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Activation of mTOR (mechanistic target of rapamycin) in rheumatic diseases

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Abstract

Mechanistic target of rapamycin (mTOR, also known as mammalian target of rapamycin) is a ubiquitous serine/threonine kinase that regulates cell growth, proliferation and survival. These effects are cell-type-specific, and are elicited in response to stimulation by growth factors, hormones and cytokines, as well as to internal and external metabolic cues. Rapamycin was initially developed as an inhibitor of T-cell proliferation and allograft rejection in the organ transplant setting. Subsequently, its molecular target (mTOR) was identified as a component of two interacting complexes, mTORC1 and mTORC2, that regulate T-cell lineage specification and macrophage differentiation. mTORC1 drives the proinflammatory expansion of T helper (T_H) type 1, T_H17, and $CD4^-CD8^-$ (double-negative, DN) T cells. Both mTORC1 and mTORC2 inhibit the development of $CD4^+CD25^+FoxP3^+$ T regulatory (T_{REG}) cells and, indirectly, mTORC2 favours the expansion of Tfollicular helper (T_{FH}) cells which, similarly to DN T cells, promote B-cell activation and autoantibody production. In contrast to this proinflammatory effect of mTORC2, mTORC1 favours, to some extent, an anti-inflammatory macrophage polarization that is protective against infections and tissue inflammation. Outside the immune system, mTORC1 controls fibroblast proliferation and chondrocyte survival, with implications for tissue fibrosis and osteoarthritis, respectively. Rapamycin (which primarily inhibits mTORC1), ATP-competitive, dual mTORC1/mTORC2 inhibitors and upstream regulators of the mTOR pathway are being developed to treat autoimmune, hyperproliferative and degenerative diseases. In this regard, mTOR blockade promises to increase life expectancy through treatment and prevention of rheumatic diseases.

Mechanistic target of rapamycin (mTOR) serves as a sensor of metabolic cues and as a regulator of growth, proliferation, and survival in eukaryotic cells. mTOR was initially identified as the molecular target of an antifungal macrolide antibiotic produced by the bacterium *Streptomyces hygroscopicus*. This bacterium was discovered in a soil sample from Easter Island, known to its inhabitants as Rapa Nui, from which the name rapamycin was derived[1]. Rapamycin is a potent inhibitor of antigen-induced proliferation of T cells[2] and, owing to this activity, has been developed as a medication to prevent organ transplant

Competing interests statement

The author declares no competing interests.

rejection[3]. Rapamycin was approved by the FDA to preserve renal allografts under the generic name sirolimus[4].

The potency of sirolimus in blocking T-cell activation was first found to be beneficial in the treatment of rheumatic diseases in the context of systemic lupus erythematosus (SLE), both in animal models[5] and in patients[6]. Rapamycin and its analogues (rapalogues) were also efficacious in animal models[7] and patients with rheumatoid arthritis (RA)[8], juvenile idiopathic arthritis (JIA)[9] and Sjögren syndrome[10]. In patients with systemic sclerosis (SSc), mTOR activation contributes to type I collagen production by dermal fibroblasts[11,12], and rapamycin improves skin fibrosis[13] and reduces osteopenia in a mouse model of the disease[14]. A pilot study of rapamycin in patients with SSc showed limited efficacy, but the treatment was determined safe[15]. Rapamycineluting endovascular stents have also been used to treat large-vessel vasculitis, aortitis[16] and Takayasu arteritis[17], but the drug has limited clinical efficacy in patients with granulomatosis with polyangiitis (GPA)[18], despite lowering titers of myeloperoxidase and perinuclear anti-neutrophil cytoplasmic antibodies (pANCA)[19]. By stimulating autophagy, rapamycin improves the survival of human articular chondrocytes and, thereby, benefits patients with osteoarthritis (OA)[20].

A long list of studies supports a role for the mTOR pathway in the pathogenesis of both inflammatory and degenerative rheumatic diseases. In this Review, I critically evaluate the mechanisms of mTOR activation and the means for its pharmacological blockade, which have broad implications for the pathogenesis, diagnosis and management of rheumatic diseases.

Biology of mTOR complexes

As a serine/threonine kinase, mTOR phosphorylates four signature substrates: S6K (ribosomal S6 kinase), which controls protein translation via ribosome bio-genesis[21]; 4E–BP1 (eukaryotic translation initiation factor 4E-binding protein 1), which regulates mRNA translation[22]; signal transducer and activator of transcription (STAT)3 (on Ser727) in response to amino acid excess[23]; and AMBRA1 (activating molecule in BECN1 (beclin-1)-regulated autophagy protein 1), which prevents serine/threonine-protein kinase ULK1/ATG1 from binding to membranes and starting autophagosome formation[24,25] (FIG. 1). mTOR-dependent growth signals are triggered by metabolic cues (FIG. 1) such as amino acid sufficiency[26,27] and oxidative[28,29] or nitrosative stress[30]. In turn, activation of mTOR executes cell-type-specific commands for growth, proliferation and survival via two interactive complexes — mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2) (FIG. 1).

Intracellular localization and trafficking

The presence of mTOR in several cellular compartments could be key to its ability to sense stress and execute cell-growth signals. mTORC1 was initially detected in the cytoplasm as a stimulator of protein translation by its ability to phosphorylate S6K[21] and 4E-BP1 (REF. 31). Later, observations showing that mTOR was associated with endosomal compartments brought the trafficking-regulatory small Rab GTPases Rab7 and Rab4A, as well as the Rag family of Ras-related GTP-binding proteins, to the forefront of the cell-signalling field[30,32].

mTOR was also reported to translocate to the outer mitochondrial membrane, where it senses changes in the mitochondrial transmembrane potential, ATP depletion and oxidative stress[33]. Additionally, mTOR can also be detected inside the nucleus, where it might have a role in the transcription of RNA polymerase I-dependent and RNA polymerase III-dependent genes[34,35]. Under conditions of cell stress, mTORC1 is sequestered in an astrin (also known as sperm-associated antigen 5)-dependent manner within stress granules, limiting cell growth and promoting cell survival[29].

Consensus is increasing that mTORC1 activation occurs at the surface of the lysosomal membrane in response to changes in amino acid sufficiency[27], which is transduced via the Rag family of small GTPases to mediate the translocation of mTORC1 from the cytoplasm to the surface of the lysosome, where mTORC1 is activated by GTP-binding protein Rheb (FIG. 2).

The translocation of mTOR to the lysosomal membrane occurs via endosome traffic that is regulated by Rab7 (REF. 32), Rab5 (REFS 36–38) and Rab4A. Each of these GTPases also regulates autophagy[37,39–42] (FIG. 2). Rab4A forms a positive feedback loop with mTORC1 and negative feedback loop with mTORC2 (REF. 43), and binds to the p85 regulatory subunit of phosphatidylinositide 3-kinase (PI3K), altering its ability to control endocytic recycling[44–47]. Notably, Rab4A and Rab5 are overexpressed in T cells of patients with SLE[30] and in mouse models of this disease[41]; thus, these small GTPases are possible regulators of abnormal T-cell signal transduction in SLE. Furthermore, overexpression of Rab4A, but not Rab5, also precedes the production of antinuclear antibodies (ANA) and SLE onset[41]. Importantly, pharmacological inhibition of Rab GTPases by 3-(3-pyridyl)-2-hydroxy-2-phosphono propanoic acid (3-PEHPC) prevents T-cell dysfunction, ANA production, and nephritis in lupus-prone mice[41] (FIG. 2).

The cell-type-specific activation of mTORC1, and its localization to the lysosome during autophagy, are subject to intricate control by metabolic regulatory net-works[48]. Moreover, the traffic of endosomes to lysosomes has long been implicated in interferon production and inflammation, because these structures also carry Toll-like receptors, which are able to sense nucleic acids, particularly in dendritic cells (DCs)[49].

