## Phylogeny

• SMG1 is a member of the phosphatidylinositol-3-kinase-related kinase (PIKK) family that also contains ATM, ATR, DNA-PKcs, mTOR and TRRAP (ariaspalomo2011thenonsensemediatedmrna pages 1-3).  
• Kinome surveys position SMG1 within the ATM/ATR branch of the human kinome tree (langer2021cryoemreconstructionsof pages 19-19).  
• Verified orthologs exist in Mus musculus (Smg1), Drosophila melanogaster (Smg1) and Caenorhabditis elegans (smg-1) (langer2021cryoemreconstructionsof pages 17-18).  
• No SMG1 ortholog is detected in Saccharomyces cerevisiae (langer2021cryoemreconstructionsof pages 19-19).

## Reaction Catalyzed

ATP + protein-L-Ser/Thr([S/T]Q) → ADP + protein-L-phospho-Ser/Thr([pS/pT]Q) (langer2020structureofsubstratebound pages 2-5).

## Cofactor Requirements

Catalytic activity requires Mg²⁺, as shown by in-vitro kinase assays performed in the presence of MgCl₂ (langer2020structureofsubstratebound pages 9-10).

## Substrate Specificity

• Strict preference for serine or threonine followed immediately by glutamine, defining a [S/T]Q consensus (langer2020structureofsubstratebound pages 6-9).  
• Peptide-library profiling indicates strong enrichment of a hydrophobic residue, particularly leucine, at the −1 position, generating an optimal L-[S/T]Q motif (langer2021cryoemreconstructionsof pages 17-18).  
• Canonical sites in UPF1 include Ser1073, Ser1078, Ser1096 and Ser1116, all embedded in LSQ motifs (langer2020structureofsubstratebound pages 2-5).

## Structure

• Domain organisation: N-terminal HEAT repeats (~1 000 aa); FAT domain; PI3K-like kinase domain (~370 aa); FATC tail; unique C-terminal insertion (C-insertion/PRD) >1 000 aa (deniaud2015anetworkof pages 2-3).  
• Cryo-EM at 2.9 Å reveals a two-part architecture with a flexible HEAT “arch” and a compact head containing FAT, kinase and FATC domains (langer2020structureofsubstratebound pages 2-5).  
• The catalytic loop and activation segment adopt the conserved PIKK configuration and coordinate ATP with two Mg²⁺ ions (langer2021cryoemreconstructionsof pages 1-2).  
• The C-insertion folds back across the substrate path, creating an intrinsic autoinhibitory element (ariaspalomo2011thenonsensemediatedmrna pages 1-3).  
• Regulatory cofactors: the SMG9 G-domain grips the HEAT arch, while the SMG8 C-terminus tethers the C-insertion, stabilising the inhibited conformation (langer2021cryoemreconstructionsof pages 8-10).  
• Substrate-bound maps position an extended UPF1 peptide across the active-site cleft, with the +1 glutamine anchoring the chain for precise phosphotransfer (langer2020structureofsubstratebound pages 6-9).

## Regulation

Post-translational modifications  
• Autophosphorylation at Ser1096 has been mapped and promotes full kinase activity (langer2020structureofsubstratebound pages 1-2).  
• ATM-dependent phosphorylation of SMG1 links the enzyme to DNA-damage signalling (langer2020structureofsubstratebound pages 14-14).

Protein-protein and allosteric control  
• SMG1 forms the SMG1C complex with SMG8 and SMG9; the SMG8 C-terminus and SMG1 C-insertion act cooperatively to impose autoinhibition (zhu2019cryoemstructureof pages 6-7).  
• Removal or truncation of SMG8 or of the C-insertion yields a hyperactive kinase, demonstrating negative regulation in trans and in cis (langer2021cryoemreconstructionsof pages 8-10).  
• SMG9 stabilises SMG8 incorporation and maintains the inhibited state (zhu2019cryoemstructureof pages 2-4).

## Function

Expression  
• Transcriptomic and proteomic surveys show broad expression of SMG1 across human tissues, with elevated levels in neural tissues (langer2020structureofsubstratebound pages 13-14).

Signalling roles  
• Central kinase in nonsense-mediated mRNA decay: phosphorylates UPF1 within the SURF complex (SMG1-UPF1-eRF1-eRF3) assembled on stalled ribosomes (yamashita2013roleofsmg‐1‐mediated pages 2-3).  
• Phospho-UPF1 recruits SMG5/6/7 and associates with UPF2/UPF3 to trigger degradation of premature-termination-codon transcripts (deniaud2015anetworkof pages 1-2).  
• Acts in genotoxic-stress response; can phosphorylate p53 and contributes to optimal p53 activation following DNA damage (langer2020structureofsubstratebound pages 14-14).

Interaction network  
• Confirmed partners include UPF1, UPF2, UPF3, SMG8, SMG9, eRF1 and eRF3 (ariaspalomo2011thenonsensemediatedmrna pages 6-7).

## Inhibitors

• SMG1i is an ATP-competitive small molecule that binds the kinase active site and stabilises the SMG1-SMG8 autoinhibited conformation, as visualised by cryo-EM (langer2021cryoemreconstructionsof pages 8-10).

## Other Comments

• Pathogenic variants in SMG1 are associated with microcephaly, leukodystrophy and cellular radiosensitivity (langer2021cryoemreconstructionsof pages 18-19).  
• Mutations in SMG8 or SMG9 that disrupt SMG1C assembly produce related congenital anomalies (langer2021cryoemreconstructionsof pages 18-19).

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