1. Phylogeny  
   The serine/threonine‐protein kinase mTOR belongs to the phosphatidylinositol 3‐kinase‐related kinase (PIKK) family, a group of evolutionarily conserved large kinases that can be traced back to the Last Eukaryotic Common Ancestor. In lower eukaryotes such as yeast, two TOR homologs (TOR1 and TOR2) exist, whereas in mammalian species a single MTOR gene encodes the mTOR protein, reflecting a divergence and consolidation during evolution. mTOR is part of a core set of TOR pathway genes that include regulators (e.g., TSC1/2, Rheb) and associated proteins forming multiprotein complexes that are evolutionarily conserved from yeast to mammals (fingar2004targetofrapamycin pages 1-2, inoki2005signalingbytarget pages 1-1).
2. Reaction Catalyzed  
   mTOR catalyzes the transfer of a phosphate group from ATP to serine or threonine residues on target protein substrates. The reaction can be summarized as: ATP + [protein]-(L-serine or L-threonine) → ADP + [protein]-(L-serine/threonine)-phosphate + H⁺ (ballou2008rapamycinandmtor pages 1-2, fingar2004targetofrapamycin pages 1-2).
3. Cofactor Requirements  
   The catalytic activity of mTOR requires the presence of divalent cations, most notably Mg²⁺, which functions as an essential cofactor by helping to stabilize ATP binding in the kinase active site (ballou2008rapamycinandmtor pages 1-2).
4. Substrate Specificity  
   mTOR phosphorylates serine/threonine residues on a broad range of substrates and is documented to directly or indirectly regulate the phosphorylation of over 800 proteins. Its well‐characterized substrates include key regulators of mRNA translation and ribosome biogenesis (e.g., EIF4EBP1 and p70S6K1). Although a precise consensus substrate motif is not as rigorously defined as in some other kinase families, mTOR predominantly targets residues that are part of serine/threonine‐rich regions within substrates that control anabolic processes (agulnik2012newdevelopmentsin pages 1-2, alqurashi2013chemicalinhibitorsand pages 1-4).
5. Structure  
   mTOR is an exceptionally large protein composed of approximately 2549 amino acids and has a molecular weight near 289 kDa. Its domain organization is characterized by an N-terminal region containing multiple HEAT repeats that mediate key protein–protein interactions; a central FAT domain (named for its homology with FRAP, ATM, and TRRAP) that plays a role in the regulatory architecture; an FRB (FKBP12-rapamycin binding) domain immediately preceding the kinase domain; a kinase catalytic domain that shares structural similarity with lipid kinases; and a C-terminal FATC domain critical for enzyme activity (alqurashi2013chemicalinhibitorsand pages 1-4, chong2010mammaliantargetof pages 1-2, lian2008themammaliantarget pages 1-2). Structural studies and models indicate the kinase domain features the classical bilobal structure with an activation loop, a C-helix, and a hydrophobic spine that are central to catalytic function. mTOR also assembles into two distinct multiprotein complexes, mTORC1 and mTORC2, each with unique accessory proteins that further influence substrate specificity and regulation (foster2010mammaliantargetof pages 1-2, alqurashi2013chemicalinhibitorsand pages 4-6).
6. Regulation  
   mTOR activity is regulated by a complex network of post-translational modifications and protein–protein interactions. Key phosphorylation sites on mTOR include serine 2448, often phosphorylated by kinases such as Akt and S6K in response to nutrient and growth factor signals, and serine 2481, which serves as an autophosphorylation marker correlating with intrinsic catalytic activity (fingar2004targetofrapamycin pages 2-3, ballou2008rapamycinandmtor pages 2-4). Other residues such as threonine 2446 and serine 1261 are also implicated in modulating activity in response to cellular energy and nutrient status. Moreover, mTOR activity is allosterically inhibited by the binding of the FKBP12–rapamycin complex to its FRB domain, which leads to dissociation or conformational shifts in mTORC1 (ballou2008rapamycinandmtor pages 1-2, chong2012sheddingnewlight pages 2-3). Upstream regulators include growth factor-activated PI3K/Akt signals, which relieve inhibition by phosphorylating and inactivating the TSC1/TSC2 complex, thereby allowing the small GTPase Rheb to activate mTORC1. In contrast, AMPK, activated during cellular energy stress, phosphorylates TSC2 and other targets to inhibit mTOR signaling (ms, maiese2014takingaimat pages 2-3, inoki2005signalingbytarget pages 10-11).
7. Function  
   mTOR functions as a central regulator of cellular metabolism, growth, and survival by integrating inputs from nutrients, growth factors, hormones, and stress signals. Within mTORC1, activation promotes anabolic processes including protein, lipid, and nucleotide synthesis; this is achieved through phosphorylation of downstream targets such as 4E-BP1, which when phosphorylated releases its inhibition of eukaryotic initiation factor 4E (eIF4E), and activation of ribosomal S6 kinases (RPS6KB1 and RPS6KB2), which in turn modulate ribosomal protein S6 and support translation initiation (agulnik2012newdevelopmentsin pages 1-2, alqurashi2013chemicalinhibitorsand pages 15-17, foster2010mammaliantargetof pages 2-3). mTORC1 also stimulates the pyrimidine biosynthesis pathway by acute phosphorylation of enzymes like CAD and through transcriptional upregulation of the pentose phosphate pathway, thereby supporting cell proliferation (agulnik2012newdevelopmentsin pages 1-2). In addition, mTORC1 negatively regulates catabolic processes such as autophagy by phosphorylating ULK1, thus preventing the initiation of autophagic degradation pathways (maiese2014takingaimat pages 2-3). mTORC2, on the other hand, is primarily involved in the regulation of the actin cytoskeleton and cell survival; it phosphorylates members of the AGC kinase family including Akt (at Ser473) and SGK1, and modulates protein kinase C isoforms, thereby affecting cell proliferation and cytoskeletal reorganization (foster2010mammaliantargetof pages 2-3, chong2010mammaliantargetof pages 1-2). mTOR is expressed in a wide range of tissues, with significant roles in organs such as the brain, liver, kidney, and testis, and it functions as an integrator ensuring that cell growth is tightly coupled to nutrient availability and energy status (chong2012sheddingnewlight pages 3-4, jesus2017mammaliantargetof pages 3-4).
8. Other Comments  
   Numerous specific inhibitors target mTOR, the most prominent being rapamycin and its derivatives (rapalogs) such as temsirolimus, everolimus, and ridaforolimus, which bind FKBP12 and inhibit mTORC1 primarily. Second-generation ATP-competitive inhibitors have also been developed to block the kinase activity of both mTORC1 and mTORC2, aiming for more comprehensive inhibition of mTOR signaling (ballou2008rapamycinandmtor pages 6-7, alqurashi2013chemicalinhibitorsand pages 15-17). Dysregulation of mTOR activity underlies several pathological conditions, including a wide spectrum of cancers, neurodegenerative disorders, metabolic diseases, and conditions related to abnormal autophagy. mTOR’s ability to phosphorylate a large number of substrates—more than 800—underscores its extensive involvement in cellular physiology, and as such, it remains a major focus of clinical and experimental therapeutic studies (agulnik2012newdevelopmentsin pages 1-2, chong2010mammaliantargetof pages 1-2).
9. References  
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   foster2010mammaliantargetof pages 1-2;  
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   jesus2017mammaliantargetof pages 3-4;  
   kaur2017mammaliantargetof pages 1-3;  
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   magnuson2012regulationandfunction pages 1-2;  
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