Metabolic regulatory networks

Signalling pathways that control the proliferation, survival and differentiation of cells in the immune system also regulate the metabolic processes that provide the nutrients required to support these specialized lymphocyte functions[50]. Although mTOR drives proinflammatory lineage specification in the T-cell compartment[51], it might also have anti-inflammatory effects driven by shifting macrophage polarization from a proinflammatory M1 phenotype to an anti-inflammatory M2 phenotype (REFS 52,53). Nevertheless, M2 macrophages can also contribute to inflammation, for example by serving as hosts to cytomegalovirus (CMV), which might explain the potent anti-CMV effects of mTOR inhibitors after organ transplantation[54].

Outside the immune system, mTOR activation contributes to type I collagen production by dermal fibroblasts and to fibrosis in patients with SSc[11,12]. In chondrocytes, genetic

inactivation of mTOR prevented the development of OA induced by peroxisome proliferator-activated receptor-γ (PPARγ) deficiency[55]. Furthermore, mTOR blockade with *N*-acetylcysteine (NAC), an amino acid precursor of glutathione, reduced cognitive attention deficit hyperactivity disorder symptoms in patients with SLE[56]. Given all the evidence for a pathogenetic role for mTOR in rheumatic diseases and associated comorbidities, the metabolic pathways sensed and regulated by this signalling molecule are important to understand.

Amino acids—The branched chain amino acids leucine and isoleucine are stimulators of mTOR[57], and glutamine, a particularly important amino acid in cell-growth control, can activate mTORC1 (REF. 58). Unlike leucine, which relies on RagA and RagB, glutamine utilizes a different GTPase, ADP-ribosylation factor 1, to activate mTORC1 on the lysosome[59] (FIG. 1). A comprehensive metabolome analysis identified a redox-dependent accumulation of kynurenine, an aminoacid metabolite of tryptophan, in lymphocytes from patients with SLE[60]; kynurenine also triggers mTORC1 activation in T cells[60].

Pentose-phosphate pathway—Upon activation, mTORC1 promotes the transcription of genes involved in glycolysis, in the pentose-phosphate pathway (PPP) and in *de novo* lipogenesis[61]. Upregulation of glycolysis is mediated via the transcription factor hypoxia-inducible factor 1α (HIF1α)[62,63] (FIG. 1). As shown in a 2013 metabolomic study, most of the mTORC1-regulated metabolites are part of the PPP[64]. Notably, mTORC1-dependent activation of the PPP was found to be dependent on oestrogen[65], which promotes surface expression of GLUT1 (glucose transporter type 1, also known as solute carrier family 2, facilitated glucose transporter member 1) and GLUT4 (solute carrier family 2, facilitated glucose transporter member 4) — two proteins that are required for glucose uptake to fuel the PPP[65]. This finding could be associated with the increased prevalence of SLE in women, who display increases in both expression and activity of the PPP enzyme transaldolase, and increased activation of mTORC1 (REF. 30).

cAMP—The second messenger cAMP regulates a diverse array of biological processes, mostly via its downstream effector, protein kinase A (PKA)[66]. Ample evidence supports the existence of crosstalk between the PKA and mTOR pathways: for example, cAMP can stimulate mTORC1 (REFS 67,68) or inhibit both mTORC1 and mTORC2 in a cell-type-dependent manner[60,69]. Importantly, blockade of mTORC1 activation in T cells reduces cAMP levels in peripheral blood lymphocytes (PBL) from patients with SLE after treatment with NAC *in vivo*[70].

Fatty acid synthesis—*De novo* fatty-acid synthesis is essential for the proliferation and differentiation of T helper (T_H) type 17 cells, whereas fatty-acid catabolism via β-oxidation is important for the development of $CD8^+$ memory T cells[71] and $CD4^+$ T regulatory (T_{REG}) cells[72]. In addition to serving as a source of energy, lipids contribute to cellular structures and signalling. Sphingolipids, particularly sphingosine-1-phosphate (S1P), are emerging as vital lipid mediators[73] (FIG. 1). S1P signals through five known G-protein–coupled receptors, S1P receptors 1–5 ($S1P_1$ to $S1P_5$)[74]. $S1P_1$, the main S1P receptor that facilitates the egress of T cells from lymphoid organs[75], exerts a negative control of the thymic

generation and suppressive activity of natural T_{REG} cells, a process which is dependent on the Akt–mTOR axis[76]. Transgenic overexpression of $S1P_1$ in T cells inhibits the differentiation of T_{REG} cells in favour of the development of T_H1 cells[77] (FIG. 1).

Oxidative stress—Oxidative stress activates the mTOR pathway in most cells[28–30,33] by a process that involves cysteine oxidation of Rheb[78] and raptor (regulatory-associated protein of mTOR)[28,79]. With escalation of oxidative stress, astrin recruits the mTORC1 component raptor to stress granules, thereby preventing mTORC1-hyperactivation in HeLa cells[78]. Whether astrin is expressed and capable of similarly controlling mTORC1 activation in primary cells is currently unknown, but such a mechanism could be important in the survival of $CD4^-CD8^-$ (double-negative, DN) T cells in SLE, and possibly in other proinflammatory cells, such as fibroblasts or osteo clasts, which are exposed to oxidative stress in patients with rheumatic diseases.

Stimulatory and inhibitory signal transducers

The mTOR pathway is largely controlled by upstream checkpoints at three levels: receptor tyrosine kinases and G-protein-coupled receptors, which detect growth factors; the PI3K–PDK1 (phosphoinositide-dependent kinase-1)–AKT (RAC-α serine/threonine-protein kinase) axis, which channels stimulatory signals towards mTORC1 activation; and the key negative regulators PTEN, AMPK (5′-AMP-activated protein kinase catalytic subunit α2), TSC1 and TSC2 (the latter two are also known as hamartin and tuberin, respectively).

The PI3K–AKT–mTOR axis—At the level of the organism, the PI3K–AKT–mTOR signalling network enables the development of cell-type-specific responses that integrate changes in intracellular metabolism and exposure to a variety of growth factors, as well as transmitting signals from intercellular receptor–ligand interactions.

The upstream enzyme of this signalling network is class I PI3K. PI3K is activated by receptor tyro sine kinases and autophosphorylation in response to extracellular signals such as ligand binding (FIG. 1). Upon activation, PI3K generates phosphatidylinositol-3,4,5-trisphosphate (PIP_3)[80], which recruits pleckstrin homology domain-containing signalling proteins such as AKT to the plasma membrane[81]. PDK1, which also contains a pleckstrin homology domain and can bind PIP_3, is then recruited to the plasma membrane upon activation of PI3K and leads to the phosphorylation of AKT and its partial activation. Full activation of AKT occurs upon phosphorylation of Ser473 by mTORC2 and other kinases[82] (FIG. 1).

Class II PI3K interacts with Rab5 and thereby controls endosomal activation of AKT[83]. The class III PI3K vacuolar protein sorting-associated protein 34 (VPS34, also known as PI3K catalytic subunit type 3), is tethered to endosomal membranes and directs the trafficking of proteins and vesicles, thus contributing to phagocytosis and autophagy[81]. The activity of VPS34 during autophagy is regulated by AMPK in response to nutrient stress responses[84].

PTEN—PTEN dephosphorylates membrane phosphatidylinositols and, thereby, can operate as an inhibitor of the AKT–mTORC1 axis (FIG. 1). PTEN directly antagonizes PI3K by dephosphorylating PIP_3 and has important roles in chromosome stability, DNA repair, and

cell-cycle arrest in the nucleus[85]. Mutations of PTEN cause Cowden syndrome, which has been associated with inflammatory arthritis[86] and SLE[87].

