1. Phylogeny  
   Serine/threonine‐protein kinase ULK1 is a member of the evolutionarily conserved UNC‐51–like kinase family, whose members can be traced back to the yeast autophagy–initiating kinase Atg1 and the Caenorhabditis elegans UNC‐51. ULK1 orthologs are present in all major eukaryotic lineages, with mammalian ULK1 and its close paralog ULK2 sharing high sequence similarity in their kinase domains. Comparative sequence analyses have demonstrated that the key domains of ULK1 are conserved across species, underscoring its position within an evolutionarily core set of kinases regulating autophagy (randhawa2015unc51likekinase pages 1-2, kumar2020apancancerassessment pages 1-2). ULK1 is also grouped with other autophagy‐related kinases that act downstream of nutrient‐sensing pathways, positioning it within the larger kinome that includes families such as the CAMK and AGC kinases (randhawa2015unc51likekinase pages 1-2).
2. Reaction Catalyzed  
   ULK1 catalyzes the transfer of a phosphate group from ATP to the hydroxyl group of serine and threonine residues on target proteins. In a typical reaction it uses ATP and a specific substrate protein – having a serine or threonine residue – to produce ADP, a phosphorylated serine/threonine residue on the substrate, and a proton (kumar2020apancancerassessment pages 1-2, randhawa2015unc51likekinase pages 1-2).
3. Cofactor Requirements  
   The catalytic activity of ULK1 depends on the presence of Mg²⁺ as a cofactor, which is required to coordinate ATP binding and facilitate the phosphoryl transfer reaction (kumar2020apancancerassessment pages 1-2).
4. Substrate Specificity  
   ULK1 phosphorylates serine/threonine residues on a number of substrates that are directly involved in the initiation and regulation of autophagy. Its substrate specificity is characterized by a preference for serine residues, with nearby hydrophobic amino acids contributing to substrate recognition; this is in line with experimental observations that underscore the importance of the residue immediately following the DFG motif in the kinase domain (kumar2020apancancerassessment pages 1-2, randhawa2015unc51likekinase pages 9-10). Although a definitive consensus motif has not been universally established, ULK1 has been reported to phosphorylate key autophagy proteins such as ATG13 and beclin-1 in regions that conform to this serine/hydrophobic preference (zachari2017themammalianulk1 pages 11-12).
5. Structure  
   ULK1 is a large protein of approximately 1050 amino acids comprising several distinct regions. The N-terminal region contains the catalytic kinase domain, which adopts a canonical bilobal fold with an N-lobe that includes a glycine-rich P-loop for ATP binding and a C-lobe that houses the activation loop. This activation loop contains key phosphorylation sites, most notably Thr180, which is critical for the catalytic activity and proper alignment of the active site (zhang2018unc51likekinase1 pages 1-2, kumar2020apancancerassessment pages 1-2). Following the kinase domain, ULK1 possesses a proline/serine-rich linker region that is largely unstructured and implicated in mediating protein–protein interactions. The C-terminal domain functions in assembling the ULK complex by providing binding sites for key regulatory proteins such as ATG13, FIP200, and ATG101 (chaikuad2019conservationofstructure pages 4-7, randhawa2015unc51likekinase pages 1-2). In addition, the structural studies reveal that ULK1 displays features common to kinases, including a conserved catalytic lysine (K46) that forms a salt bridge with a glutamate (E63) in the C-helix, as well as typical motifs such as DFG and APE, thereby firmly placing its catalytic mechanism within that established for serine/threonine kinases (kumar2020apancancerassessment pages 3-4, zachari2017themammalianulk1 pages 5-6).
6. Regulation  
   ULK1 activity is modulated by a network of post-translational modifications that integrate upstream signals from nutrient and energy sensors. Under nutrient‐rich conditions, mTORC1 phosphorylates ULK1 (for example at Ser757) to inhibit its activity, thereby suppressing autophagy. In contrast, under starvation conditions, the AMP-activated protein kinase (AMPK) phosphorylates ULK1 at residues including Ser317, Ser555, and Ser777, which activates ULK1 and triggers the autophagic process (zhang2018unc51likekinase1 pages 2-4, zachari2017themammalianulk1 pages 7-9). ULK1 undergoes autophosphorylation at Thr180, a modification that is essential for achieving the correct active conformation of its kinase domain (chaikuad2019conservationofstructure pages 7-10, dorsey2009mappingthephosphorylation pages 3-4). In addition, ULK1-mediated phosphorylation events participate in feedback loops; ULK1 has been reported to phosphorylate AMPK subunits (PRKAA1, PRKAB2, and PRKAG1) leading to a reduction in AMPK activity, and it may also phosphorylate components such as ATG13 and RPTOR, the latter linking ULK1 function to mTORC1 signaling (zhang2018unc51likekinase1 pages 2-4, Information section). Further regulation of ULK1 includes ubiquitination by E3 ligases like KLHL20 and acetylation by TIP60, which together modulate ULK1 stability and turnover during prolonged starvation (zhang2018unc51likekinase1 pages 2-4).
7. Function  
   ULK1 functions as an essential regulator of autophagy, a catabolic pathway that degrades cytosolic components to maintain cellular homeostasis under metabolic stress. Upon nutrient deprivation, ULK1 becomes activated and initiates the formation of the autophagophore by phosphorylating a set of substrates, including members of the VPS34 lipid kinase complex, which is responsible for generating phosphatidylinositol 3-phosphate (PI3P) and recruiting downstream autophagy proteins (chaikuad2019conservationofstructure pages 1-4, zachari2017themammalianulk1 pages 1-3). In addition, ULK1 is involved in regulatory feedback loops with mTORC1, acting downstream of AMPK while also modulating components of the mTOR signaling pathway, thereby linking cellular energy status with autophagic activity (zhang2018unc51likekinase1 pages 2-4, Information section). ULK1 is ubiquitously expressed in mammalian tissues and contributes to early steps of neuronal differentiation; its activity is critical for autophagosome biogenesis as well as for functions in selective autophagy such as mitophagy, where it phosphorylates specific substrates like FUNDC1 (Information section, zachari2017themammalianulk1 pages 7-9).
8. Other Comments  
   Several small-molecule inhibitors and experimental chemical probes have been developed to target ULK1, including SBI0206965, MRT68921, and compound 6, which inhibit its kinase activity. Structural studies have revealed that ULK1 possesses a flexible ATP-binding pocket with plasticity that allows dual targeting of ULK1 and its paralog ULK2; however, some inhibitors show off-target effects on kinases like Aurora A (chaikuad2019conservationofstructure pages 12-15, xiang2020targetingautophagyrelatedprotein pages 1-5). ULK1 is implicated in a range of disease contexts, with dysregulation of its autophagic function being associated with cancer, neurodegenerative disorders, and lysosomal storage diseases. Notable missense mutations in ULK1 found in cancer, as identified in pan-cancer analyses, affect kinase activity and protein stability, and these mutations have been characterized using molecular dynamics and free energy calculations (kumar2020apancancerassessment pages 10-11, kumar2020apancancerassessment pages 13-14). Furthermore, ULK1 is involved in feedback regulatory loops with mTORC1 and AMPK, and its interaction with regulatory proteins such as ATG13 and FIP200 is crucial for autophagy initiation (wong2013theulk1complex pages 1-2, zachari2017themammalianulk1 pages 1-3). Disease association data from Open Targets indicate that ULK1 is linked to lysosomal storage diseases, Parkinson disease, multiple sclerosis, Alzheimer disease, and other neurodegenerative conditions based on evidence from affected pathways and CRISPR screens (OpenTargets Search: -ULK1).
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