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## mTOR activation is a biomarker and a central pathway to autoimmune disorders, cancer, obesity, and aging

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### Abstract

The mechanistic target of rapamycin (mTOR) is a ubiquitous serine/threonine kinase that plays pivotal roles in integrating growth signals on a cellular level. To support proliferation and survival under stress, two interacting complexes that harbor mTOR, mTORC1 and mTORC2, promote the transcription of genes involved in carbohydrate metabolism and lipogenesis, enhance protein translation, and inhibit autophagy. While rapamycin was originally developed as an inhibitor of T cell proliferation for preventing organ transplant rejection, its molecular target, mTOR, has been subsequently identified as a central regulator of metabolic cues that drive lineage specification in the immune system. Owing to oxidative stress, the activation of mTORC1 has emerged as a central pathway for the pathogenesis of systemic lupus erythematosus and other autoimmune diseases. Paradoxically, mTORC1 has been also identified as a mediator of the Warburg effect that allows cell survival under hypoxia. Rapamycin and new classes of mTOR inhibitors are being developed to block not only transplant rejection and autoimmunity but also to treat obesity and various forms of cancer. Through preventing these diseases, personalized mTOR blockade holds promise to extend life span.

### Keywords

metabolism; autoimmunity; inflammation; T cell activation; systemic lupus erythematosus; oxidative stress; hypoxia; mitochondria; glutathione; mTOR; autophagy; pathogenesis; keloid disease; glycolysis; pentose phosphate pathway; kynurenine; biomarker; treatment; rapamycin; sirolimus

### Introduction

The mechanistic target of rapamycin (mTOR) is a serine/threonine kinase that is ubiquitous to eukaryotic cells. mTOR is named after rapamycin, an antifungal macrolide antibiotic. Rapamycin is produced by the bacterium *Streptomyces hygroscopicus*, which was isolated from a soil sample originating from Rapa Nui, commonly known as Easter Island.<sup>1</sup> Rapamycin is a potent inhibitor of antigen-induced proliferation of T cells and antibody production.<sup>2</sup> Such blockade of T cell activation has been found to be effective for inhibiting the development of a systemic autoimmune inflammatory disease, lupus, both in animal

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models<sup>3</sup> and in patients with systemic lupus erythematosus (SLE).<sup>4</sup> Demonstration of the robust immunosuppressive activity of rapamycin in animal models of organ transplantation led to clinical trials and subsequent approval by regulatory authorities for prophylaxis of renal graft rejection, under the pharmaceutical designation of sirolimus (Rapamune).<sup>5,6</sup> Interest in sirolimus as an immunosuppressive therapy in organ transplantation derives from its unique mechanism of action, its unique side effect profile, and its ability to synergize with other immunosuppressive agents.<sup>7</sup> The molecular mechanism underlying the antifungal, antiproliferative, and immunosuppressive activities of rapamycin involves the formation of a high-affinity complex with a 12-kD intracellular protein that binds FK506 and was thus named FKBP12.<sup>8</sup> This complex of rapamycin and FKBP12 blocks the activation of mTOR in systems ranging from yeast<sup>9</sup> to mammalian cells.<sup>10</sup> mTOR is present in two distinct complexes. mTOR complex 1 (mTORC1) is composed of mTOR, regulatory-associated protein of TOR (Raptor), mammalian lethal with sec-13 protein 8 (mLST8), DEP domain-containing mTOR-interacting protein (Deptor), and proline-rich Akt substrate of 40 kD (PRAS40).<sup>11</sup> mTORC1 integrates growth signals reflecting the availability of nutrients and energy to promote either proliferation when conditions are favorable or autophagy when conditions are unfavorable. mTORC1 activation occurs on the surface of the lysosomal membrane in response to amino acid sufficiency (Fig. 1).<sup>12</sup> Alternatively, low ATP levels lead to the AMPK-dependent activation of TSC2 and phosphorylation of Raptor to reduce mTORC1 signaling (Fig. 2).<sup>13</sup> mTORC1 has a number of downstream substrates that control the translation of mRNA via the phosphorylation of downstream targets (4E-BP1 and p70 S6 Kinase), suppression of autophagy (Atg13, ULK1), ribosome biogenesis, and activation of transcription.<sup>14,15</sup> mTOR complex 2 (mTORC2) comprises mTOR, rapamycin insensitive companion of mTOR (Rictor), stress-activated protein kinase interacting protein 1 (mSIN1), Protor, GβL, Deptor, and mLST8 (Fig. 2). mTORC2 promotes cellular survival by activating Akt.<sup>16</sup> Although mLST8 is present in both complexes, its absence primarily compromises mTORC2 activity.<sup>17</sup> Given that mTOR plays a pivotal role in integrating growth signals on a cellular level, it is not surprising that both complexes have been targeted for reversing increased proliferation associated with carcinogenesis.<sup>18,19</sup> In SLE patients, mTORC1 is activated,<sup>20,21</sup> while mTORC2 is reduced.<sup>22</sup> The activation of mTORC1 causes the proinflammatory increased production of IL-4 and necrotic death of CD4<sup>-</sup>CD8<sup>-</sup> double-negative (DN) T cells and depletion of CD4<sup>+</sup>CD25<sup>+</sup>FoxP3<sup>+</sup> regulatory T cells in SLE.<sup>23</sup> Accordingly, the therapeutically effective blockade of mTORC1 is accompanied by correction of these T cell abnormalities in SLE patients.<sup>23</sup> Increased mTORC1 was also noted in T lymphocytes of patients with another autoimmune disease, multiple sclerosis (MS), which was underlying the contraction of regulatory T (T<sub>reg</sub>) cells in these patients.<sup>24</sup> Rapamycin has shown therapeutic benefits in mice with experimental autoimmune encephalomyelitis (EAE),<sup>25</sup> an animal model of multiple sclerosis (MS). Along these lines, genetic inactivation of mTORC1 prevents the development of EAE in mice.<sup>26</sup> Obviously, rapamycin is the drug of choice for treatment of genetic causes of mTORC1 activation, such as lymphangioleiomyomatosis<sup>27</sup> and tuberous sclerosis.<sup>28</sup> mTORC1 activation has been associated with epilepsy,<sup>29–31</sup> learning, and memory.<sup>32,33</sup> Given such broad implications of mTOR pathway activation and its involvement in a wide spectrum of common diseases, overall lifespan, and social adaptation, this chapter will critically review its relevance for health and personalized medicine.