The role of PTEN in pathogenesis of rheumatic diseases is also supported by mechanistic studies. PTEN is essential for the maintenance of functional capacity of T_{REG} cells, which restrain the expansion of proinflammatory T_H1, T_H17, and T follicular helper (T_{FH}) cells in autoimmune diseases[88–90]. In B cells from patients with SLE, increased levels of microRNA (miR)-7, miR-21 and miR-22 inhibit PTEN expression[91]. Loss of PTEN also increases the osteoclastogenic potential of myeloid cells, leading to enhanced local inflammation and bone destruction[92].

LKB1–AMPK axis—The axis formed by liver kinase B1 (LKB1) and 5′-AMP-activated protein kinase (AMPK) is an important regulator of the mTORC1-dependent translation process. AMPK activation by LKB1 inhibits the mTORC1 pathway via phosphorylation of TSC2 (REF. 93) and Raptor[94]. Under energy starvation conditions, an increase in AMP levels stimulates the activity of AMPK[95] and inhibits mTORC1 signalling[93] (FIG. 1). In activated T cells, AMPK serves as a glucose-sensitive metabolic checkpoint that regulates mRNA translation and glutamine-dependent mitochondrial metabolism: T cells lacking AMPKα1 display reduced mitochondrial bioenergetics and cellular ATP levels in response to glucose deprivation *in vitro* or pathogenic challenge *in vivo*[93]. AMPKα1 is also essential for T_H1 and T_H17 cell development and for primary T-cell responses to viral and bacterial infections *in vivo*; AMPKα1-deficient macrophages and DCs exhibit heightened inflammatory function, an enhanced capacity for antigen presentation and favour T_H1 and T_H17 responses[96]. Further studies are necessary to examine whether the effects of AMPK on T-cell and B-cell development are independent from its inhibitory effect on the mTORC1 pathway.

AMPK also has a key role in activating proautophagic VPS34 complexes[84] by phosphorylating beclin-1. This initial step of autophagy can be blocked by mTOR through phosphorylation of AMBRA1; conversely, mTORC1 inhibition leads to phosphorylation of beclin-1 and propagates autophagosome formation[97]. PBLs from patients with SLE exhibit increased mTORC1 activity[30] and profoundly diminished beclin-1 expression, a state that is reversed by rapamycin treatment *in vivo*[41]. Remarkably, mechanical stress, which is the primary inducer of OA, reduces beclin-1 expression and autophagy in chondrocytes, and treatment with rapamycin reverses these changes[98]. Thus, mTORC1-dependent beclin-1 expression is a cell-type-specific regulator of autophagy in rheumatic diseases.

Cell-type-specific activation of mTOR

The mTOR pathway has critical roles in the development and function of the innate and adaptive arms of the immune system. An essential role of mTOR in T-cell development was uncovered[51] when mTORC1 was found to be required for the differentiation of T_H1 and T_H17 cells, whereas T_H2-cell development depends on mTORC2 (REF. 51). mTORC1 also inhibits the survival of $CD8^+$ memory T cells, an effect that can be reversed by rapamycin treatment[99,100]. Both mTORC1 and mTORC2 seem to interfere with the differentiation and

function of $CD4^+CD25^+FoxP3^+$ T_{REG} cells[51,77,101], but mTORC1 might also support T_{REG}-cell function[102] by inhibiting the mTORC2 pathway[103].

Despite its complex role in T_{REG}-cell function, the largely proinflammatory changes elicited by mTORC1 activation in the adaptive immune system are in apparent contrast with its anti-inflammatory effects on the innate immune system (for example, mTORC1 favours M2 over M1 polarization of macrophages[52]). The cell-type-specific activation of mTORC1 also varies between rheumatic diseases, as mTORC1 is activated in T cells of patients with SLE[30], but not in those of patients with RA[104]. These divergent effects of mTOR activation in T cells might be connected to alternative use of glucose between glycolysis and the PPP[105].

mTOR — biomarker and pathogenetic factor

mTORC1 activation in SLE

In patients with SLE, mTORC1 is activated[30,70] and mTORC2 is inhibited[106] (FIG. 2). A central role for mTORC1 in abnormal T-cell lineage specification and function in SLE[30,107,108] is consistent with its effects on shaping T-cell development[51].

The involvement of mTOR in SLE was initially suggested by the successful blockade of T-cell hyperactivity and nephritis in rapamycin-treated lupus-prone MRL/lpr mice[5]. Later, rapamycin was shown to block T-cell activation in patients with SLE[30], with remarkable therapeutic efficacy[6,109]. Interestingly, activation of mTORC1 preceded disease flares by 4 months, and was reduced by therapeutic intervention with rapamycin[109]. Thus, measurement of mTORC1 and mTORC2 activity by intracellular staining for phosphorylated 40S ribosomal protein S6 (at Ser235 and Ser236) and phosphorylated AKT (at Ser473), respectively, can be used as biomarkers for pathogenesis, prediction of flares and monitoring of treatment efficacy of mTOR blockade in SLE[70,106,109]. Measuring the activity of mTORC1 and mTORC2 in cells of patients with SLE and other autoimmune diseases could be another step in achieving personalized or precision medicine[110].

Rapamycin blocks the proinflammatory, necrotic death of DN T cells and the depletion of T_{REG} cells[109], and mTORC1 inhibition by NAC had similar effects[111] (FIG 1,FIG 2; TABLE 1). Diminished T_{REG}-cell frequency has been linked to mTORC1-sensitive methylation of the *Foxp3* promoter[112], whereas rapamycin treatment reduced the production of IL-4 by DN T cells *in vivo*[109], accounting for an increased production of anti-DNA autoantibodies by B cells[113,114]. The benefits of rapamycin can also be attributed to T_{REG}-cell expansion[109] via activation of mTORC2, at least in patients with SLE[106]. Given the role of mTORC2 signalling in T_{REG} cells and in regulating the development of T_{FH} cells[89,90,115], which are expanded in mouse models of lupus[116] and in patients with active SLE[117], the impact of rapamycin on the proinflammatory DN T-cell subset merits further investigation. The documentation of the first clinical case of fulminant SLE in a patient with tuberous sclerosis also support a fundamental role of mTOR pathway activation in the pathogenesis of both these diseases[118]: in accordance with a negative regulatory role for the TSC1–TSC2 complex, all lymphocyte subsets of this patient exhibited robust mTORC1 activation[118].

mTORC1 is also activated in B cells[119] and nephritic kidneys of lupus-prone mice[120] (FIG. 3).

Antiphospholipid antibodies (aPL) trigger considerable pathology and are one of the diagnostic criteria for SLE[121–123]. Moreover, aPL can elicit antiphospholipid syndrome (APS) in patients with or without SLE[124]. As shown in a 2014 study, seven of ten patients with APS nephropathy treated with rapamycin (70%) had a functioning allograft 144 months after transplantation, versus only three of 27 patients who were not treated with rapamycin (11%)[125]. Notably, the majority of the patients with APS had also been diagnosed with SLE (20 of 32 patients, 62%)[125]. Unfortunately, the researchers did not document how many of the seven patients who benefited from rapamcyin[125] also had SLE. mTORC1 activity is not elevated in major PBL subsets of patients with SLE who also have APS, relative to those without APS[126]. Therefore, rapamycin might have benefited renal transplant recipients with underlying SLE[125].

