHEB, and promoting mTORC1 activity. AMPK can also directly phosphorylate Raptor to inhibit mTORC1. Hypoxia can also enhance TSC2 function by upregulating REDD1. Adequate amino acids promote the binding of Rag A/B-GTP to Rag C/D-GDP, guiding the translocation of mTORC1 to the surface of lysosomes and activating it through interaction with RHEB. V-ATPase enhances this process by adjusting the pH value inside the cavity. The increase in mTORC1 activity can be inhibited by S6K1 phosphorylation of IRS-1 and Grb10 to suppress mTORC2, forming a negative feedback regulation of insulin signaling.

4E-BP1 contains multiple phosphorylation sites, including Thr37, Thr46, Ser65, and Thr70. mTOR regulates 4E-BP1 phosphorylation through at least two mechanisms: first, the protein kinase activity of mTOR directly phosphorylates Thr37 and Thr46; second, mTOR inhibits phosphatases that would otherwise dephosphorylate Ser65 and Thr70.[28] Phosphorylation of 4E-BP1 reduces its binding affinity for Eukaryotic Initiation Factor 4E (eIF4E), resulting in the release of this cap-binding protein. eIF4E subsequently participates in forming the eIF4F complex, a heterotrimer composed of eIF4E, the RNA helicase eIF4A, and a large scaffolding protein eIF4G. This complex recruits ribosomes to mRNA, thereby initiating the process of protein translation.[29]

In parallel, amino acid sufficiency activates mTORC1-S6K1 signaling pathway.[30] mTORC1 directly phosphorylates S6K1 at the hydrophobic motif site Thr389, resulting in partial activation and exposing a docking site for PDK1. PDK1 then binds and phosphorylates S6K1 at the activation loop site Thr229, leading to full kinase activation.[6] Once activated, S6K1 translocates to the cytoplasm, where it directly phosphorylates RPS6 (Ribosomal protein S6), a major component of the 40S ribosomal subunit.[31] Phosphorylation of RPS6 enhances the translational efficiency of ribosomes, promoting the synthesis of proteins required for cell growth and proliferation.[32]

Beyond RPS6, S6K1 promotes protein translation by phosphorylating additional regulators of the translational machinery. These include Eukaryotic Initiation Factor 4B (eIF4B) and Programmed Cell Death Protein 4 (PDCD4).[33] eIF4B acts as a positive regulator of the eIF4F complex; its phosphorylation by S6K1 enhances its interaction with eIF4A, facilitating mRNA unwinding and translation initiation. Conversely, PDCD4 functions as a negative regulator of eIF4Aby sequestering it and inhibiting its helicase activity. Through an indirect mechanism involving S6K1, PDCD4 is phosphorylated and subsequently targeted for degradation, thereby relieving this inhibition and further promoting translation initiation[34] (Figure 2).

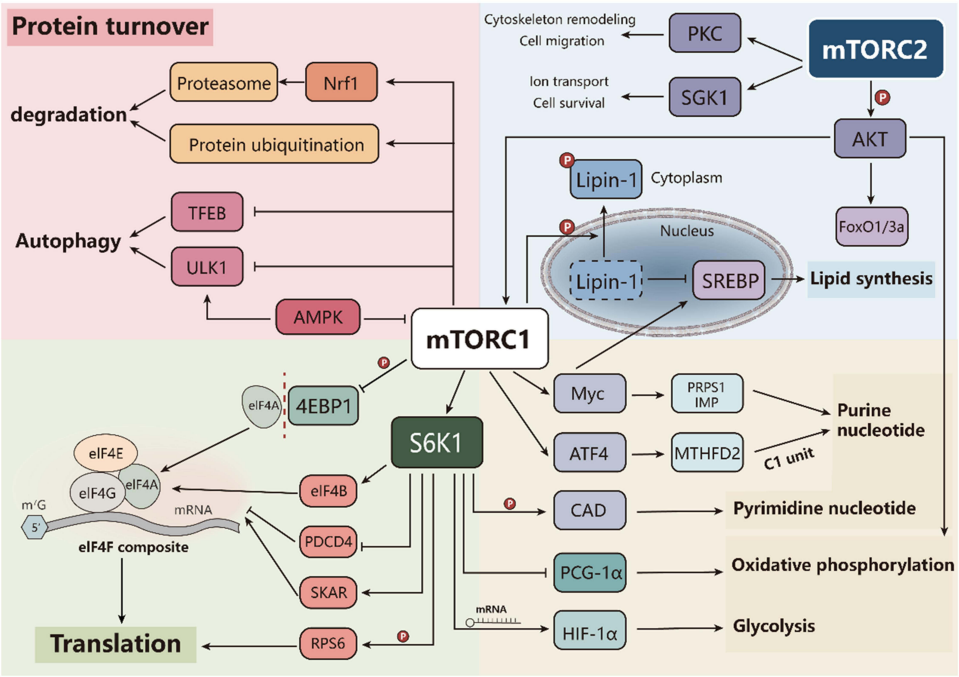

Figure 2 Downstream regulatory pathways of mTOR. Activated mTORC1 promotes protein translation by phosphorylating S6K1 and 4E-BP1, regulating the activity of eIF4E, eIF4B, and their related complexes. In nucleotide metabolism, the expression of MTHFD2 can be upregulated, and pyrimidine and purine synthesis can be promoted by activating CAD and transcription factor Myc. In addition, by enhancing the translation induced glycolysis of HIF-1 α and inhibiting the expression or activity of PGC-1 α, the oxidative phosphorylation level is reduced. In lipid metabolism, lipid synthesis is promoted by activating the SREBP pathway. MTORC2 participates in regulating cell metabolism, skeletal remodeling, and cell survival by phosphorylating Akt, PKC, and SGK1. In terms of protein turnover, mTORC1 inhibits the activity of ULK1 and TFEB, thereby negatively regulating autophagy. At the same time, upregulation of Nrf1 can enhance the expression of proteasome subunits and maintain protein homeostasis.