## The causes and consequences of mTOR pathway activation

mTORC1 is activated by nutrients and the availability of cellular energy, such as amino acids and ATP<sup>11</sup> (Fig. 1). In turn, growth factors (e.g., insulin) stimulate mTORC1 via the tuberous sclerosis complex (TSC), comprising TSC1 and TSC2. Further upstream, phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K) belongs to a family of enzymes that phosphorylate the 3 position hydroxyl group of the inositol ring of phosphatidylinositol and thus transmit growth signals and block apoptosis via activating another kinase, Akt (Fig. 2).<sup>34</sup> As an example, insulin stimulates the PI3K–AKT kinase complex, which phosphorylates TSC2 (also known as tuberin). While TSC1 serves as a stabilizer of the TSC complex, TSC2 acts as a GTPase-activating protein (GAP) to promote the activity of the small GTPase RAS homologue enriched in brain (Rheb). Amino acid sufficiency is transduced via the RAS-related GTP-binding protein (RAG) family of small GTPases which mediate the translocation of mTORC1 from the cytoplasm to the surface of the lysosome (Fig. 1), where mTORC1 is activated by Rheb. Redox-dependent activation of mTORC1 involves cysteine oxidation and interaction with Rheb<sup>35</sup> and Raptor.<sup>35,36</sup> These findings are consistent with earlier observations that mitochondrial oxidative stress is a trigger of mTORC1 activation.<sup>37</sup>

Upon activation, mTORC1 controls protein synthesis by inducing ribosome biogenesis<sup>38</sup> and mRNA translation.<sup>39,40</sup> mTORC1 phosphorylates S6 ribosomal kinase (S6K) to induce protein synthesis and 4E binding protein 1 (4E-BP1) to promote translation.<sup>41</sup> Specifically, mTORC1 phosphorylates S6K on Thr389, which activates S6K to phosphorylate ribosomal protein S6 (S6RP), a component of the 40S ribosomal subunit. mTORC1 also phosphorylates the translation inhibitor 4E-BP1, causing the liberation of a key initiation factor of eukaryotic translation initiation, factor eIF4E. However, these fundamental checkpoints do not exert complete control of *de novo* protein synthesis in skeletal muscle and liver tissue.<sup>42</sup> Mice lacking S6K and S6RP activate a compensatory mechanism through inhibition of 4E-BP.<sup>38</sup> These findings indicate significant cross talk between the ribosome biogenesis and protein translation pathways, which are separately controlled by mTORC1 via S6K and 4E-BP1, respectively. mTORC1 promotes the transcription of genes involved in glycolysis, the pentose phosphate pathway (PPP), and *de novo* lipogenesis.<sup>43</sup> Upregulation of glycolysis is mediated via the transcription factor hypoxia-inducible factor 1  $\alpha$  (HIF1 $\alpha$ )<sup>44,45</sup> (Fig. 2). As revealed by a recent metabolomic study, most of the mTORC1-regulated metabolites belong to the PPP.<sup>46</sup> A signature substrate of mTORC1, S6K, directly phosphorylates serine 1859 of the enzyme CAD (carbamoyl-phosphate synthetase 2, aspartate transcarbamoylase, dihydroorotase), which catalyzes the first three steps of *de novo* nucleotide synthesis<sup>46</sup> (Fig. 2).