The mTORC1 inhibitor NAC reversed the depletion of reduced glutathione (GSH) in PBLs of patients with SLE in a double-blind, placebo-controlled, phase I–II clinical trial[70]. Of relevance to its mechanism of action, NAC also reversed the strong activation of mTORC1 in DN T cells, which is consistent with a role of oxidative stress as a regulatory checkpoint. Oxidative stress originates from increased mitochondrial oxygen consumption by complex I of the electron transport chain in T cells from patients with SLE[127]. Along this line, inhibition of mitochondrial oxidative stress with metformin also reduced mTORC1 activity and prevented nephritis in lupus-prone mice[128]. Therefore, these findings support a role for oxidative stress in both activation of mTORC1 and the pathogenesis of lupus nephritis in mice[28,29].

In addition to oxidative stress, traffic to the lysosomal membrane and the detection of amino-acid sufficiency have been implicated in the activation of mTORC1 (REF. 27). A 2015 metabolome analysis unveiled a NAC-responsive accumulation of kynurenine in SLE PBLs[60] as the strongest metabolic predictor of SLE when comparing patients with matched healthy individuals[60]. Kynurenine was also the strongest predictor of the NAC effect on the mTOR pathway in patients with SLE. In addition to lowering kynurenine levels, NAC greatly augmented the levels of NADPH, an effect thought to occur via sparing of NADPH through enhancement of *de novo* GSH synthesis[129,130] (FIG. 2). Importantly, kynurenine also triggered mTORC1 activation, particularly in DN T lymphocytes[60]. Therefore, NAC-responsive accumulation of kynurenine is a biomarker of oxidative stress and a trigger of mTORC1 activation — two mechanistically connected metabolic checkpoints in SLE pathogenesis[60]. This comprehensive metabolomic study also revealed a depletion of cysteine in SLE PBLs[60], further supporting the use of NAC treatment in SLE.

Rheumatoid arthritis

The role of mTOR is far less thoroughly characterized in RA than it is in SLE[131]. Unlike CD4 T cells in SLE, CD4 T cells from patients with RA show no significant changes in mTOR activity[104,132]. Of note, RA T cells exhibit diminished glycolytic activity, thus depriving them of the energy required to generate oxidative stress or to execute autophagy[104]. Despite the lack of changes in mTOR activity in RA T cells, rapamycin and

rapalogues have shown efficacy in reducing joint inflammation in animal models of arthritis[7] and in patients with RA[8] or JIA[9]. Such clinical benefits might accrue from the inhibition of mTORC1 activation in fibroblast-like synoviocytes (FLS)[133] (FIG. 3). In support of this notion, rapamycin decreased the invasive properties of RA FLS[133]. Additional evidence of the benefits of mTORC1 inhibition in RA includes the ability of IL-17 to induce mTORC1-dependent proliferation of RA FLS[134], the increase in mTORC1 activity in osteoclasts from patients with RA and in arthritic transgenic mice[7], and the downregulation of extracellular matrix digestive enzymes and induction of apoptosis in osteoclasts elicited by mTOR inhibition[7] (FIG. 3). Taken together, these observations suggest a therapeutic benefit from mTOR blockade in RA that might involve the intra-articular cells that mediate erosive joint destruction.

Ankylosing spondylitis

Ankylosing spondylitis (AS) is a chronic inflammatory disease that predominantly affects the axial skeleton, with variable involvement of the peripheral joints and nonarticular structures, such as the heart valves and the eyes[135]. HLA-B27 has been recognized as the most important genetic risk factor for AS, but genome-wide association studies (GWAS) have now identified two AS-associated chromosomal loci independent of HLA-B27 that encode four endoplasmic reticulum aminopeptidases (ERAPs), which are involved in peptide processing before MHC class I presentation[136–138]. Although MHC class I peptides are primarily presented to CD8 T cells, IL-12$^+$ and IL-23$^+$ CD4 T cells (which can be converted to T_H17 cells), have been also implicated as responders to antigen-presenting macrophages and DCs in the inflamed spine of patients with AS[139].

The upregulation of let-7i miRNA, which contributes to IFNγ production, might also account for T-cell hyper-reactivity in patients with AS[140], as insulin-like growth factor-1 receptor (IGF-1R) is a direct target of let-7i in T cells from these patients[141]. IGF-1R mediates its effect by activation of the PI3K–AKT–mTOR path-way[140–143]. Interestingly, let-7i overexpression increases autophagy, but inhibits apoptosis; thus, let-7i contributes to T-cell dysfunction in patients with AS[141]. Mo r e o v e r, unbiased proteomics studies found evidence for activation of PI3K, fatty-acid oxidation and insulin signalling in fibroblast-like ligament cells of patients with AS[144]. Given all these findings, mTOR-controlled metabolic pathways are likely to shape the repertoire of both adaptive and innate inflammatory cells in AS (FIG. 3).

Psoriatic arthritis

T_H17 cells have pivotal roles in orchestrating the inflammation in the skin and joints of patients with psoriatic arthritis (PsA)[145]. Regarding the prominent expansion of T_H17 cells, a paucity of studies have examined its association with mTOR activation in PsA or psoriasis. Importantly, GWAS in patients with psoriasis (20–30% of whom also have PsA) uncovered a link with a single-nucleotide polymorphism in Raptor, a component of mTORC1 (REF. 146). Whereas the functional consequences of this genetic association have not been evaluated, the involvement of mTORC1 in PsA is independently supported by mechanistic studies. As is also observed in patients with RA, the proliferation of FLSs (which can be triggered by IL-22) is mediated by the PI3K–Akt–mTOR cascade in patients with PsA[147]

(FIG. 3). Unlike RA T cells, however, PsA T cells exhibit increased signalling through the AKT– mTOR axis[148]; this observation may result from increased expression of programmed death-1 (PD-1) in T cells from patients with PsA[148].

The mTOR pathway has also been implicated in keratinocyte hyperproliferation (FIG. 3), as rapamycin was found to arrest human keratinocyte stem cells in the G1 phase[149]. Evidence of mTORC1 activation is also provided by the increased phosphorylation of mTOR and S6K in punch biopsy samples of psoriatic skin lesions[150,151].

Systemic sclerosis

Activation of the mTOR pathway has a central role in the proliferation of fibroblasts (FIG. 3), the cells that mediate skin lesions in the limited cutaneous form of SSc and in other involved organs in progressive SSc. Signalling through the PI3K–AKT–mTOR axis can be initiated by transforming growth factor β (TGFβ) and its proximal effectors, Smad2 and Smad3 (REFS 152,153). Supporting a critical role for mTOR in these diseases, rapamycin abrogates TGFβ-induced fibroblast growth[154]. As mentioned previously, mTORC1 activation also contributes to type I collagen production by fibroblasts, the process that leads to fibrosis in SSc skin lesions[11,12] and is inhibited by rapamycin[13]. In a pilot study of patients with progressive SSc, rapamycin was safe, although it had limited efficacy[15]. TGFβ also activates mTORC2 in skin fibroblasts, as evidenced by increased phosphorylation of AKT at Ser473[154], and mTORC2 activity also contributes to kidney fibrosis[155].