Metabolism Regulation

mTORC1 coordinates multiple aspects of cellular metabolism, including lipid, glucose, and nucleotide metabolism, to support cell growth and proliferation.

In lipid metabolism, mTORC1 promotes lipogenesis by regulating the activity of sterol regulatory element-binding proteins (SREBPs), master transcription factors for fatty acid and cholesterol synthesis. mTORC1 phosphorylates lipin-1, a phosphatidic acid phosphatase that functions as a transcriptional coactivator, causing its nuclear exclusion and thereby alleviating its inhibitory effect on SREBP activity.[3] Additionally, mTORC1 activates SREBP1 through an S6K1-dependent mechanism. However, the underlying mechanism remains unclear.[35]

Regarding glucose metabolism, mTORC1 promotes a metabolic shift from oxidative phosphorylation to aerobic glycolysis, a phenomenon known as the Warburg effect.[3] As previously described, mTORC1 enhances HIF-1α mRNA translation through activation of the 4E-BP1 pathways. HIF-1α subsequently induces the expression of glycolytic enzymes and lactate dehydrogenase, thereby increasing glycolytic flux.[35] Concurrently, mTORC1 signaling through inhibiting the expression and activity of peroxisome proliferator-activated receptor gamma coactivator 1α (PGC-1α), a key regulator of mitochondrial biogenesis and oxidative phosphorylation, further reinforcing the shift toward glycolysis.[36]

As for nucleotide metabolism, mTORC1 regulates nucleotide metabolism through both substrate supply and biosynthetic enzyme regulation. To supply one-carbon units for purine synthesis, mTORC1 increases ATF4-dependent expression of methylenetetrahydrofolate dehydrogenase 2 (MTHFD2), a critical enzyme in the mitochondrial tetrahydrofolate cycle.[37] For pyrimidine synthesis, mTORC1 enhances the activity of carbamoyl-phosphate synthetase 2, aspartate transcarbamylase, and dihydroorotase (CAD), the rate-limiting enzyme complex in de novo pyrimidine biosynthesis that catalyzes the first three steps from glutamine to dihydroorotate. This activation occurs through S6K1-mediated direct phosphorylation of CAD, which increases its enzymatic activity.[38] Furthermore, mTORC1 indirectly promotes purine

nucleotide synthesis by activating transcription factors such as Myc, which upregulate the expression of key purine synthesis enzymes, including phosphoribosyl pyrophosphate synthetase 1 (PRPS1) and IMP dehydrogenase.[39]

mTORC2 primarily regulates cellular metabolism and survival through its downstream kinase targets. One of the most critical functions of mTORC2 is the phosphorylation and activation of AKT at Ser473. Fully activated AKT promotes cell survival, proliferation, and growth by inhibiting pro-apoptotic factors such as FoxO1 and FoxO3a, enhancing glucose metabolism through increased glucose transporter expression and glycolytic enzyme activity, and activating mTORC1.[40,41] mTORC2 also phosphorylates members of the protein kinase C (PKC) family, which modulates cytoskeletal remodeling, cell polarity, and cell migration.[42–45] Additionally, mTORC2 phosphorylates and activates serum/glucocorticoid regulated kinase 1 (SGK1), which regulates ion transport, cell survival, and growth[46] (Figure 2).

Protein Turnover

In addition to the various anabolic processes mentioned above, mTORC1 also promotes cell growth by suppressing catabolic pathways, particularly autophagy.[47] The Unc-51 Like Autophagy Activating Kinase 1 (ULK1) complex, which comprises ULK1, ATG13, FIP200, and ATG101, serves as a critical initiator of autophagosome formation. mTORC1 directly phosphorylates ULK1, thereby preventing its activation by AMPK, a critical regulator of autophagy. Under conditions of energy depletion, activated AMPK can directly phosphorylate ULK1 at alternative sites, initiating autophagy even in the presence of residual mTORC1 activity. Therefore, the relative activities of mTORC1 and AMPK coordinately determine the extent of autophagy induction.[47,48] Additionally, mTORC1 phosphorylates and inhibits Unc-51 Like Autophagy Activating Kinase 1 (TFEB), a master regulator of autophagy and lysosomal gene expression, thereby indirectly suppressing autophagic flux.[34]

The ubiquitin-proteasome system (UPS) represents the second major pathway for intracellular protein degradation. The relationship between mTORC1 signaling and proteasomal activity is complex and context-dependent. Acute mTORC1 inhibition has been shown to robustly promote protein ubiquitination, suggesting that active mTORC1 signaling normally suppresses this degradation pathway.[1,49,50] Conversely, sustained mTORC1 activation upregulates proteasome subunit expression via the transcription factor Nrf1, thereby enhancing proteasomal activity to maintain protein homeostasis under conditions of elevated protein synthesis demands[51] (Figure 2).