In addition to responding to growth signals and promoting cell proliferation, mTORC1 is also actively involved in blocking autophagy, a complex lysosomal degradation pathway that allows cell survival during starvation. The initiation of autophagy is inhibited by mTORC1 through phosphorylation of autophagy/beclin-1 regulator 1 (AMBRA1).<sup>47</sup> Upon separation from mTORC1, unc-51-like kinase 1/autophagy related gene 1 (ULK1/ATG1) phosphorylates beclin-1 and binds to membranes to start autophagosome formation.<sup>47</sup>

Although mTORC2 regulation is less well understood, it involves its PI3K-dependent association with ribosomes and phosphorylation of Akt (Fig. 2).<sup>48</sup> Further downstream, mTORC2 promotes insulin-like growth factor 2 (IGF2) production and ultimately cell proliferation by phosphorylating IGF2 mRNA-binding protein 1 (IMP1).<sup>49</sup> Similar to mTORC1, mTORC2 activates SREBP1 transcriptionally and posttranslationally to enhance glycolysis and lipogenesis.<sup>50</sup> Via mTORC2, insulin also promotes cell survival via cytoskeleton reorganization<sup>51–53</sup> (Fig. 2).

### **Duration and selectivity of mTORC1 and mTORC2 blockade is critical for control of diabetes and obesity**

Increased mTOR signaling has been implicated in metabolic diseases, such as diabetes and obesity.<sup>54</sup> mTORC1 and its downstream target S6K are involved in amino acid-induced insulin resistance. Combined hyperaminoacidemia and postprandial hyperinsulinemia increase S6K phosphorylation and inhibitory insulin receptor substrate-1 (IRS-1) phosphorylation at Ser312 and Ser636.<sup>55</sup> Activation of mTORC1 is also required for the differentiation of adipocytes in mice<sup>56</sup> and humans.<sup>57</sup> Accordingly, long-term blockade of mTORC1 by rapamycin reduced high-fat diet-induced obesity in mice.<sup>58</sup> However, this beneficial effect of mTORC1 blockade impaired glucose tolerance.<sup>59</sup> It appears that short-term blockade of mTORC1, for 2 weeks or so, causes insulin resistance,<sup>60,61</sup> which is likely to occur via secondary activation of mTORC2.<sup>16</sup> As reinforced by a seminal follow-up study, the duration of treatment with rapamycin is critical. While 2-week treatment has detrimental metabolic effects, 6-week treatment leads to a metabolic transition and 20-week treatment improves metabolic profiles and insulin sensitivity.<sup>62</sup>

### **Proinflammatory effects of mTOR pathway activation within the adaptive and innate immune systems**

Signaling pathways that control the proliferation, survival, and differentiation of cells in the immune system regulate metabolic pathways to provide nutrients required to support specialized lymphocyte functions.<sup>63</sup> Recently, mTOR was identified as a central integrator of metabolic cues that drive lineage specification in the T cell compartment.<sup>26</sup> In order to support cell proliferation, mTORC1 promotes the transcription of genes involved in glycolysis, the pentose phosphate pathway (PPP) and *de novo* lipogenesis.<sup>43</sup> In particular, mTORC1 induces glucose 6-phosphate dehydrogenase (G6PD) and 6-phosphogluconate dehydrogenase (6PDG).<sup>43</sup> It has been generally assumed that mTORC1 signaling increases flux through the oxidative PPP to generate NADPH, which is needed for reducing power and for many biosynthetic processes, and ribose 5-phosphate, which is needed for the synthesis of nucleotides.<sup>43</sup> Earlier studies suggest that myc- and mTORC1-dependent activation of T cells involves dramatic upregulation of glucose consumption via PPP.<sup>64</sup> Selective activation of mTORC1 is required for the development of T<sub>H</sub>17 cells that mediate the development of EAE, which is induced by myelin oligodendrocyte glycoprotein (MOG) immunization of mice.<sup>26</sup> Both mTORC1 and mTORC2 are required for T<sub>H</sub>1 development, while only mTORC2 is required for T<sub>H</sub>2 development.<sup>26</sup> Inactivation of both mTORC1 and

