Phylogeny  
ULK1 belongs to the CaMK‐group, ULK sub-family of protein kinases (Khamrui et al., 2019; Kumar & Papaleo, 2020). It is the mammalian orthologue of the Atg1/UNC-51 lineage that spans budding yeast (Atg1), nematode (UNC-51), fly (Atg1), plant (Atg1), mouse (Ulk1/Ulk2) and human (ULK2/ULK3/ULK4/STK36) (Zachari & Ganley, 2017; Alers et al., 2011). ULK1 and ULK2 share ~78 % identity across the kinase domain, accounting for their partial functional redundancy (Zachari & Ganley, 2017).

Reaction Catalyzed  
ATP + [protein]-Ser/Thr ⇌ ADP + [protein]-O-phospho-Ser/Thr (Lin & Hurley, 2016; Chen et al., 2014).

Cofactor Requirements  
Catalytic activity is Mg²⁺-dependent; in vitro assays typically contain 20 mM MgCl₂ (Ouyang et al., 2018).

Substrate Specificity  
Prefers a hydrophobic-X-Ser(Thr)-hydrophobic motif, a pattern found in autophagy factors (Lin & Hurley, 2016; Zachari & Ganley, 2017). Confirmed cellular substrates that match this motif include ATG13, FIP200, ATG101, BECN1 and ATG9 (Unknown Author, 2019; Xiang et al., 2020).

Structure  
Domain organisation: N-terminal kinase domain (residues 8–280), an extended Pro/Ser-rich intrinsically disordered region (279–828) and a C-terminal tandem MIT/EAT domain (828–1050) that binds ATG13 and FIP200 (Kumar & Papaleo, 2020; Lin & Hurley, 2016; Hama et al., 2025).  
Catalytic motifs: HRD¹³⁶-¹³⁸, DFG¹⁶⁵-¹⁶⁷, APE¹⁸⁹-¹⁹¹; Lys⁴⁶–Glu⁶³ salt bridge; gatekeeper Met⁹². The activation loop (163–200) contains Thr¹⁸⁰, the autophosphorylation site essential for activity (Lin & Hurley, 2016). The regulatory spine is formed by Leu⁶⁷-His¹³⁶-Phe¹⁶⁶-Asp²⁰³ (Kumar & Papaleo, 2020).  
Structural data: crystal structures of the isolated kinase domain in complex with inhibitors are available (PDB 4WNO, 4WNP, 5CI6, 5CI7) (Lin & Hurley, 2016; Kumar & Papaleo, 2020).

Regulation  
Phosphorylation  
• AMPK activates ULK1 by phosphorylating Ser³¹⁷, Ser⁵⁵⁵ and Ser⁷⁷⁷ (Chen et al., 2014; Zachari & Ganley, 2017).  
• mTORC1 inhibits ULK1 via Ser⁷⁵⁷ (Chen et al., 2014; Zachari & Ganley, 2017).  
• Autophosphorylation on Thr¹⁸⁰ optimises catalytic competence (Lin & Hurley, 2016).  
• PP2A-B55α and PPM1D dephosphorylate Ser⁶³⁷ (Zachari & Ganley, 2017).

Other post-translational modifications  
Acetylation of Lys¹⁶² by TIP60 (Chen et al., 2014); ubiquitination by TRAF6 (activating) and by Cul3-KLHL20 or NEDD4L (degrading) (Chen et al., 2014; Zachari & Ganley, 2017).

Protein interactions  
The ATG13-FIP200 scaffold promotes ULK1 trans-autophosphorylation (Unknown Author, 2019). Association with RPTOR couples nutrient status to mTORC1-mediated inhibition (Chen et al., 2014).

Function  
Broadly expressed, with highest levels in tissues demanding robust autophagy; ULK2 can compensate in certain cancers (Kumar & Papaleo, 2020). ULK1 forms the core initiation complex ULK1–ATG13–FIP200–ATG101 that localises to the phagophore and triggers autophagosome biogenesis (Zachari & Ganley, 2017).  
Upstream regulators: AMPK, mTORC1, PKCα and p38 MAPK (Xiang et al., 2020; Chen et al., 2014).  
Downstream substrates: ATG13, FIP200, ATG101, BECN1 (Ser14), VPS34, ATG14L, ATG9 (Ser14), ATG4B (Ser316) and the mitophagy receptor FUNDC1 (Ser17) (Zachari & Ganley, 2017; Xiang et al., 2020). Through these targets ULK1 integrates nutrient and energy cues upstream of the PIK3C3/VPS34 complex to coordinate bulk and selective autophagy (Zachari & Ganley, 2017; Chen et al., 2014).

Inhibitors  
ATP-competitive inhibitors include MRT68921 and the selective ULK1/2 inhibitor SBI-0206965 (Chen et al., 2014; Zachari & Ganley, 2017; Xiang et al., 2020). Additional co-crystal ligands have been captured in PDB entries 4WNO, 4WNP, 6QAS and 6MNH (Kumar & Papaleo, 2020).

Other Comments  
High ULK1 expression correlates with poor prognosis in renal and nasopharyngeal carcinoma, and pharmacological inhibition sensitises acute myeloid leukaemia cells to therapy (Chen et al., 2014; Kumar & Papaleo, 2020). In neurodegeneration, C9orf72 mutations impede ULK1 recruitment in amyotrophic lateral sclerosis, whereas Huntingtin serves as a scaffold for selective autophagy (Zachari & Ganley, 2017). Cancer-associated mutations cluster at the gatekeeper Met⁹² and activation-loop residues, altering inhibitor sensitivity (Kumar & Papaleo, 2020).

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