The Role of mTOR in SLE

The pathogenesis of SLE involves three major immunological disturbances: activation of the innate immune system, production of self-reactive antibodies, and emergence of autoreactive T cells.[52] As a key driver of metabolic stress and inflammatory lineage development, mTOR is widely implicated in the metabolic reprogramming and functional alterations of immune cells in SLE, playing an important role in both innate and adaptive immunity.[53] The mTOR signaling pathway influences immune cells proliferation, differentiation, and inflammatory cytokines secretion through its regulation of anabolism, energy metabolism, and autophagy, which is essential to SLE pathogenesis.[54] Notably, studies have demonstrated that in SLE patients, mTORC1 is activated while mTORC2 is inhibited, suggesting a complex and differential involvement of the two mTOR complexes in disease mechanisms.[55,56]

Regulation of Macrophages by mTOR

Macrophages are indispensable components of innate immune systems and serve as a critical link between innate and adaptive immune through antigen presentation. Macrophage abnormalities represent a vital factor in the occurrence and development of SLE.[57] Macrophage infiltration has been reported in association with lupus nephritis, indicating their direct involvement in organ damage.[58] Depending on environmental cues, macrophages can polarize into two distinct phenotypes: classically activated M1 macrophages, which primarily exert pro-inflammatory activity, and alternatively activated M2 macrophages, which predominantly possess anti-inflammatory properties.[59] An imbalance in macrophage polarization is also a typical characteristic of SLE. Abnormally activated M1 macrophages promote the release of inflammatory cytokines, exacerbating tissue damage.[60] In contrast, M2 macrophages participate in immune regulation and tissue repair by releasing anti-inflammatory factors and suppressing pro-inflammatory cytokines expression.[61] Adoptive transfer of M2 macrophages or induction of M2 polarization macrophages has been shown to alleviate SLE

manifestations, whereas M1 macrophage transfer exacerbates disease progression.[62,63] Collectively, impaired phagocytic ability and the dysregulation of M1/M2 macrophages balance contribute significantly to SLE pathogenesis.

mTOR is an important regulatory factor for macrophage activation and metabolism, with numerous studies demonstrating its essential role in macrophage polarization.[19] However, the underlying mechanisms are complex, and conflicting findings regarding mTOR-mediated macrophage activation have been reported. Myeloid cell-specific deletion of PTEN in mice leads to constitutively enhanced PI3K and mTOR signaling, resulting in increased expression of M2 macrophage markers and enhanced activation of the Signal transducer and activator of transcription 6 (STAT6), a transcription factor important for M2 macrophage polarization signaling pathway, which is critical for M2 polarization.[64] Conversely, inhibition of mTORC1 with rapamycin stimulates M1 macrophage polarization.[65]

Studies involving TSC1 deletion have yielded particularly complex results. Ablation of TSC1, which leads to increased mTORC1 activation and decreased mTORC2 activation, has been shown to promote M1 macrophage polarization while reducing M2 polarization. This effect occurs through two distinct mechanisms: first, TSC1 deletion promotes M1 polarization independently of STAT6 and Peroxisome Proliferator-Activated Receptor Gamma (PPARγ) by activating a GTPase–Rapidly Accelerated Fibrosarcoma 1 (RAF1)–Mitogen-Activated Protein Kinase Kinase (MEK)–Extracellular Signal-Regulated Kinase (ERK) pathway that operates independently of mTORC1; second, it reduces M2 polarization by activating mTORC1, which in turn suppresses the expression of CCAAT/Enhancer-Binding Protein Beta (CEBPβ).[66] In contrast, another study found that TSC1 deletion promotes both M1 and M2 macrophage polarization.[67] This discrepancy may be attributed to differences in experimental design, with one study examining functional responses upon inflammatory stimulation and the other accessing steady-state responses under basal conditions. AKT, a core component of the PI3K/AKT/mTOR signaling pathway, also plays a critical role in macrophage polarization, with different isoforms exerting opposing effects. Ablation of AKT1 promotes M1 macrophages polarization, whereas deletion of AKT2 favors M2 polarization.[68] Consistent with these findings, AMPK deletion enhances M1 macrophage polarization by reducing AKT activation. Collectively, these results demonstrate that PI3K-AKT-mTOR pathway controls macrophage polarization, although the precise functions and interactions of each pathway member require further investigation. Impaired macrophage phagocytic ability, along with dysregulated autophagy and apoptosis, represents an essential link in SLE pathogenesis.[69,70] Accumulation of apoptotic cells promotes the formation of autoimmune antigens and antibodies, thereby aggravating inflammatory response. Given that mTORC1 inhibits autophagy by phosphorylating ULK1, mTORC1 inhibition promotes autophagic progression, which may influence the clearance of apoptotic debris[71] (Figure 3). In summary, the effects of mTOR on macrophage function are multifaceted and complex. Further research is needed to elucidate how modulation of macrophage polarization and autophagy through the mTOR pathway might be harnessed to improve clinical outcomes in SLE patients.

