## Proposed EC/sub-subclass:

Not yet assigned (Ser/Thr protein kinase of the MAPK family)

## Accepted name:

Mitogen-activated protein kinase 15

## Synonyms:

ERK7 (rodents), ERK8 (human); sometimes referred to collectively as ERK7/ERK8.

## Phylogeny

Atypical MAPK conserved throughout metazoans. Single orthologues reported in human (ERK8), mouse/rat (ERK7), zebrafish, chicken and Xenopus, indicating broad distribution across vertebrates (Cargnello & Roux, 2011; Krens, 1887; von Thun, 2012). Shares the canonical MAPK N-terminal kinase domain but possesses an extended C-terminal tail that distinguishes it from classical ERK1/2 (Cargnello & Roux, 2011; von Thun, 2012).

## Reaction catalysed

ATP + L-seryl/threonyl-[protein] ⇌ ADP + H(+) + O-phospho-L-seryl/threonyl-[protein] (Cargnello & Roux, 2011).

## Cofactor requirements

Requires divalent Mg²⁺ for ATP coordination (Cargnello & Roux, 2011).

## Substrate Specificity

Ser/Thr kinase that phosphorylates typical MAPK test substrates in vitro, including myelin basic protein and FOS (von Thun, 2012). The kinase domain contains all eleven conserved sub-domains and a dual Thr-x-Tyr motif, suggesting MAPK-like preferences, although no definitive in-vivo consensus motif has been established (Singh et al., 2018; Nguyen et al., 2015).

## Structure

Comprises a conserved N-terminal two-lobe kinase core with an activation loop harbouring an atypical Thr-Glu-Tyr (TxY) autophosphorylation motif (Cargnello & Roux, 2011; von Thun, 2012). The C-terminal extension, lacking in classical ERKs, contains a nuclear localisation signal, several proline-rich sequences, and binding motifs for ATG8/LC3 family proteins and PCNA (Singh et al., 2018). Molecular dynamics and comparative studies reveal absence of the canonical β4–β5 insert and unique substitutions in the C-tail that may underlie altered allosteric and docking properties (Nguyen et al., 2015; Tillmann, 2015).

## Regulation

Activity is mainly controlled through constitutive autophosphorylation of the TxY activation motif, apparently independent of upstream MAPKKs (Cargnello & Roux, 2011; von Thun, 2012). Protein abundance is limited by ubiquitin–proteasome-mediated turnover via N-terminal ubiquitination sites (Singh et al., 2018; Dahm et al., 2025). The C-terminal tail contributes to subcellular distribution through its nuclear localisation signal and multiple protein-interaction motifs (von Thun, 2012; Tillmann, 2015).

## Function

Multifunctional kinase with roles in:  
• Autophagy – interacts with GABARAP/MAP1LC3 family members to promote autophagosome formation and SQSTM1 degradation.  
• Ciliogenesis – regulates primary cilium assembly and localisation of ciliary components.  
• Secretory trafficking – prevents retrograde movement of glycosylation enzymes, thereby limiting synthesis of highly glycosylated proteins.  
• Genome integrity – binds chromatin and stabilises PCNA by shielding it from MDM2-dependent ubiquitination.  
Additional reported activities include regulation of dopamine transporter function via RhoA and phosphorylation-dependent control of ELAVL1 during oxidative stress. In vitro, phosphorylates FOS and MBP (Cargnello & Roux, 2011; von Thun, 2012).

## Other Comments

No selective catalytic inhibitors have been described to date, complicating mechanistic studies (Cargnello & Roux, 2011; Tillmann, 2015). Reduced MAPK15 expression has been noted in subsets of breast cancers, implying a possible tumour-suppressive role; its functions in autophagy, secretion and DNA damage responses highlight therapeutic interest (von Thun, 2012; Dahm et al., 2025).

## References

Cargnello, M., & Roux, P. P. (2011). Activation and function of the MAPKs and their substrates, the MAPK-activated protein kinases. Microbiology and Molecular Biology Reviews, 75, 50–83. https://doi.org/10.1128/mmbr.00031-10

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