mTORC2 favor the development of T<sub>reg</sub> cells.<sup>26</sup> Inhibition studies with rapamycin suggest that mTORC1 blocks the development of CD8<sup>+</sup> memory T cells.<sup>65</sup>

## mTOR pathway activation: a biomarker for diagnosis and target for treatment in SLE

The fundamental role for mTOR pathway activation in T cell lineage specification is consistent with its involvement in transplant rejection<sup>6,7</sup> and autoimmunity, as demonstrated by its central role in the pathogenesis of the prototypical systemic autoimmune disease, SLE.<sup>20,66,67</sup> The involvement of mTOR activation was initially suggested by successful blockade of T cell activation, autoimmunity, and nephritis in rapamycin-treated lupus-prone mice.<sup>3</sup> Rapamycin also blocked T cell activation in patients with SLE<sup>20</sup> with remarkable therapeutic efficacy.<sup>4,23</sup> The activation of mTORC1 preceded disease flares by 4 months and responded to therapeutic intervention with rapamycin.<sup>23</sup> In particular, rapamycin blocked the proinflammatory, necrotic death of CD4<sup>-</sup>CD8<sup>-</sup> DN T cells and depletion of CD4<sup>+</sup>CD25<sup>+</sup>FoxP3<sup>+</sup> T<sub>reg</sub> cells.<sup>23</sup> Diminished T<sub>reg</sub> frequency may be linked to mTORC1-sensitive methylation of the *Foxp3* promoter.<sup>68</sup> Diminished expression of FoxP3 in T<sub>reg</sub> cells may be due to reduced mTORC2 activity in lupus T cells.<sup>22,69,70</sup> Rapamycin treatment *in vivo* reduced the production of IL-4 by DN T cells,<sup>23</sup> which accounts for increased production of anti-DNA auto-antibodies by B cells.<sup>71,72</sup> The benefit of rapamycin may also be attributed to T<sub>reg</sub> expansion<sup>23</sup> via activation of mTORC2.<sup>22</sup>

Antiphospholipid antibodies (APLA) represent a component of the diagnostic criteria for SLE.<sup>73-75</sup> They also contribute to significant pathologies, specifically antiphospholipid syndrome (APS) in patients with or without SLE.<sup>76</sup> In a retrospective study of 10 patients with APS nephropathy who required renal transplantation and received treatment with sirolimus (i.e., rapamycin), 7 of 10 patients (70%) had a functioning allograft 144 months after transplantation, versus 3 of 27 patients treated without sirolimus (11%).<sup>77</sup> Interestingly, the majority of APS patients in this study also had SLE (16/28 = 57%).<sup>77</sup> However, it has not been disclosed how many of the seven patients who actually benefited from sirolimus<sup>77</sup> satisfied the diagnosis of SLE.<sup>73,74</sup> mTOR activity has not been measured within the immune system itself,<sup>77</sup> which is considered to be the principal mediator of autoimmunity both in APS<sup>78</sup> and SLE.<sup>79</sup> Therefore, it is likely that sirolimus may selectively benefit renal transplant recipients with underlying SLE.

*N*-acetylcysteine (NAC), which is a precursor of glutathione, reversed the depletion of this natural antioxidant in peripheral blood lymphocytes (PBL) of patients with SLE in a double-blind placebo-controlled phase I/II clinical trial.<sup>21</sup> Importantly, this biological effect of NAC was safe and clinically effective over a 3-month intervention. NAC treatment also reversed the prominent activation of mTORC1 in DN T cells, which is consistent with the role of oxidative stress as a regulatory checkpoint. Oxidative stress originates from increased oxygen consumption by complex I of the mitochondrial electron transport chain (ETC) in lupus T cells.<sup>80</sup> In turn, inhibition of mitochondrial oxidative stress by blocking ETC complex I with metformin also reduced mTORC1 activity and prevented nephritis in lupus-prone mice.<sup>81</sup>

The reliance of certain T cell subsets (e.g., T<sub>H</sub>17 cells) on mTORC1 during mitochondrial dysfunction–driven oxidative stress<sup>82</sup> and the compensatory activation of glycolysis via HIF1 $\alpha$ <sup>83</sup> are likely to underlie the markedly altered T cell development in SLE.<sup>84,85</sup> This is consistent with the induction of HIF1 $\alpha$  by oxidative stress<sup>86</sup> and its dependence on mTORC1.<sup>87</sup> Therefore, the reversal of GSH depletion by NAC may be a particularly safe and mechanistically driven therapeutic intervention in SLE.