Regulation of Dendritic Cells by mTOR

Dendritic cells (DCs) are the most powerful and important antigen-presenting cells in the immune system, capable of initiating primary immune responses. DCs can both activate effective immune responses and maintain immune tolerance to prevent autoimmunity through the secretion of various cytokines.[72] In SLE, DCs secrete cytokines that promote DC maturation, B cell differentiation, Th cell polarization, and cytotoxic T cell activation, thereby amplifying subsequent immune responses. Dysregulation of DC function has been implicated in SLE pathogenesis, and alterations in the mTOR pathway may represent an upstream regulatory mechanism contributing to DC dysfunction in this disease.[73]

The mTOR pathway regulates multiple aspects of DC differentiation and function. Fms-related tyrosine kinase 3 ligand (Flt3L) is a growth factor essential for DC development and differentiation, and the mTOR pathway regulates Flt3L-mediated activation of resting dendritic cells through Toll-like receptors (TLR) via the PI3K/AKT/TSC/mTOR axis, driving the differentiation of resting DCs into mature DCs.[53] Abnormally activated mTOR also affects DC differentiation through the IFN-α pathway. Specifically, enhanced mTOR signaling promotes plasmacytoid DCs (pDCs) to secrete large amounts of IFN-α, driving myeloid DCs (MDCs) to release IL-12. These cytokines initiate a cascade of immune activation with dual consequences. First, IFN-α and IL-12 synergistically induce Th1 cell polarization, promote abnormal T cell proliferation, and stimulate B cell activation and proliferation, leading B cells to secrete antinuclear antibodies (ANA) and other autoantibodies.[72,74] Second, mature DCs highly express the costimulatory

molecules B7-1 (CD80) and B7-2 (CD86), which bind to costimulatory receptors on the surface of T cells, strongly activating autoreactive T cells and further amplifying the autoimmune response.[73] On the contrary, accumulating evidence indicates that abnormal mTOR activation disrupts the regulatory balance between DCs and regulatory T cells (Treg). Dysregulated mTOR signaling inhibits the differentiation and function of $FOXP3^+$ Treg cells, thereby weakening Treg-mediated immunosuppressive effect of DCs, and releasing constraints on DC immunogenicity. In turn, elevated cytokines within the SLE microenvironment including IFN-α, IL-6, and IL-18, further exacerbate mTOR-mediated DC dysfunction. This creates a self-perpetuating cycle in which abnormal mTOR signaling leads to excessive DC maturation, enhanced antigen presentation, massive release of pro-inflammatory cytokines (IFN-α, IL-12), impaired Treg suppressive function, activation of autoreactive lymphocytes, and abundant autoantibody production.[75,76] This cascade continuously triggers autoimmune inflammatory damage, ultimately promoting the onset and progression of SLE. The detailed molecular mechanism underlying these processes require further investigation (Figure 3).

