## Phylogeny

• Belongs to the CMGC kinase group and segregates with the atypical MAPK sub-family distinct from canonical ERK/JNK/p38 branches (lau2019regulationofhuman pages 4-7).  
• Human MAPK15 (ERK8) and rat ERK7 share 69 % overall and 82 % kinase-domain sequence identity; both proteins are unified under the HGNC symbol MAPK15 (dahm2024atypicalmapksin pages 7-8).  
• Additional orthologs are reported in mouse, Caenorhabditis elegans and Xenopus laevis, indicating conservation from nematodes to vertebrates (dahm2024atypicalmapksin pages 13-15, rossi2016mapk15upregulationpromotes pages 1-2).

## Reaction Catalyzed

ATP + protein-Ser/Thr ⇌ ADP + protein-O-phospho-Ser/Thr (abe2002erk8anew pages 12-12).

## Cofactor Requirements

Catalytic activity requires Mg²⁺ (abe2002erk8anew pages 12-12).

## Substrate Specificity

• A global consensus phosphorylation motif for MAPK15 has not been established in the cited literature (abe2002erk8anew pages 12-12).  
• Validated substrates and modification sites:  
– c-Jun, Ser63/Ser73 (dahm2024atypicalmapksin pages 13-15).  
– ULK1, activation-loop threonine residues that enhance AMPK-dependent Ser317 phosphorylation (colecchia2018mapk15ispart pages 2-3).  
– ATG13, Ser318 downstream of ULK1 activation (colecchia2018mapk15ispart pages 11-13).  
– MAP1LC3B, reduction of inhibitory phosphorylation to promote lipidation (colecchia2012mapk15erk8stimulatesautophagy pages 2-3).  
– IκBα, Ser32/Ser36 leading to NF-κB activation (lau2019regulationofhuman pages 11-12).  
– CapZIP within the MAPK15/Dishevelled axis that controls ciliogenesis (lau2019regulationofhuman pages 12-13).

## Structure

• N-terminal serine/threonine kinase domain (~aa 1–300) contains the canonical VAIK lysine (Lys42) and the TEY activation loop (Thr175/Tyr177); mutation of Lys42 or either TEY residue abrogates activity (dahm2024atypicalmapksin pages 7-8).  
• C-terminal regulatory region harbours:  
– Two SH3-binding PXXXP motifs mediating c-Src interaction (abe2002erk8anew pages 1-1).  
– A PCNA-interacting PIP box (aa 297-308) and multiple additional PXXXP repeats that promote chromatin binding (dahm2024atypicalmapksin pages 1-3).  
– A conserved LC3-interacting region (aa 300-373) required for docking on autophagosomes (colecchia2012mapk15erk8stimulatesautophagy pages 8-10).  
– Two LXXLL motifs for nuclear receptor binding, a nuclear localisation sequence and a di-RG motif implicated in protein interactions (lau2019regulationofhuman pages 4-7).  
• No experimental crystal structure for human MAPK15 is available; a computational model of the kinase domain has been generated for mechanistic studies (lau2019regulationofhuman pages 12-13).

## Regulation

• Autophosphorylation of Thr175 and Tyr177 within the TEY motif activates the kinase; either-site mutation eliminates activity (dahm2024atypicalmapksin pages 7-8).  
• Additional phosphorylation sites mapped by mass spectrometry include Ser192, Ser331, Thr352, Ser362, Ser379, Thr381 and Ser415 (lau2019regulationofhuman pages 7-8).  
• Arg449 methylation modulates SH3-mediated interactions (lau2019regulationofhuman pages 7-8).  
• The N-terminal 20 residues confer ubiquitin-proteasome–dependent turnover; specific ubiquitin-ligating enzymes remain unidentified (dahm2024atypicalmapksin pages 7-8).  
• Two C-terminal SH3 motifs recruit c-Src; Src kinase activity enhances MAPK15 activation (abe2002erk8anew pages 1-1).  
• Kinase activity is further modulated by serum factors, endogenous phosphatases, nutrient starvation and oxidative stress (colecchia2012mapk15erk8stimulatesautophagy pages 6-8).  
• Oncogenic BCR-ABL1 directly binds and activates MAPK15, augmenting autophagy and proliferation (colecchia2015mapk15mediatesbcrabl1induced pages 10-14).

## Function

• Highest basal expression detected in lung, kidney and testis; strong up-regulation in male germ-cell tumours (abe2002erk8anew pages 1-1, rossi2016mapk15upregulationpromotes pages 1-2).  
• Autophagy: binds LC3B, GABARAP and GABARAPL1 via its LIR to drive basal and starvation-induced autophagosome formation and SQSTM1 degradation (colecchia2012mapk15erk8stimulatesautophagy pages 2-3).  
• Early autophagy initiation: integrates into the ULK complex and promotes ULK1/ATG13 phosphorylation; catalytic inactivation or ULK1/2 knock-down blocks this step (colecchia2018mapk15ispart pages 4-5).  
• Mitophagy: recruits damaged mitochondria to autophagosomes, limits mitochondrial ROS and prevents oxidative-stress-induced senescence (unknownauthors2022mapk15inducesmitophagy pages 1-6, franci2022mapk15protectsfrom pages 8-9).  
• Genome integrity: binds PCNA through the PIP box, preventing PCNA degradation and limiting DNA damage (dahm2024atypicalmapksin pages 1-3).  
• Ciliogenesis: phosphorylates CapZIP downstream of Dishevelled, regulating primary cilium assembly (lau2019regulationofhuman pages 12-13).  
• Secretion control: under amino-acid starvation, shifts ULK1 activity toward SEC16A phosphorylation, inhibiting ER-to-Golgi trafficking (colecchia2018mapk15ispart pages 5-7).  
• Signal transduction: phosphorylates IκBα to activate NF-κB (lau2019regulationofhuman pages 11-12) and c-Jun to enhance tumour cell migration and invasion (dahm2024atypicalmapksin pages 13-15).  
• Oncogenesis: required for BCR-ABL1-driven autophagy, proliferation and tumour formation in CML models (colecchia2015mapk15mediatesbcrabl1induced pages 10-14) and supports growth of colon, gastric and germ-cell tumours (rossi2016mapk15upregulationpromotes pages 1-2, colecchia2018mapk15ispart pages 8-10).

## Inhibitors

• Ro-318220, a broad PKC inhibitor, suppresses MAPK15-dependent autophagy in cultured cells (colecchia2012mapk15erk8stimulatesautophagy pages 8-10, colecchia2015mapk15mediatesbcrabl1induced pages 10-14).  
• SU6656 attenuates MAPK15-driven phosphorylation events within the ULK1 pathway (colecchia2018mapk15ispart pages 2-3).  
• Several ATP-competitive CK2 inhibitors display off-target activity toward MAPK15 in biochemical assays; potency values are not reported in the cited literature (lau2019regulationofhuman pages 12-13).  
• No highly selective small-molecule inhibitor has been described (colecchia2018mapk15ispart pages 5-7).

## Other Comments

• Copy-number gain and over-expression documented in gastric, colon and male germ-cell tumours (rossi2016mapk15upregulationpromotes pages 1-2, colecchia2018mapk15ispart pages 8-10).  
• Implicated in chronic obstructive pulmonary disease and neuroprotection in Parkinson’s disease models through regulation of mitophagy (unknownauthors2022mapk15inducesmitophagy pages 24-28).  
• Four nonsynonymous human variants—p.A54P, p.T221K, p.P358L and p.S505P—map to conserved regions and may influence kinase function (lau2019regulationofhuman pages 7-8).

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