Osteoarthritis

The pathogenesis of OA originates from excessive mechanical stress and a systemic susceptibility[156]. The disease process is characterized by progressive cartilage loss, subchondral bone remodelling, osteophyte formation and synovial inflammation. Notably, cartilage loss might be therapeutically targeted via mTOR blockade. Mechanical stress activates the mTOR pathway in chondrocytes during chondrogenesis and cartilage development[157] (FIG. 3). In turn, treatment with rapamycin blocks the mechanical-stress-induced proliferation of chondrocytes *in vitro*[157]. Thus, blockade of mTORC1 in chondrocytes might not itself be beneficial, but human articular chondrocytes also employ the mTOR pathway to control autophagy, which initiates the release of articular cartilage vesicles (ACVs) into the cartilage matrix[20]. Interestingly, rapamycin promotes autophagy and consequently increases the release of ACVs by normal chondrocytes, whereas OA chondrocytes fail to increase ACV release in response to mTOR inhibition. These findings indicate that the autophagy defects in OA are downstream of mTOR activation[20]. Nevertheless, intervening at a critical step in the regulation of autophagy could potentially slow the adverse effects of ageing on cartilage homeostasis, which increase the risk of developing OA[158]. Indeed, cartilage-specific inactivation of mTOR enhances autophagy and protects against meniscus-ablation-induced OA; treated animals show a substantial reduction in articular cartilage degradation, apoptosis and synovial fibrosis[159]. This substantial effect of rapamycin treatment on OA prevention is remarkable, given that it also extends lifespan in mice[160]. Moreover, the inhibition of OA by rapamycin might also improve the quality of life of patients with this disease.

mTOR as a therapeutic target in rheumatic disease

As mentioned previously, sirolimus was initially approved by the FDA for preservation of renal allograft function owing to its capacity to inhibit T-cell proliferation[4]. As its molecular target, mTOR[161], is involved in many cellular processes (including protein translation, growth, proliferation, survival and autophagy) that function abnormally in autoimmune, inflammatory and degenerative diseases (as well as in cancer) in a cell-type-specific manner, >1,800 clinical trials have been registered[162] to test this drug in diverse disease conditions; this number does not include studies of sirolimus analogues (for example, everolimus), dual mTORC1 and mTORC1 inhibitors, PI3K or AKT inhibitors[163–167].

Rapamycin, rapalogues and mTORC1/2 inhibitors

Rapamycin is an allosteric inhibitor of mTOR that acts by forming a high-affinity complex with the 12 kD intracellular protein FKBP12 (peptidylprolyl *cis-trans* isomerase FKBP1B)[168] (FIG. 1). The resulting complex of rapamycin and FKBP12 blocks mTOR activation in yeast[169] and mammalian cells[161]. mTOR blockade by rapamycin seems to primarily affect mTORC1 (REFS 170,171), and might cause a secondary activation of mTORC2 (REF. 82).

The duration of treatment with rapamycin is critical for mTORC1 selectivity. Whereas 2 weeks of treatment in mice blocks only mTORC1, leading to detrimental metabolic effects, 6 weeks of treatment leads to a state of metabolic transition, and 20 weeks of treatment improves metabolic profiles and insulin sensitivity by also reducing activity of mTORC2 (REF. 172). In T cells from healthy individuals and patients with SLE, rapamycin treatment *in vitro* reduced mTORC1 and enhanced mTORC2 activity[106]. Although the activity of mTORC2 is reduced in DN T cells from these patients, as evidenced by diminished phosphorylation of AKT at Ser473[106], whether long-term treatment with rapamycin also activates mTORC2 *in vivo* is currently unknown. Therefore, whether the therapeutic benefit of rapamycin in patients with SLE originates solely from blockade of mTORC1, or whether it also involves activation of mTORC2, is also unclear. Given the role of mTORC2 in control of T_{REG}-cell survival and function[88–90], studies should be pursued in patients with SLE and other autoimmune diseases to dissect the exact mechanism of action of rapamycin. In the event that mTORC2 is activated by rapamycin *in vivo*, ATP-competitive, dual mTORC1 and mTORC2 inhibitors (such as torin 1 or sapanisertib) could be even more effective[173]. Importantly, the ATP-competitive dual inhibitor torkinib reduces the expression of cholesterol biosynthesis genes in a 4E–BP1-dependent manner[174]. Dual inhibitors are currently in clinical trials in cancer patients.

Rapamycin has shown great potency in blocking the development of SLE in the MRL/lpr[5] and NZB/W F1 animal models[41,175], in which autoimmunity, T-cell hyper-reactivity, titres of ANA and anti-DNA antibodies, glomerular immunoglobulin deposition, proteinuria, nephritis, and overall survival were all improved. Importantly, rapamycin also attenuates the severity of established nephritis[176]. In patients with SLE, rapamycin improved clinical outcomes as measured by the reduction of overall SLE Disease Activity Index (SLEDAI) and BILAG (British Isles Lupus Assessment Group) scores[6,109]. More over, a retrospective study showed diminished protein uria and improved renal function in six patients with lupus

nephritis treated with rapamycin[177]. A prospective open-label clinical trial of rapamycin in 40 patients with SLE is due for completion in 2015, and should provide additional information about the organ systems that respond to mTOR blockade[178].

Beyond its effects on T cells in SLE, rapamycin blocks fibroblast proliferation, collagen production and dermal fibrosis in the skin[11,12] and holds promise for the treatment of patients with SSc[15] (TABLE 1). Interestingly, mTORC2 mediates kidney fibrosis[155], which could explain the limit ed efficacy of mTORC1 blockade by rapamycin in this setting, and suggests that dual ATP-competitive mTOR inhibitors might show improved efficacy (TABLE 1). As noted previously in this Review, rapamycin treatment enhances the survival of human OA chondrocytes *in vitro*, whereas genetic inactivation of mTOR prevents OA in mice[55,159]. These studies suggest that mTOR blockade and stimulation of autophagy in chondrocytes could have therapeutic benefits in OA. Conversely, rapamycin showed limited efficacy in a controlled study of patients with severe psoriasis[179]. The newer agent everolimus provided clinical benefit for patients with RA when used in combination with methotrexate, and had an acceptable safety and tolerability profile[8]. Thus, everolimus might offer a new treatment option in patients with RA who have an inadequate response to methotrexate[8].

PI3K inhibitors

The PI3K–AKT–mTOR pathway is activated in CD4 T cells from mice with lupus-like symptoms induced by graft-versus-host disease[180], or as a consequence of the MRL/lpr genetic background[181], and in those collected from patients with SLE[182]. Accordingly, pharmacological blockade of PI3Kγ with AS605240 blocks T-cell activation, autoantibody production, renal infiltration and TNF release by macrophages, and ameliorates glomerulonephritis, thus extending lifespan in mouse models of lupus[181,183]. Additionally, the broad PI3K inhibitor LY294002 improves the survival of mesenchymal stem cells (MSCs), which exhibit enhanced senescence in patients with SLE[184]. PI3Kδ is highly expressed in the synovium and cultured FLS of patients with RA[185], and its expression is selectively induced over other PI3K isoforms by TNF. Moreover, a novel PI3Kδ inhibitor, INK007, blocks TNF-induced AKT activation[185] (TABLE 1).

N-acetylcysteine

The therapeutic use of NAC in SLE has been based on increasing evidence of oxidative stress being involved in the pathogenesis of this disease[186], including effects on abnormal T-cell activation[187,188], the antigenicity of DNA[189] and self proteins[190], and production of ANA[191] (TABLE 1). The rationale for reversing oxidative stress with NAC is supported by several observations. Intracellular GSH levels are decreased in PBLs and T cells from patients with SLE[30,192–195], and GSH depletion and oxidative stress contribute to T-cell dysfunction in these patients[189,192,196]. Additionally, NAC and GSH-sparing antioxidants improve the clinical outcome of lupus in mice[197–199], and the fact that large dosages (up to 8 g daily) of NAC can be safely administered to humans[200] (and that similar dosages of NAC improve fatigue in healthy individuals[201]) further supports the use of NAC in this context. NAC also limits the myelotoxicity of immunosuppressive medications[202], which are also commonly used in patients with SLE.