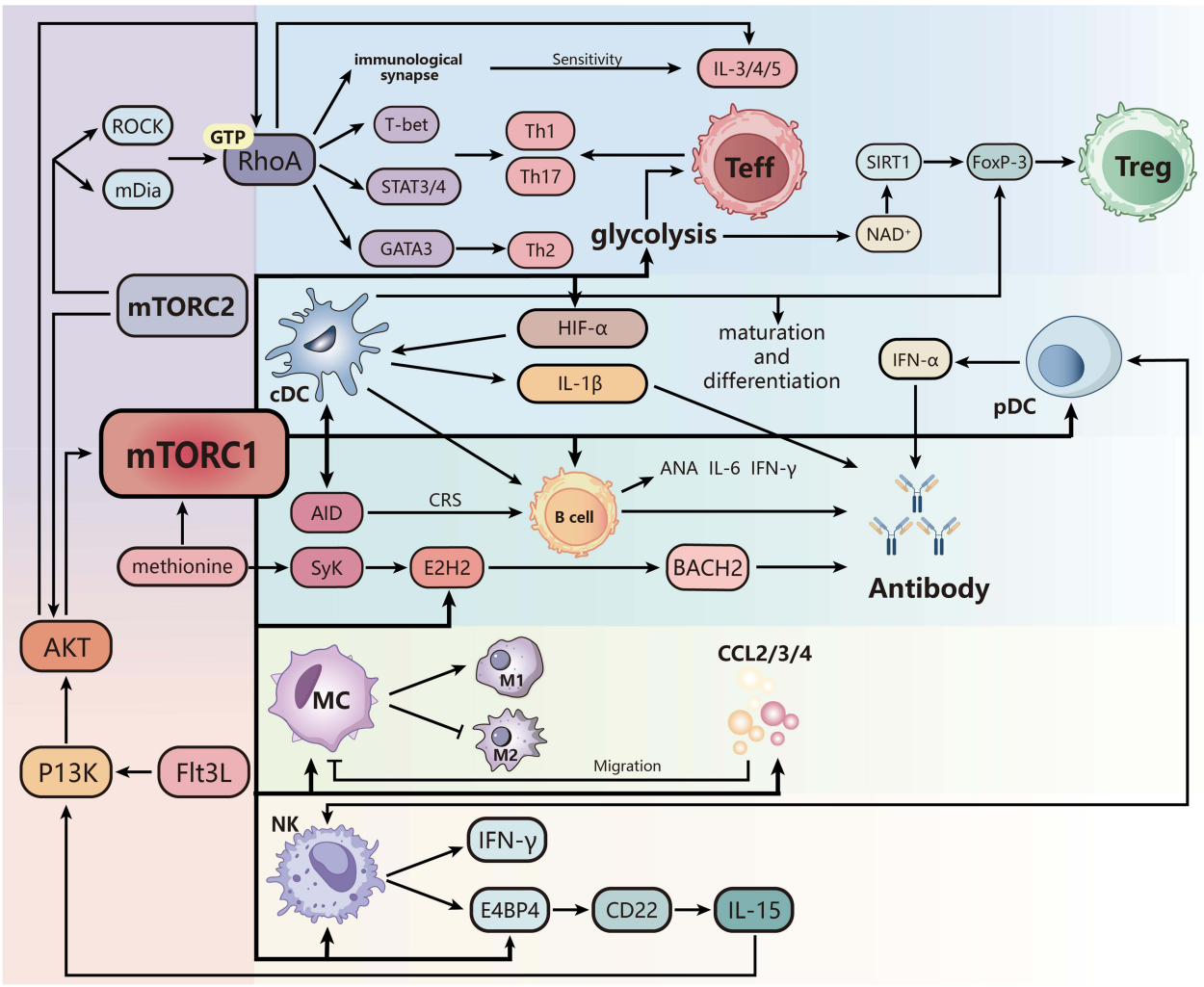

Figure 3 The role of mTOR in SLE. MTORC1 drives glycolysis in T cells, enhances effector T cell differentiation, and inhibits SIRT1 activity through an imbalance of NAD +/NADH ratio, thereby reducing Foxp3 expression and weakening Treg homeostasis. MTORC2 promotes the differentiation of Th1, Th2, and Th17 cells and enhances the production of IL-3/4/5 by activating the RhoA/Akt pathway. In dendritic cells, mTORC1 promotes cDC maturation and IL-1 β release, enhances pDC production of IFN-α, and interferes with antigen presentation by upregulating antigen uptake receptors and co stimulatory molecules; In addition, mTOR signaling drives DC induced B cells to promote IL-6, IFN-γ, and ANA production, while inhibiting Treg function through FoxP-3. MTORC1 upregulates AID in B cells, promotes antibody class switching, and induces EZH2 expression in synergy with Syk, inhibits BACH2, and promotes plasma cell differentiation. In macrophages, mTORC1 promotes M1 polarization and inhibits M2 differentiation, while downregulating CCL2, CCL3, and CCL4, limiting their chemotactic migration. IL-15 regulates NK cell development through the PI3K/AKT/mTORC1 axis and induces E4BP4 upregulation of CD22 to form a positive feedback; MTORC1 also enhances the synergy between NK and pDC, promotes the secretion of IFN-α and IFN-γ, and exacerbates SLE related inflammatory responses.

Regulation of Natural Killer Cells by mTOR

Natural killer (NK) cells participate in both protective and pathogenic immunity, rapidly mediating killing of intracellular pathogens and malignant cells, although their self-directed cytotoxicity can also exacerbate tissue pathology. Additionally, NK cells secrete cytokines and chemokines such as IFN-γ, enabling coordination with other immune cells. A hallmark of SLE is activation of type I interferon system, triggered by nucleic acid-containing immune complexes, leading to tissue inflammation and damage. In SLE pathogenesis, NK cells interact with pDCs to strongly promote pDC-derived IFN-α production. Conversely, pDC-derived IFN-α promotes NK cell development, maturation, and IFN-γ production, establishing a reciprocal NK-pDC crosstalk that contributes to SLE pathogenesis.[77]

mTOR is involved throughout NK cell development, and its dysregulation directly links NK cell dysfunction to SLE pathogenesis.

NK cell development is triggered by IL-15, which activates the PI3K/AKT/TSC1/mTORC1 axis to regulate early cell development. In turn, NK cells induce the NK cell-specific transcription factor E4BP4 through this pathway, which also upregulates CD22, thereby amplifying IL-15 activity by positive feedback. Notably, TSC1 functions as a negative regulatory factor that modulates the duration of mTORC1, although it is not indispensable for the final maturation, survival, or function of NK cells.[78] During immune responses, activated NK cells rely on mTORC1-dependent aerobic glycolysis to achieve their effector functions. In SLE patients, overactivation of mTORC1 in immune cells disrupts the delicate balance of NK cell development and metabolism This dysregulation can lead to two distinct but equally detrimental outcomes: either NK cells become overactivated, enhancing pathogenic NK-pDC crosstalk and promoting excessive IFN-α production, or they develop functional defects that impair immune homeostasis. Both situations can lead to breakdown of immune tolerance and drive SLE progression[53] (Figure 3).