As recently revealed, oxidative stress is associated with global metabolome changes in SLE that affect 27 of 80 Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways, with the most prominent impact on the PPP.<sup>88</sup> Moreover, cysteine was depleted and cystine and methionine sulfoxide were accumulated, all of which reflect oxidative stress. Area under the receiver operating characteristic curve (AUC) logistic regression approach identified kynurenine (AUC = 0.859), as the top metabolite predictor of SLE. NAC treatment significantly reduced kynurenine levels relative to placebo *in vivo* (raw  $P = 2.8 \times 10^{-7}$ , FDR corrected  $P = 6.6 \times 10^{-5}$ ). Kynurenine was also the top predictor of the NAC effect in SLE (AUC = 0.851). The accumulation of kynurenine may be a result of decreased catabolism by kynurenine hydroxylase owing to NADPH dependence of this enzyme.<sup>89</sup> Along these lines, NAC dramatically augmented the levels of NADPH, which can occur through sparing of NADPH via the enhancement of *de novo* GSH synthesis by NAC.<sup>90,91</sup> Thus, the marked suppression of kynurenine in NAC-treated patients can be attributed to the NADPH-sparing effect of NAC.<sup>90</sup> Kynurenine stimulated mTOR activity in healthy control PBL *in vitro*. Therefore, the PPP-connected and NAC-responsive accumulation of kynurenine and its stimulation of mTORC1 are identified as a novel biomarker and as metabolic checkpoints in lupus pathogenesis.<sup>88</sup>

A fundamental role of mTOR pathway activation is also illustrated by the first clinical case of fulminant lupus in a patient with TSC.<sup>92</sup> In accordance with a negative regulatory role for the TSC1/TSC2 complex, robust mTORC1 activation was documented in all lymphocyte subsets of this patient.<sup>92</sup>

As evidenced by diminished phosphorylation of serine<sup>473</sup> in Akt, activity of mTORC2 is reduced in DN T cells of SLE patients.<sup>22</sup> Rapamycin treatment reduced mTORC1 and enhanced mTORC2 activities of lupus T cells *in vitro*.<sup>22</sup> This is consistent with an inhibitory role for mTORC1/S6K-mediated phosphorylation of Rictor in mTORC2 and Akt signaling.<sup>93</sup> It is presently unknown whether the therapeutic benefit of rapamycin is solely associated with blockade of mTORC1 or whether it also involves the activation of mTORC2. Pursuit of such studies is justified by the notion that TOR inhibitors other than rapamycin may be more effective. As examples, Torin1 or INK128, two ATP-competitive inhibitors of mTOR, inhibit both mTORC1 and mTORC2.<sup>94</sup> Such dual inhibitors are currently in clinical trials in patients with cancer. Using flow cytometry, dual monitoring of mTORC1 and mTORC2 via intracellular staining for pS6RP<sup>Ser235/236</sup> and pAkt<sup>Ser473</sup> has been clearly delineated and proposed as relevant biomarkers for disease pathogenesis, prediction of flares, and monitoring of treatment efficacy of mTOR blockade in SLE.<sup>21–23</sup>

## mTOR is a metabolic regulator of survival in cancer cells

Inherited mutations in the tuberous sclerosis genes TSC1 and TSC2 cause autosomal-dominant hamartomas<sup>95</sup> and lymphangiomyomatosis.<sup>96</sup> The first clinical case of lupus in a patient with mTORC1 activation due to tuberous sclerosis was recently documented.<sup>92</sup> However, most cancers do not carry genetic defects in TSC1 or TSC2, and the activation of mTORC1 is triggered by mutations that inactivate p53.<sup>97,98</sup> p53 restrains mTORC1 by transactivating its negative regulators, namely TSC2 and AMPK $\beta$ 1.<sup>99</sup> Downstream, the role of mTOR in carcinogenesis is linked to multiple layers of metabolic regulatory networks that activate glycolysis via increasing the expression of pyruvate kinase.<sup>100</sup> This enzyme, isoenzyme M2, has been identified as the mediator of the so-called Warburg effect, which is a long-recognized metabolic feature of cancer cells that rely on glycolysis rather than mitochondrial respiration.<sup>101</sup> This allows cancer cell survival under hypoxic conditions through reliance on glycolysis, which involves the transcription factor HIF1 $\alpha$ , which orchestrates the coordinate upregulation of glycolytic gene expression.<sup>44,45</sup>