NAC is inexpensive and widely accessible to patients in health-food stores, but is currently unavailable as an oral medication by prescription. Therefore, we initiated a randomized, double-blind, placebo-controlled phase I–II study to evaluate the safety and tolerability of NAC, as well as its metabolic, immunological and therapeutic effects, in 36 patients with SLE. The results of this study indicate that NAC is safe and reduces disease activity and fatigue over 3 months[70]. The therapeutic action of NAC is mediated by the reversal of GSH depletion and blockade of mTORC1 (REF. 70), which is a sensor of oxidative stress[28–30,33,79]. The clinical efficacy of NAC in patients with SLE is hypothesized to occur through a newly identified molecular mechanism: disruption of the mitochondrial hyperpolarization (MHP)–oxidative stress–mTOR axis in T cells[186]. DN T cells exhibit the greatest mTORC1 activation[70,109] and are predisposed to proinflammatory necrotic cell death[70,109]; consequently, along with the blockade of their mTORC1 activity, proliferation of these cells is reversed by NAC treatment[70]. Thus, elimination of DN T cells can contribute to the efficacy of NAC.

The use of NAC instead of rapamycin to block mTOR might have additional benefits. Rapamycin induces hyperlipidaemia, at least in renal transplant recipients[203], and infections are common adverse events in these patients, with pneumonia and sepsis being most frequent[204]. These unwanted consequences of rapamycin are of concern, because infections and cardiovascular disease are the leading causes of mortality in patients with SLE[205]. Thus, given that oxidative stress contributes to cardiovascular disease[206], patients might have additional benefit from treatment with NAC instead of rapamycin, at least those with end-stage renal disease[207]. Future studies should focus on whether GSH depletion and activation of mTORC1 predict responsiveness to treatment by NAC and mTOR inhibitors, and whether selective or non-selective mTORC1, mTORC2 or dual mTORC1/mTORC2 inhibitors deliver differential clinical benefits (TABLE 1).

Targets under development

Metformin activates AMPK and, thus, inhibits mTORC1 (REF. 208; TABLE 1). Metformin also reduces mTORC1 activity by moderating mitochondrial oxidative stress, which has been implicated in the prevention of nephritis in lupus-prone mice[128], and inhibits inflammatory arthritis in the K/B × N model of lupus[209]. Beyond inhibiting mTORC1-dependent inflammation, metformin might also reduce metabolic comorbidities such as hyperlipidaemia and atherosclerosis in patients with SLE or RA[210].

Fingolimod, a S1P–receptor antagonist with effects upstream of mTORC1 (REFS 211,212), has been introduced for the treatment of multiple sclerosis[213]. Fingolimod sequesters lymphocytes in the secondary lymphoid organs by inducing S1P receptor internalization and degradation[213], and blocks the expansion of DN T cells and prevents nephritis in MRL/lpr mice[214,215]. Given their potentially synergistic mechanism of action, fingolimod, metformin, NAC and rapamycin might be combined for the treatment of these autoimmune diseases.

Among the pharmacological interventions currently in preclinical development for the treatment of rheumatic diseases, targeting of calcium/calmodulin-dependent protein kinase type IV (CaMK-IV) seems to be promising (TABLE 1). Overexpression of CaMK-IV in T cells from lupus-prone mice[216] might act upstream of mTORC1; but given that rapamycin

treatment in vivo restores T-cell activation-induced Ca2+ fluxing[6], CaMK-IV might also act downstream of mTORC1. Similarly to mTORC1 blockade, pharmacological inhibition of CaMK-IV with KN-93 expanded TREG cells[217], decreased the expression of the co-stimulatory molecules CD86 and CD80 on B cells, decreased ANA production and suppressed nephritis and skin disease in MRL/lpr mice[218]. KN-93 also inhibited CaMK-II *in vitro*, and blocked the proliferation of FLSs from patients with RA[219]. Another CaMK-II inhibitor, rimacalib, which has anti-inflammatory effects on macrophages[220], has entered clinical trials for the treatment of RA (TABLE 1).

Conclusions

The activation of mTORC1 observed in patients with rheumatic diseases is particularly relevant in light of the fact that these individuals have reduced life expectancy. mTORC1 blockade with rapamycin increases lifespan in mice[160], and enhanced mTORC1 activation[221] and related autophagy defects are implicated in endothelial inflammation, atherosclerosis and vascular ageing[222]. Remarkably, rapamycin also inhibits vascular ageing[222,223]. These preclinical studies provided a rationale for new clinical trials aimed at improving cardiovascular outcomes and overall survival in elderly individuals. Such clinical benefit could be highly relevant for patients with SLE or RA, in whom cardiovascular disease is a major cause of increased mortality[205,224–226]. Therefore, mTOR blockade might be highly beneficial for patients with these rheumatic diseases by reducing mortality due to cardiovascular disease, arthritis, nephritis or neurological disease.

Despite these potential advantages, the blockade of mTORC1 with rapamycin or everolimus has unique adverse effects[227]. Mucositis, rash, metabolic derangements such as hyperglycaemia, hyperlipidaemia and hypophosphataemia[227], and an increased risk of infections[204] are among the most common adverse effects of rapamycin or everolimus in patients who had a renal transplant[203]. The latter are of particularly concern, as infections are a leading cause of increased mortality in patients with SLE[205] and are more common in patients with RA than in the general population[228]. Notably, inhibition of mTORC1 by agents that act at metabolic checkpoints — such as the reversal of GSH depletion and oxidative stress by NAC[70] — can reduce the toxicity of this therapeutic approach, and has the added benefit of reducing cardiovascular disease[207]. NAC might also benefit patients with RA by moderating the toxicity of methotrexate[229], which remains a mainstay of treatment in these patients. Future studies should determine whether oxidative stress, GSH depletion and activation of mTORC1 predict responsiveness to treatment with NAC, metformin and other mTOR inhibitors, alone or in combination, in patients with rheumatic diseases.

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Key points

- The mechanistic target of rapamycin (mTOR) is a serine/threonine kinase that regulates growth, proliferation, survival and autophagy in a cell-type-specific manner
- mTOR forms two interacting complexes, mTORC1 and mTORC2
- mTORC1 drives the proinflammatory expansion of T helper (T_H) type 1, T_H17, and $CD4^-CD8^-$ double-negative T cells, which collectively orchestrate the pathogenesis of autoimmune diseases
- mTORC1 contributes to erosive arthritis by mediating the proliferation of fibroblasts-like synoviocytes and osteoclasts, and contributes to osteoarthritis by restraining autophagy in chondrocytes
- Blockade of the mTOR pathway offers new treatments and prevention strategies for rheumatic diseases