Regulation of T Cells by mTOR

T lymphocytes play a crucial role in the pathogenesis of SLE. Effector T cells (Teff cells), particularly Th1, Th2, and Th17 cells, represent important pro-inflammatory T cell populations that activate other immune cells by secretion of inflammatory cytokines such as IL-17, IL-22, and IL-6, leading to enhanced inflammatory responses. In contrast, Regulatory T cells (Treg cells) are responsible for maintaining immune tolerance and preventing excessive immune responses and the development of autoimmune diseases. Dysfunction of Treg cells impairs the immune system's ability to control the activity of Teff cells, further promoting the progression of SLE.[79] Therefore, the overactivation of Teff cells and the dysfunction of Treg cells are major causes of immune dysregulation in SLE patients.[80] Among these processes, mTOR signaling plays an important regulatory role in the proliferation and differentiation of T cell lineages, with mTORC1 and mTORC2 contributing in different ways.[81]

mTORC1 Regulates T Cell Differentiation

mTORC1 promotes the conversion of oxidative phosphorylation to glycolysis through HIF-1α, facilitating the differentiation of T cells into effector T cells (especially Th1 and Th17 cells).[82] Glycolysis, as a rapid energy-producing pathway, better meets the energy and metabolite demands required for the rapid proliferation of Th1 and Th17 cells compared to oxidative phosphorylation, and its ability to function without relying on oxygen is crucial for the quick response and adaptability of T cells under various conditions.[83,84] In contrast, the increase in glycolysis induced by mTORC1 and HIF-1α activation may inhibit the differentiation and function of Treg cells for two reasons: First, unlike effector T cells (such as Th1 and Th17 cells), Treg cells generally need to remain in the periphery for long periods after an immune response to maintain immune tolerance.[34,85] Therefore, they require a stable energy supply, and oxidative phosphorylation provides sufficient energy support for long-term survival. Excessive glycolysis may disrupt Treg cell function.[86] Second, glycolysis not only suppresses the expression of Treg-specific transcription factor (Foxp3) but its byproducts may also affect Foxp3 stability. NAD+ is a substrate for deacetylases such as sirtuin 1 (SIRT1), which are crucial for the deacetylation and stability of Foxp3.[87] Changes in the NAD+/NADH ratio during glycolysis lead to the accumulation of NADH, inhibiting the regeneration of NAD+, reducing SIRT1 activity, and subsequently affecting the deacetylation and expression of Foxp3, further leading to the loss of Treg cell function.

PTEN, as a tumor suppressor gene, can inhibit the activity of mTORC1 by dephosphorylating key molecules in the PI3K/Akt signaling pathway, thereby indirectly regulating the differentiation of Treg cells.[88] Notably, (Indoleamine 2,3-dioxygenase) upregulates PTEN expression, which in turn inhibits the mTORC1 signaling pathway and promotes the differentiation of Treg cells.[89] Additionally, the deficiency of amino acids such as leucine and serine also suppresses mTORC1 activity, limiting the differentiation of T cells into effector T cells, further demonstrating the crucial role of mTORC1 in the differentiation process of immune cells[90] (Figure 3).

mTORC2 Regulates T-Cell Differentiation

mTORC2 regulates T cell differentiation through upstream activation of RhoA, a small GTPase, via pathways such as Rho-associated kinases (ROCKs) or Mammalian Diaphanous-related formin 1 (mDia1), which directly modulate RhoA.[91] Additionally, mTORC2 can indirectly enhance RhoA activity by activating Akt, an important downstream effector of mTORC2, which regulates molecules associated with RhoA activation. This process promotes the differentiation and function of Th2 cells.[92] Studies have shown that T cells with mTORC1 defects cannot differentiate into Th1 or Th17 cells, whereas T cells with mTORC2 defects cannot differentiate into Th2 cells.[93,94] Furthermore, mTORC2 also exerts a negative regulatory effect on Treg cells.[95]

Regulation of B Cells by mTOR

B cells play an important role in SLE pathogenesis through antibody production, cytokine production, and antigen presentation.[96] It has been reported that the Dysregulated balance of B cell subsets, including dysfunctional regulatory B cells (Bregs), expanded T-bet+ CD11c+ B cells, and increased plasma cells, is closely associated with SLE disease activity, autoantibody generation, and organ injury.[97–99] And mTOR signaling pathway is essential for regulating the development, metabolism, and function of B cells.

Studies have found that the mTORC1 signaling pathway is significantly activated in early B cell development.[100] Meanwhile, mice with knockout of mTOR or Raptor gene exhibit a development blockade in early B cells.[100,101] Besides mTORC1 signaling pathway plays an important role in the humoral immune response of B cells by regulating antibody production, somatic hypermutation, and class switch recombination.[102]

It has been reported that the mTOR pathway in B cells from SLE patients is activated, and mTOR can induce plasmablast differentiation through metabolic and transcription factor regulation. Two of the pathways that have been extensively studied are the PI3K-Akt-mTOR pathway and the essential amino acids-mTOR pathway.[103] Researchers have found enhanced PI3K-Akt signaling is critical for B-cell proliferation and survival.[104] Hyperactivity of mTORC1 promotes the differentiation of plasma cells.[105] Meanwhile, mTORC1 plays a critical role in B-cell antibody class switching.[106] Conversely, mTORC2, independent of mTORC1, inhibits antibody class switching by regulating AKT.[107] Splenic tyrosine kinase (Syk) is vital for the effective induction of CD40 and TLR signaling by BCR, and the increase of sky phosphorylation in B cells is positively correlated with disease activity.[108,109] Methionine, which can regulate syk and mTORC1 signals, is important for plasmablast differentiation.[110] In the presence of methionine, Syk and mTORC1 signals can synergistically induce EZH2 (an enzyme highly correlated with the activity of SLE) expression, which suppresses BACH2 expression through epigenomic modification, and promotes plasmablast differentiation in SLE.[110]