mTORC1 also promotes carcinogenesis by inhibiting physiological protein turnover via autophagy. This occurs at the phase of autophagosome formation, which is inhibited by mTORC1 through phosphorylation of AMBRA1.<sup>47</sup> Therefore, mTORC1 promotes tumorigenesis both through reversing glycolysis and promoting autophagy. While mTORC2 is essential for cell survival, its activation is a critical mediator of cancer cells lacking PTEN.<sup>102</sup> Meta-analyses indicate that mTOR blockade reduces the incidence of a variety of cancers.<sup>103</sup> The efficacy of such treatment may depend on the relative involvement of mTORC1 and mTORC2.

## Pharmacological blockade of mTOR beyond rapamycin

Since mTOR forms an integral part of both enzyme complexes, mTORC1 and mTORC2, inhibitors have been developed that compete with ATP for access to the active site of mTOR. For example, Torin1, an ATP-competitive mTOR inhibitor, directly inhibits both mTORC1 and mTORC2.<sup>104</sup> Torin1 blocks cell growth and proliferation to a far greater degree than rapamycin.<sup>104</sup> These effects are independent of mTORC2 inhibition, and they are thought to be mediated by mTORC1-dependent and relatively rapamycin-resistant phosphorylation of 4E-BP1.<sup>104</sup> Therefore, these direct inhibitors of mTORC1 kinase activity may be more successful than rapamycin for cancer treatment<sup>105</sup> via inhibiting tumor growth and triggering autophagy that depend on mTORC1.<sup>104</sup> ATP-competitive inhibitors that target the active sites of the holoenzymes in both PI3K and mTOR have been also developed.<sup>105</sup> These drugs, which also exert greater proapoptotic and antiproliferative effects over rapamycin,<sup>106</sup> have entered phase I clinical trials.<sup>107</sup> While the overall safety and potency of rapalogs and ATP-competitive mTOR and dual PI3P/mTOR inhibitors are unknown, their large numbers offer tremendous hope for treatment of various forms of cancer.<sup>105</sup>

## Personalized mTOR blockade for extension of life span

mTORC1 blockade by rapamycin is associated with increased life span in mice.<sup>108</sup> Such beneficial effect of rapamycin is independent of calorie restriction,<sup>109</sup> and it does not

compromise mitochondrial homeostasis and muscle endurance.<sup>110</sup> However, the blockade of mTORC2 by rapamycin increases insulin resistance, which appears to be independent from extending life span.<sup>16</sup> Although this is presently far from certain, blockade of mTORC2 may compromise the extension of life span in subjects with obesity and hyperglycemia. In contrast, blocking of both mTORC1 and mTORC2 favors the development of T<sub>reg</sub> cells;<sup>26</sup> thus, an ATP-competitive mTOR inhibitor may have greater therapeutic benefit and potency for extension of life span over rapamycin in patients with the autoimmune disease SLE. Oral rapamycin increases life span without changes in body weight, even when started late in life.<sup>108</sup> Such an effect was reproduced in C57BL/6 mice were treated with rapamycin at 4 mg/kg body weight by intraperitoneal injection every other day for 6 weeks starting at age 22 months.<sup>111</sup> However, 1 mg/kg rapamycin given 3 times weekly markedly reduced the body weight of lupus-prone mice, while completely blocking autoimmunity and nephritis.<sup>112</sup> Interim analysis of a prospective open-label clinical trial with rapamycin in SLE patients revealed marked improvement of disease activity with blockade of mTORC1.<sup>23</sup> Final analysis of rapamycin impact on weight, glucose tolerance, and hyperlipidemia are expected following the completion of this study in 2015. Owing to its potent anti-proliferative effects on fibroblasts, rapamycin has been used to block keloid disease<sup>113</sup> and to maintain patency of coronary artery stents.<sup>114</sup>

