## Phylogeny

Mechanistic Target of Rapamycin (mTOR) is an atypical serine/threonine protein kinase belonging to the phosphatidylinositol-3-kinase-related kinase (PIKK) family, together with ATM, ATR, DNA-PK, SMG1 and TRRAP (Chao & Avruch, 2019). Single TOR orthologues are present throughout eukaryotes—TOR1/TOR2 (Saccharomyces cerevisiae), dTOR (Drosophila melanogaster) and LET-363 (Caenorhabditis elegans)—whereas higher vertebrates carry two nearly identical paralogues (> 95 % identity in human, mouse and rat) (The mammalian target…, 2005; The role of phosphorylation…, 2004).

## Reaction Catalyzed

ATP + [protein]-Ser/Thr → ADP + [protein]-Ser/Thr-phosphate (mTOR kinase structure…, 2013).

## Cofactor Requirements

Requires two Mg²⁺ ions that coordinate ATP within the active site (mTOR kinase structure…, 2013).

## Substrate Specificity

• Catalytic domain prefers Ser/Thr followed by Pro within a hydrophobic Φ-Φ-[ST]-P motif (Chao & Avruch, 2019).  
• mTORC1 substrates additionally contain an N-terminal TOR-signalling (TOS) motif (Φ-Φ-x-x-Φ) that docks on RAPTOR (Tafur et al., 2020).  
• Verified mTORC1 targets: S6K1, 4E-BP1 and PRAS40.  
• Verified mTORC2 targets: Akt Ser473, SGK1 and multiple conventional/novel PKC isoforms (Scaiola et al., 2020; Chao & Avruch, 2019).

## Structure

mTOR polypeptide: N-HEAT (≈ 32 repeats) → M-HEAT → FAT solenoid → FRB insertion → PI3K-like kinase domain with LBE insertion binding mLST8 → C-terminal FATC tail (Chao & Avruch, 2019; mTOR kinase structure…, 2013).  
mTORC1: lozenge-shaped dimer of mTOR–RAPTOR–mLST8 heterotrimers (PDB 6BCU); RAPTOR’s caspase-like domain abuts the FRB gate for substrate docking (Aylett et al., 2016).  
mTORC2: compact rhomboid dimer in which RICTOR and SIN1 encircle the catalytic cores, explaining rapamycin resistance (Scaiola et al., 2020).  
The FAT domain clamps kinase lobes, widening the active site; Rheb-GTP binding realigns these elements and activates catalysis (Chao & Avruch, 2019).  
Activation loop is pre-ordered and phosphorylation-independent; FRB helix forms the rapamycin-binding steric gate (mTOR kinase structure…, 2013).

## Regulation

Post-translational modifications  
• Ser2448 (S6K1 feedback or Akt—conflicting data) (Bai & Jiang, 2010; Figueiredo et al., 2017).  
• Thr2446 phosphorylated by AMPK under energy stress (Bai & Jiang, 2010).  
• Ser2481 autophosphorylation reports intrinsic activity (Bai & Jiang, 2010).  
• Ser2159 and Ser1261 phosphorylation enhance mTORC1 output (Tchevkina & Komelkov, 2012).  
• Lys1218 acetylation may affect complex stability (Chao & Avruch, 2019).

Allosteric and contextual control  
• Rheb-GTP engagement removes FAT clamp and increases k\_cat (Chao & Avruch, 2019).  
• Rag GTPases loaded with amino acids recruit mTORC1 to lysosomes for Rheb-dependent activation (Chao & Avruch, 2019).  
• Inhibitory partners PRAS40, FKBP38 and DEPTOR block FRB/RAPTOR interfaces (Chao & Avruch, 2019; Wälchli et al., 2021).  
• AMPK phosphorylates RAPTOR to suppress mTORC1 in low-energy states (Bai & Jiang, 2010).  
• FKBP12-rapamycin complex binds FRB and sterically excludes substrates without complex disassembly (Bai & Jiang, 2010).

## Function

GTEx data show ubiquitous MTOR expression, highest in muscle, liver and brain (Chao & Avruch, 2019).  
mTORC1 promotes anabolic growth—stimulates protein and lipid synthesis (S6K1, 4E-BP1, ULK1, TFEB) and represses autophagy (Bai & Jiang, 2010; Chao & Avruch, 2019).  
mTORC2 phosphorylates Akt, SGK1 and PKCs to control survival, ion transport and cytoskeleton (Scaiola et al., 2020).  
Upstream PI3K-Akt signalling inhibits TSC1/2, elevating Rheb-GTP and activating mTORC1; AMPK counteracts under ATP depletion (Inoki et al., 2005).  
Active complexes localise mainly to lysosomal membranes, with additional cytoplasmic/nuclear pools (Chao & Avruch, 2019; The role of phosphorylation…, 2004).

## Inhibitors

• Allosteric macrolides: rapamycin and rapalogs (temsirolimus, everolimus, AP23573) form FKBP12–drug complexes that bind FRB and selectively inhibit mTORC1 (The mammalian target…, 2005; Bai & Jiang, 2010).  
• ATP-competitive inhibitors: Torin1/2, PP242, MLN0128, PI-103 occupy the catalytic cleft and suppress both complexes; stacking against Trp2239 underlies selectivity (mTOR kinase structure…, 2013; Tafur et al., 2020).

## Other Comments

Hyperactive MTOR signalling drives cancers, metabolic and neurological disorders (Scaiola et al., 2020; Wälchli et al., 2021).  
Recurrent activating (E1799K, S2215Y, F2415I) or drug-resistant (S2035F/I) mutations cluster in functional domains (Tafur et al., 2020; Chao & Avruch, 2019; The role of phosphorylation…, 2004).

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