Recently, researchers found that glutaminolysis is abnormally enhanced in lymphocytes from SLE patients, which is related to mTOR/P70S6K/4EBP1 and NLRP3/caspase-1/IL-1β pathways.[111] Besides Wu et al reported that the mTORC1 pathway in atypical memory B cells (ie, CD11c+ T-bet+ B cells) is abnormally activated[112] (Figure 3).

mTOR-Targeted Therapy

mTOR Inhibitors

Rapamycin, an allosteric inhibitor of mTOR, has been shown to control antigen-induced autoimmunity, T cell hyperreactivity, and titers of antinuclear antibodies (ANA) and anti-dsDNA antibodies, thereby inhibiting SLE development.[11]

Sirolimus has been successfully used in clinical trials for the treatment of SLE, with both efficacy and safety profiles assessed.[113] One study demonstrated that systemic administration of rapamycin in SLE patients effectively inhibited overactivated T cells, B cells, and hepatocytes.[114] In an open-label Phase 1/2 trial, sirolimus treatment inhibited antigen-induced T-cell

proliferation, reversed the deficiency of circulating regulatory T cells, and significantly improved skin, mucosal, and musculoskeletal manifestations in participating. Moreover, rapamycin reduces high levels of IL-4 and IL-17, further contributing to symptomatic improvement.[54] Notably, most sirolimus-associated side effects were mild, with dyslipidemia being the most common adverse reaction, which can be managed with statins. Its use in combination can reduce the dose of other disease-mod antirheumatic drugs required during the treatment of SLE.[115,116] However, high doses of everolimus, one of the most commonly used sirolimus analogues, are associated with proteinuria.[116] Therefore, the therapeutic efficacy of sirolimus in LN remains unclear, and further experiments are required to determine the optimal dosage for its use in LN treatment.

Compared with the first-generation mTOR inhibitors, second-generation mTOR inhibitors, namely Dual PI3K/mTOR inhibitors can produce better biological responses, enhance therapeutic potential, and minimize resistance.[117] A study demonstrated that INK128 effectively suppresses disease activity in lupus mice by targeting the mTOR signaling pathway to regulate the proportion of $CD11b^{+}Gr1^{+}$ cells (MDSCs), a cell type that plays a critical role in the early stages of SLE pathogenesis.[118] In summary, mTOR inhibitor is effective in treating patients with clinically active SLE, especially those with musculoskeletal and mucocutaneous manifestations, through various means. However, further studies are required to determine its optimal regimen and dosage.[119] Importantly, not all studies have shown consistent benefits. A cohort study reported that sirolimus treatment was associated with notable tolerability issues, leading to discontinuation in 5 out of 16 patients, primarily due to drug-related adverse effects. Additionally, although renal function remained stable in most patients, one individual with pre-existing stage 4 chronic kidney disease progressed to end-stage renal failure, and another experienced a renal flare despite treatment. Worsening dyslipidemia was also observed in a subset of patients, underscoring the need for careful metabolic monitoring.[120] These observations suggest that patient stratification and combination strategies may be necessary to mitigate risks and optimize long-term outcomes.

N-Acetylcysteine

The therapeutic action of NAC is mainly to increase the level of glutathione (GSH, one of the most critical intracellular antioxidants) in the cell, which affects the mitochondrial membrane potential ($\Delta\psi m$) and oxidative stress processes, further preventing mTORC1 activation and regulating T cell differentiation.[121] Moreover, GSH directly scavenges and neutralizes reactive oxygen species (ROS), and by reducing ROS, GSH can inhibit this signal and prevent mTOR overactivation. With the blockage of its mTORC1 activity, the prevention and treatment of SLE are achieved.[122] In summary, through its antioxidant effects, NAC can modulate mitochondrial membrane potential and oxidative stress to indirectly influence the mTOR pathway.[123] Thus, the inhibitory effect of NAC on mTOR is non-targeted. NAC is considered an oxidation-reduction sensitive driving factor in the pathogenesis of lupus.[124]

Partial preclinical studies have demonstrated that NAC can reduce autoantibody levels and ameliorate organ damage in SLE mouse models.[125–127] Clinical studies have shown that N-acetylcysteine (NAC) reduces oxidative stress in lymphocytes and inhibits mTORC1 activity in patients with SLE.[56,124,128] Another clinical trial indicated that NAC treatment significantly alleviated attention deficit hyperactivity disorder (ADHD) symptoms in patients with SLE.[129] A recent randomized double-blind clinical trial found that NAC therapy significantly reduces disease activity and complication rates in SLE patients.[130] Therefore, NAC holds significant promise as an adjunctive therapy for SLE.