However, mTOR blockade is associated with serious side effects. For example, rapamycin treatment induces hyperlipidemia, at least in renal transplant recipients.<sup>115</sup> Of the potentially fatal adverse events, the most common were pneumonia (30.8%) and sepsis (38.5%).<sup>103</sup> These potential side effects are of concern because infections and cardiovascular disease are the leading causes of increased mortality in SLE.<sup>116</sup> Importantly, oxidative stress significantly contributes to cardiovascular disease,<sup>117</sup> which is responsive to treatment with NAC in patients with end-stage renal disease.<sup>118</sup> NAC was also shown to increase high-density lipoprotein (HDL) cholesterol in patients with hyperlipidemia,<sup>119,120</sup> which has long been recognized as a hallmark of enhanced atherosclerosis in SLE.<sup>121–129</sup> mTORC2 protects the heart from ischemic damage.<sup>130,131</sup> Thus, in line with selectively blocking mTORC1, NAC may also be beneficial for reducing cardiovascular disease and fatigue in SLE. Fatigue is a common side effect noted in clinical trials, even with the newer rapalogs, everolimus and temsirolimus.<sup>132</sup> Future studies should be directed at deciphering whether GSH depletion and activation of mTORC1 predict responsiveness to treatment by NAC and mTOR inhibitors, alone or in combination, and whether selective or non-selective mTORC1, mTORC2, or dual mTORC1/mTORC2 inhibitors deliver greater clinical benefit (Table 1).

Constitutive mutations in TSC1/TSC2 lead to hamartomas<sup>95</sup> and lymphangioliomyomatosis via activation of mTORC1.<sup>96</sup> In turn, cell type-specific inactivation of p53 triggers uncontrolled cell proliferation in lung and thyroid cancer<sup>133</sup> and other solid tumors via upregulation of mTORC1 as well.<sup>97–99</sup> Therefore, the preferential blockade of mTORC1 by rapamycin and rapalogs may be the optimal treatment for these types of neoplasia (Table 1). In contrast, the selective blockade of mTORC2 is preferred in another subset of cancers that exhibit the loss of PTEN, such as prostate cancer<sup>102</sup> and breast cancer.<sup>134</sup> Nevertheless, the importance of preserving mTORC2 function is supported by the notion that no spontaneous mutations have been found in essential components of this complex. Along these lines, inactivation of mTORC2 via disruption of Rictor causes



embryonic lethality.<sup>17</sup> mTORC2 is required for the expression of FoxP3.<sup>69,70</sup> Diminished mTORC2 activity may underlie the reduced expression of FoxP3 and loss of T<sub>reg</sub> cells in patients with SLE.<sup>22</sup> Therefore, the selective blockade of mTORC1 is desirable for SLE<sup>23</sup> and prevention of autoimmunity in general.<sup>70</sup> Moreover, owing to the involvement of mTORC1 in lipogenesis, the inhibition of this complex is likely to be advantageous in most clinical cases of obesity. Taken together, the personalized blockade of mTORC1—in time and space—appears to be a promising approach to extend life span via preventing obesity and the development of some cancers, as well as autoimmune inflammatory and connective tissue diseases.