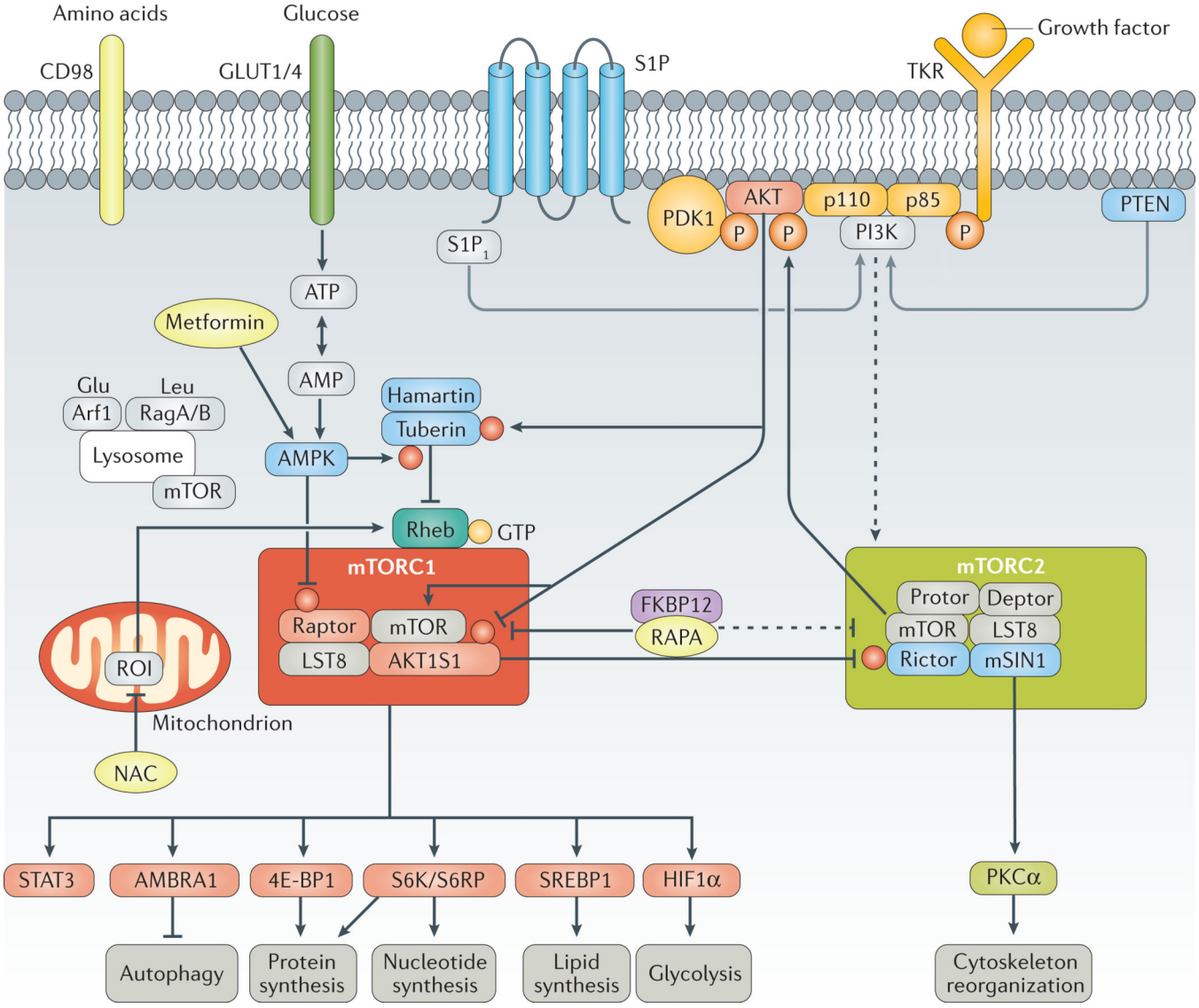

Figure 1. mTOR pathway activation

Mechanistic target of rapamycin (mTOR) is regulated by metabolic cues, primarily glucose and amino acids, as well as by growth factors, hormones and cytokines. Glucose and amino acids enter cells via surface receptors such as glucose transporter type 1, erythrocyte/brain (GLUT1) or glucose transporter type 4, insulin-responsive (GLUT4) and CD98, respectively. Growth factors stimulate tyrosine kinase receptors (TKRs), which are activated through phosphorylation of tyrosine residues. In turn, TKR signals are transmitted to mTOR through phosphati-dylinositide 3-kinase (PI3K), phosphoinositide-dependent kinase-1 (PDK1) and RAC serine/threonine-protein kinase (AKT). Signalling through sphingosine 1-phosphate receptor 1 ($S1P_1$) also activates mTOR complex 1 (mTORC1) via PI3K. Downstream, AKT phosphorylates mTOR, which forms two interacting complexes, mTORC1 and mTORC2. mTORC1 is composed of mTOR, regulatory-associated protein of TOR (raptor), TORC subunit LST8 (LST8), DEP-domain-containing mTOR-interacting protein (deptor) and proline-rich AKT1 substrate 1 (AKT1S1)[230]. mTORC2 is comprised of

mTOR, rapa-mycin-insensitive companion of mTOR (rictor), stress-activated protein kinase interacting protein 1 (mSIN1, also known as TORC2 subunit MAPKAP1), protein observed with rictor-1 (protor-1), deptor and LST8. mTORC1 integrates growth signals reflecting the availability of nutrients and energy to promote either proliferation when conditions are favourable or autophagy when conditions are unfavorable; mTORC2 promotes cellular survival by activating AKT[82]. Pharmacologically targetable checkpoints are highlighted in yellow. 4E–BP1, eukaryotic translation initiation factor 4E–binding protein 1; AMBRA1, activating molecule in BECN1-regulated autophagy protein 1; AMPK, 5'-AMP-activated protein kinase; Arf1, ADP-ribosylation factor 1; FKBP12, peptidyl-prolyl cis-trans isomerase FKBP12; HIF1α, hypoxia-inducible factor 1α; NAC, *N*-acetylcysteine; PKCα, protein kinase C α type; PTEN, phosphatidylinositol 3,4,5-trisphosphate 3-phosphatase and dual-specificity protein phosphatase PTEN; RAPA, rapamycin; Rag-A/B, Ras-related GTP-binding protein A/B; ROI, reactive oxygen intermediate; S6K, ribosomal protein S6 kinase; SREBP1, sterol regulatory element-binding protein 1; STAT3, signal transducer and activator of transcription 3.