Metformin (Met)

Metformin is a commonly used drug for treating type 2 diabetes, but it also activates AMPK and inhibits mTORC1 to exert immune regulatory effects.[131] In autoimmune diseases such as systemic lupus erythematosus, CD4+ T cells often show reduced IL-2 secretion or functional abnormalities, leading to immune system dysregulation.[132] By inhibiting mTORC1 activation, metformin reduces cellular metabolism and ROS production, decreases oxidative stress, and further improves CD4+ T cell function, thereby restoring IL-2 secretion.[133] Additionally, metformin suppressed the germinal center response and modulated T cell differentiation by reducing follicular helper T cells (Tfh) and Th17 cells while increasing Treg cells.[3]

In experiments assessing the therapeutic potential of metformin in a SLE mouse model, MET inhibited B cell differentiation into plasma cells and germinal center formation through the AMPK/mTOR/STAT3 signaling pathway, thereby reducing the production of autoantibodies and inflammation.[134] Furthermore, the study demonstrated that metformin treatment significantly reduced the risk of disease flares in patients with SLE and subsequently allowed for

a reduction in glucocorticoid dosage.[135] A recent study demonstrated that metformin-treated patients exhibited significantly lower risks of lupus nephritis (LN), chronic kidney disease (CKD), and major adverse cardiovascular events (MACE).[136]

Other mTOR Related Drugs

The PI3K–AKT–mTOR pathway is activated in B cells, CD4+ T cells, and macrophages from SLE patients.[103,137] Blockade of PI3Kγ with AS605240 can reduce the excessive number of lymphocytes, autoantibody production and the number of macrophages infiltrating the kidney, which reduces disease symptoms and prolongs life span in mouse models of lupus.[138,139] Mesenchymal stem cells (MSCs) exhibit enhanced senescence in SLE patients, while broad PI3K inhibitor LY294002 can improve this situation.[140] Therefore PI3K is a promising target for SLE.

Fingolimod, a receptor modulator targeting the S1P receptor which plays a role upstream of mTORC1, has been used to treat multiple sclerosis.[141] However, fingolimod can block the expansion of DN T cells and prevent nephritis, which effectively inhibits the development of autoimmunity and prolongs the survival of MRL/lpr mice.[142,143] Based on these research findings, fingolimod may be a promising drug adjuvant therapy or treatment of SLE.

In addition, calcium/calmodulin-dependent protein kinase IV (CaMK4) targeted therapy for SLE is also promising. Researchers found that overexpression of CaMK4 in T cells from lupus-prone mice affected the balance between Th17 cells and Tregs mainly by AKT/ mTOR pathway and increasing the binding of cAMP response element modulator α (CREM-α) to the IL17 genes.[144] Inhibition of CaMK4 with KN-93 inhibits Th17 differentiation and averts IL–17–instigated inflammation.[145] As for B cells, KN-93 can also inhibit the development of a lupus-related disease by decreasing the expression of CD86 and CD80 on B cells.[146]

Conclusion

The mTOR signaling pathway exerts multifaceted effects on SLE pathogenesis through its modulation of diverse immune cell populations. In innate immunity, mTOR influences disease onset and progression by affecting macrophage polarization and autophagy, as well as dendritic cell maturation and function. In adaptive immunity, mTOR induces the differentiation of T cells into pro-inflammatory subsets via metabolic reprogramming while concurrently promoting B cell differentiation and affecting antibody production. The pathway also modulates NK cell development and the critical regulatory balance between effector and regulatory T cells. The use of immune suppressants, while they can prevent or treat SLE, inevitably damages the body's normal immune and immune surveillance, thus increasing the probability of developing tumors and infections. Current research shows that it is feasible to treat SLE by targeting the mTOR pathway, especially those with musculoskeletal and mucocutaneous manifestations. However, given the heterogeneity of SLE and the existence of mTOR-independent immune dysregulation, mTOR-targeted therapy may not be universally effective. Patients with certain disease manifestations (eg., LN) or genetic backgrounds may require combination approaches that simultaneously target complementary pathways such as JAK-STAT or NF-κB. Future studies should focus on biomarker-driven patient selection to maximize therapeutic benefit. Treatment with mTOR inhibitors can effectively reduce disease activity and reduce the dosage of glucocorticoid. However, non-selective inhibition of mTOR may affect the normal physiological functions of the organism, such as dyslipidemia. Moreover, the therapeutic efficacy of mTOR-targeted therapy for LN remains uncertain and require further investigation. Therefore, further exploration is necessary to determine the applicability, optimal regimen, dosage, and potential adverse effects of mTOR-targeted therapy in SLE patients with different disease backgrounds.

Data Sharing Statement

No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Author Contributions

X.J. Conceptualization, Formal analysis, Visualization, Writing – original draft, Writing – review and editing; L.S. Formal analysis, Conceptualization, Writing – original draft, Writing – review and editing; J.J. Formal analysis, Writing –

original draft, Writing – review and editing; C.Z. Formal analysis, Visualization, Writing – original draft; Y.W. Conceptualization, Resources, Supervision, Writing – review and editing; H.Z. Conceptualization, Resources, Supervision, Writing – review and editing; Q.W. Conceptualization, Writing – original draft, Writing – review and editing; Q.S. Conceptualization, Writing – review and editing; F.L. Conceptualization, Funding acquisition, Writing – review and editing; S.Z. Conceptualization, Resources, Writing – review and editing; T.C. Conceptualization, Funding acquisition, Writing – review and editing.All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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