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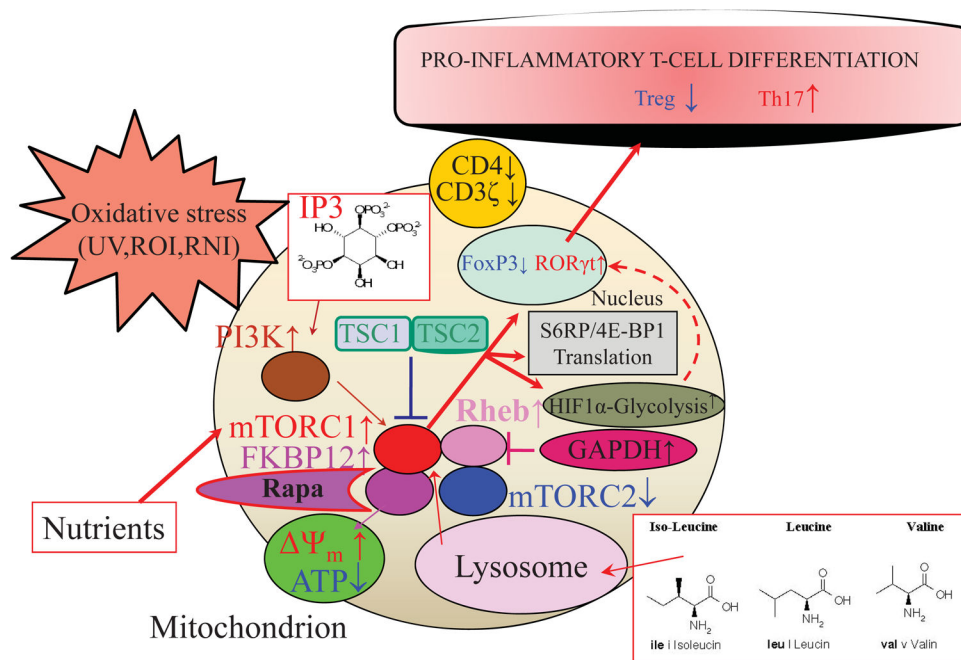
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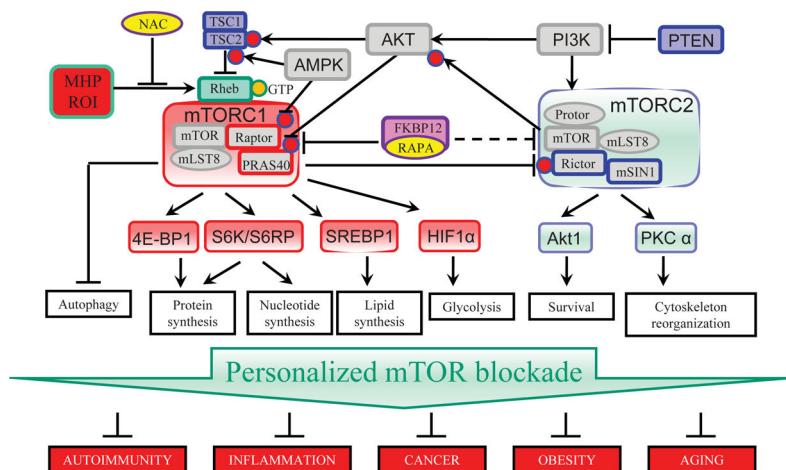
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**Figure 1.** Schematic diagram of mTOR-mediated T cell activation and lineage specification. mTOR is a sensor of metabolic stress and integrator of environmental cues. Activation of mTOR complex 1 (mTORC1) is triggered by oxidative stress,<sup>82</sup> sufficiency of amino acids, and growth factors, which, in turn, promote proinflammatory skewing of T cell development. Mitochondrial oxidative stress and activation of mTORC1 inhibit the expression of FoxP3 and contract T<sub>reg</sub> cells.<sup>21,23</sup> Downstream of mTORC1,<sup>135,136</sup> HIF1 $\alpha$ -dependent activation of glycolytic enzymes drives the proinflammatory metabolic changes,<sup>137</sup> stimulating the expression of ROR $\gamma$ t and the expansion of T<sub>H</sub>17 cells.<sup>22,26,137</sup> This is consistent on the reliance of T<sub>H</sub>17 and T<sub>reg</sub> cells on glycolysis and mitochondrial metabolism, respectively.<sup>137</sup>



**Figure 2.** Pharmacologically targetable regulatory checkpoints of the mTOR pathway. While rapamycin and rapalogs selectively block mTORC1, ATP-competitive mTOR kinase domain inhibitors abrogate both mTORC1 and mTORC2 activities. Dual inhibitors of the ATP-binding kinase domains of PI3K and mTOR provide the most overwhelming blockade of cell growth and proliferation. A personalized approach to mTOR pathway blockade holds promise to control autoimmune disease, cancer, obesity, and aging.

**Table 1**

## Pharmacological blockade of mTOR pathway activation

<b>Drug</b>	<b>Molecular Target</b>	<b>Mechanism action</b>	<b>Pathway blockade</b>	<b>Reference</b>
Rapamycin	FKBP12	Allosteric	mTORC1	1, 2, 13)
Everolimus	FKBP12	Allosteric	mTORC1	132, 139
Temsirolimus	FKBP12	Allosteric	mTORC1	132, 139
Torin1	mTOR kinase domain	ATP competitive	mTORC1/mTORC2	104
AZD8055	mTOR kinase domain	ATP competitive	mTORC1/mTORC2	140
INK128	mTOR kinase domain	ATP competitive	mTORC1/mTORC2	94
BGT226	PI3K/mTOR kinase	ATP competitive	PI3K/mTORC1/mTORC2	107
BAL	Disulfide bonds	H donor	Raptor/mTORC1	36
NAC	GSH	Antioxidant	mTORC1	21
Metformin	ETC complex I	Antioxidant	mTORC1	81