## Phylogeny

• Mechanistic target of rapamycin (mTOR) is an atypical serine/threonine kinase classified within the phosphatidylinositol-3-kinase-related kinase (PIKK) branch of the human kinome, grouping it with ATM, ATR, DNA-PK, SMG1 and TRRAP (chao2019cryoeminsightinto pages 1-3).  
• Orthologs are conserved across eukaryotes, including Saccharomyces cerevisiae TOR1/TOR2, Drosophila melanogaster dTOR, Caenorhabditis elegans LET-363, and higher vertebrate paralogs that share >95 % identity between human, mouse and rat proteins (unknownauthors2004theroleof pages 23-27, unknownauthors2005themammaliantarget pages 1-3).

## Reaction Catalyzed

• ATP + [protein]-Ser/Thr → ADP + [protein]-Ser/Thr-phosphate (unknownauthors2013mtorkinasestructure pages 10-11).

## Cofactor Requirements

• Catalysis requires two Mg²⁺ ions that coordinate ATP in the active site, as demonstrated in ADP-MgF₃-Mg²⁺ transition-state structures (unknownauthors2013mtorkinasestructure pages 10-11).

## Substrate Specificity

• The kinase domain preferentially targets serine or threonine residues followed by proline within a hydrophobic consensus Φ-Φ-[ST]-P sequence (chao2019cryoeminsightinto pages 7-8).  
• mTORC1 substrates carry an N-terminal TOR signaling (TOS) motif (Φ-Φ-x-x-Φ) that docks on the RAPTOR caspase-like domain and positions the phosphorylation site near the catalytic cleft (tafur2020structuralinsightsinto pages 2-4).  
• Experimentally validated substrates matching these motifs include S6K1, 4E-BP1 and PRAS40 for mTORC1, and Akt Ser473, SGK1 and conventional/novel PKCs for mTORC2 (scaiola2020the3.2åresolution pages 1-2, chao2019cryoeminsightinto pages 5-6).

## Structure

• Domain organization: N-HEAT (32 repeats) → M-HEAT → FAT α-solenoid → FRB (FKBP12-rapamycin binding) insertion → PI3K-like kinase domain with LBE insertion binding mLST8 → C-terminal FATC tail (chao2019cryoeminsightinto pages 1-3, unknownauthors2013mtorkinasestructure pages 3-4).  
• High-resolution cryo-EM shows mTORC1 as a lozenge-shaped dimer of mTOR–RAPTOR–mLST8 heterotrimers (PDB 6BCU) where Raptor’s caspase-like domain abuts the FRB gate to mediate substrate docking (aylett2016architectureofhuman pages 7-10).  
• mTORC2 adopts a compact rhomboid dimer in which RICTOR and SIN1 form an intertwined scaffold around the catalytic cores, rationalising rapamycin insensitivity (scaiola2020the3.2åresolution pages 1-2).  
• The FAT domain clamps the N- and C-lobes of the kinase, distorting the catalytic spine and widening the active site; Rheb-GTP binding realigns these elements and closes the cleft to activate catalysis (chao2019cryoeminsightinto pages 6-7).  
• The activation loop is pre-ordered and does not require phosphorylation; the FRB helix acts as a steric gatekeeper controlling substrate entry and providing the rapamycin pocket (unknownauthors2013mtorkinasestructure pages 6-8, bai2010keyfactorsin pages 1-2).

## Regulation

Post-translational modifications  
• Ser2448 is phosphorylated by S6K1 in a negative feedback loop, although several reports attribute this site to Akt, illustrating a documented contradiction (bai2010keyfactorsin pages 1-2, figueiredo2017considerationsonmtor pages 1-3).  
• Thr2446 is phosphorylated by AMPK under energy stress and attenuates mTORC1 signalling (bai2010keyfactorsin pages 1-2).  
• Ser2481 undergoes mTOR autophosphorylation and tracks intrinsic kinase activity (bai2010keyfactorsin pages 1-2).  
• Ser2159 and Ser1261 phosphorylation events have been reported to enhance mTORC1 output (tchevkina2012proteinphosphorylationas pages 1-4).  
• Lys1218 acetylation has been observed and proposed to modulate complex stability (chao2019cryoeminsightinto pages 7-8).