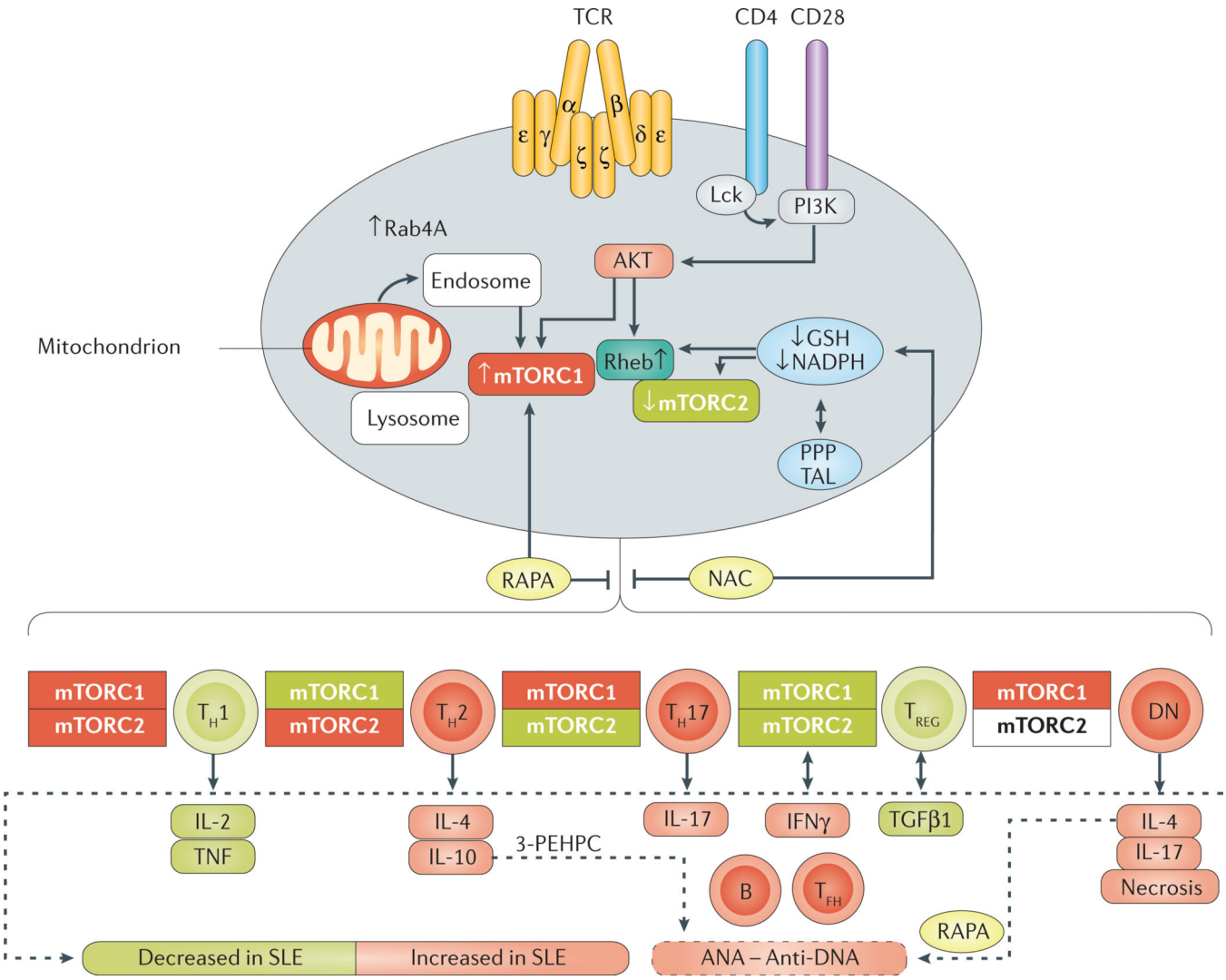

Figure 2. mTOR-mediated lineage specification in T cells

Mechanistic target of rapamycin (mTOR) is a sensor of metabolic stress and integrator of environmental cues. Activation of mTOR complex 1 (mTORC1) is triggered by oxidative stress, amino-acid levels and endosomal traffic to the lysosome by small GTPases such as Rab4A. In turn, mTORC1 promotes inflammation by skewing T-cell development. Oxidative stress is promoted by mitochondrial electron transport and balanced by the production of reduced glutathione (GSH) and its regeneration by NADPH via the pentose phosphate pathway (PPP). Oxidative stress and activation of mTORC1 inhibit the expression of FoxP3, leading to contraction of the T regulatory (TREG) cell population, and expansion of proinflammatory T-cell lineages such as T helper (TH) 1, TH17, T follicular helper (TFH) and double-negative (DN) T cells. Pharmacological interventions by rapamycin (RAPA), N-acetylcysteine (NAC) and 3-(3-pyridyl)-2-hydroxy-2-phosphonopropanoic acid (3-PEHPC) are highlighted in yellow. AKT, RAC serine/threonine-protein kinase; ANA, antinuclear antibodies; GTP-binding protein Rheb; IFNγ, interferon γ; Lck, tyrosine-protein kinase Lck; PI3K, phosphatidylinositide 3-kinase; Rheb, SLE, systemic lupus erythematosus; TAL, transaldolase; TCR, T-cell receptor; TGFβ1, transforming growth factor β1.

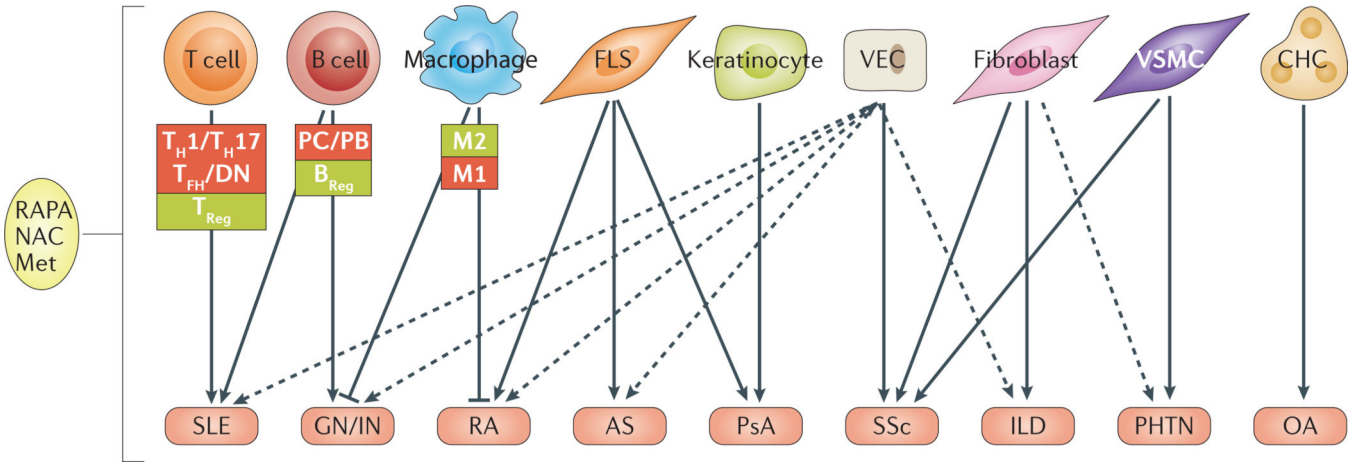

Figure 3. Cell type-specific mTOR pathway activation in rheumatic diseases

The mechanistic target of rapamycin (mTOR) pathway is functional in several types of immune cells, including T cells, B cells and macrophages, but is also present in structural cells such as fibroblasts and keratinocytes. Activation of mTOR in these cells is associated with several rheumatic diseases. AS, ankylosing spondylitis; B_{REG}, B regulatory cell; DN, CD4/CD8-double-negative cell; CHC, chondrocyte; FLS, fibroblast-like synoviocyte; GN/IN, glomerulonephritis/interstitial nephritis; ILD, interstitial lung disease; Met, metformin; NAC, *N*-acetylcysteine; OA, osteoarthritis; PB, plasmablast; PC, plasma cell; PHTN, pulmonary hypertension; PsA, psoriatic arthritis; SSc, systemic sclerosis; RA, rheumatoid arthritis, RAPA, rapamycin; SLE, systemic lupus erythematosus; T_{FH}, T folicular helper cell; T_H1, T helper cell type 1; T_H17, T helper cell type 17; T_{REG}, T regulatory cell; VEC, vascular endothelial cell; VSMC, vascular smooth-muscle cell.

Table 1

Pharmacological blockade of mTOR pathway activation in rheumatic diseases

Drug	Mechanism of action	Molecular target	Disease
Rapamycin	FKBP12/allosteric	mTORC1	SLE[6,109], lupus nephritis[5,120,176,231,232], IgA nephropathy[233,234], interstitial nephritis[235], SSc[13,15] RA and JIA[8,9], Sjögren syndrome[10], osteoarthritis[55,159]
Everolimus	FKBP12/allosteric	mTORC1	Pulmonary hypertension[236]
OSI-027	ATP-competitive	mTORC1/mTORC2	SSc, RA[237,238]
NAC	Antioxidant	GSH	SLE[56,70], RA and CIA[229,239], Sjögren syndrome[240,241] ILD[202,242]
Metformin	Antioxidant	ETC complex I	SLE[128], CIA[98,243]
Fingolimod	Receptor modulator	S1P receptor	SLE[214,215]
KN-93	Kinase inhibitor	CamK-II/CamK-IV	SLE[216–218]
Rimacalib	Kinase inhibitor	CamK-II/CamK-IV	RA[219,220]

CaMK-II/IV, calcium/calmodulin-dependent protein kinase type II/IV; CIA, collagen-induced arthritis; ETC, electron transport chain; GSH, reduced glutathione; ILD, interstitial lung disease; JIA, juvenile idiopathic arthritis; mTOR, mechanistic target of rapamycin; mTORC1/2, mechanistic target of rapamycin complex 1/2; NAC, *N*-acetylcysteine; SSc, systemic sclerosis; S1P, sphingosine-1-phosphate; SLE, systemic lupus erythematosus; RA, rheumatoid arthritis.