Allosteric and conformational control  
• Rheb-GTP engages the N-HEAT, M-HEAT and FAT surfaces, relieving the FAT clamp and boosting catalytic k\_cat (chao2019cryoeminsightinto pages 6-7).  
• Amino acid–loaded Rag GTPases recruit mTORC1 to lysosomes, enabling Rheb-dependent activation (chao2019cryoeminsightinto pages 3-5).  
• PRAS40, FKBP38 and DEPTOR bind FRB or Raptor interfaces to inhibit substrate access and reduce activity (chao2019cryoeminsightinto pages 5-6, walchli2021regulationofhuman pages 17-18).  
• AMPK phosphorylates Raptor to suppress mTORC1 when cellular energy is low (bai2010keyfactorsin pages 2-4).  
• FKBP12-rapamycin binds the FRB domain and sterically blocks substrate docking without disassembling the complex (bai2010keyfactorsin pages 1-2).

## Function

• GTEx transcriptomics demonstrates ubiquitous MTOR expression with higher levels in metabolically active tissues such as muscle, liver and brain (chao2019cryoeminsightinto pages 7-8).  
• mTORC1 drives anabolic growth by phosphorylating S6K1, 4E-BP1, ULK1 and TFEB, thereby stimulating protein synthesis, lipid production and suppressing autophagy (bai2010keyfactorsin pages 2-4, chao2019cryoeminsightinto pages 5-6).  
• mTORC2 phosphorylates the hydrophobic motif of Akt (Ser473), SGK1 and several PKC isoforms, regulating cell survival, ion transport and cytoskeletal organisation (scaiola2020the3.2åresolution pages 1-2).  
• Upstream growth-factor signalling via PI3K-Akt inhibits the TSC1/2 GAP complex, increasing Rheb-GTP and activating mTORC1, whereas AMPK counteracts this under ATP depletion (inoki2005signalingbytarget pages 1-1).  
• Subcellular localisation studies place active mTOR predominantly on lysosomal membranes, with additional cytoplasmic and nuclear pools where mTOR-Rheb assemblies have been detected (chao2019cryoeminsightinto pages 7-8, unknownauthors2004theroleof pages 23-27).

## Inhibitors

• Allosteric macrolides: rapamycin (sirolimus) and its rapalogs temsirolimus (CCI-779), everolimus (RAD001) and AP23573 form FKBP12–drug complexes that bind the FRB domain and selectively inhibit mTORC1 (unknownauthors2005themammaliantarget pages 1-3, bai2010keyfactorsin pages 1-2).  
• ATP-competitive inhibitors Torin1/2, PP242, MLN0128 and PI-103 occupy the catalytic cleft and suppress both complexes; crystal structures highlight stacking of Trp2239 as a key selectivity determinant (unknownauthors2013mtorkinasestructure pages 8-10, tafur2020structuralinsightsinto pages 2-4).

## Other Comments

• Hyperactive MTOR signalling is implicated in cancers, metabolic disorders and neurological diseases including tuberous sclerosis complex and focal cortical dysplasia (scaiola2020the3.2åresolution pages 1-2, walchli2021regulationofhuman pages 17-18).  
• Recurrent activating or drug-resistant mutations cluster in functional domains: E1799K, S2215Y and F2415I in the kinase lobe enhance activity, whereas S2035F/S2035I in the FRB domain confer rapamycin resistance (tafur2020structuralinsightsinto pages 18-19, chao2019cryoeminsightinto pages 7-8, unknownauthors2004theroleof pages 27-32).

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