## Phylogeny

MAPK3 (ERK1) is a member of the CMGC group of protein kinases and one of two closely related conventional ERK isoforms (ERK1/ERK2 share ≈83 % amino-acid identity). Orthologues are detected from yeast to vertebrates, underscoring an ancient, highly conserved signalling module that arose early in eukaryotic evolution and was later duplicated to yield the ERK1 and ERK2 genes now present in mammals (Cargnello & Roux, 2011; Keshet & Seger, 2010; Li et al., 2011; Krishna & Narang, 2008).

## Reaction Catalyzed

ATP + L-seryl/threonyl-[protein] ⇌ ADP + H⁺ + O-phospho-L-seryl/threonyl-[protein] (Pearson et al., 2001; Cargnello & Roux, 2011).

## Cofactor Requirements

Mg²⁺ is required for ATP binding and catalysis (Cargnello & Roux, 2011; Pearson et al., 2001).

## Substrate Specificity

ERK1 is a proline-directed Ser/Thr kinase that preferentially phosphorylates motifs containing Ser/Thr followed immediately by Pro (p[ST]P). A conserved docking groove further guides recognition of numerous substrates, including transcription factors ELK1, ATF2 and other regulators of cytoskeletal dynamics (Cargnello & Roux, 2011; Guo et al., 2020; Pearson et al., 2001; Krishna & Narang, 2008).

## Structure

The enzyme adopts the canonical bilobed protein-kinase fold: an N-terminal β-sheet-rich lobe with a glycine-rich loop that coordinates ATP, and a predominantly helical C-terminal lobe that houses the substrate-binding site. The activation loop bears a Thr-Glu-Tyr (TEY) motif whose dual phosphorylation is essential for full activity. Common docking (CD) sites on the kinase surface mediate interactions with upstream MEK1/2, substrates and scaffold proteins. Crystal structures and AlphaFold models show that activation-loop phosphorylation repositions catalytic residues and completes the substrate-binding cleft (Cargnello & Roux, 2011; Keshet & Seger, 2010; Lavoie et al., 2020; Kirsch, 2021).

## Regulation

• Activation: Dual phosphorylation of the TEY motif by MEK1/2 induces the active conformation (Cargnello & Roux, 2011; Kyriakis & Avruch, 2012).  
• Spatial control: Scaffold proteins (e.g., KSR) tether ERK1 to its activators and substrates, enhancing signal fidelity (Lavoie et al., 2020; Keshet & Seger, 2010).  
• Inactivation: Dual-specificity phosphatases (e.g., DUSP6) dephosphorylate the activation loop and terminate signalling (Theodosiou & Ashworth, 2002; Raman et al., 2007).  
• Feedback and additional modulators fine-tune amplitude and duration of kinase activity (Guo et al., 2020; Kirsch, 2021).

## Function

Upon activation, ERK1 translocates to the nucleus and phosphorylates transcription factors (ELK1, ATF2, FOS), regulating gene programmes that drive cell growth, differentiation and survival. Cytosolic substrates control translation, cytoskeletal reorganisation and endosomal trafficking. ERK1 participates in receptor tyrosine kinase pathways (e.g., EGF, PDGF, KIT ligand) and is involved in cell-cycle control during mitosis and meiosis. High expression levels are noted in brain, skeletal muscle, thymus and heart (Cargnello & Roux, 2011; Guo et al., 2020; Lavoie et al., 2020; Lai, 2015).

## Inhibitors

Multiple small-molecule agents inhibit the MAPK/ERK pathway by targeting MEK or ERK directly; several are in clinical evaluation for cancers with hyperactive ERK signalling (Samadani et al., 2015; Roberts & Der, 2007).

## Other Comments

ERK1 phosphorylates >160 identified substrates, underscoring its role as a central signalling hub. Dysregulated ERK activity contributes to oncogenesis, developmental disorders and other pathologies, making MAPK3 an attractive therapeutic target (Cargnello & Roux, 2011; Guo et al., 2020).

## 9. 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

Guo, Y.-J., Pan, W.-W., Liu, S.-B., Shen, Z.-F., Xu, Y., & Hu, L.-L. (2020). ERK/MAPK signalling pathway and tumorigenesis (review). Experimental and Therapeutic Medicine, 19, 1997-2007. https://doi.org/10.3892/etm.2020.8454

Keshet, Y., & Seger, R. (2010). The MAP kinase signalling cascades: a system of hundreds of components regulates a diverse array of physiological functions. Methods in Molecular Biology, 661, 3-38. https://doi.org/10.1007/978-1-60761-795-2\_1

Kirsch, K. P. (2021). Non-canonical interactions of the Mitogen Activated Protein (MAP) kinases (PhD thesis). Eötvös Loránd University. https://doi.org/10.15476/elte.2021.040

Krishna, M., & Narang, H. (2008). The complexity of mitogen-activated protein kinases (MAPKs) made simple. Cellular and Molecular Life Sciences, 65, 3525-3544. https://doi.org/10.1007/s00018-008-8170-7

Kyriakis, J. M., & Avruch, J. (2012). Mammalian MAPK signal transduction pathways activated by stress and inflammation: a 10-year update. Physiological Reviews, 92, 689-737. https://doi.org/10.1152/physrev.00028.2011

Lai, S. (2015). Investigations of the origin, regulation, and substrate specificities of protein kinases in the human kinome (Doctoral dissertation). https://doi.org/10.14288/1.0167195

Lavoie, H., Gagnon, J., & Therrien, M. (2020). ERK signalling: a master regulator of cell behaviour, life and fate. Nature Reviews Molecular Cell Biology, 21, 607-632. https://doi.org/10.1038/s41580-020-0255-7

Li, M., Liu, J., & Zhang, C. (2011). Evolutionary history of the vertebrate mitogen activated protein kinases family. PLoS ONE, 6, e26999. https://doi.org/10.1371/journal.pone.0026999

Pearson, G., Robinson, F., Gibson, T., Xu, B.-E., Karandikar, M., Berman, K., & Cobb, M. (2001). Mitogen-activated protein (MAP) kinase pathways: regulation and physiological functions. Endocrine Reviews, 22, 153-183. https://doi.org/10.1210/er.22.2.153

Raman, M., Chen, W., & Cobb, M. H. (2007). Differential regulation and properties of MAPKs. Oncogene, 26, 3100-3112. https://doi.org/10.1038/sj.onc.1210392

Roberts, P. J., & Der, C. J. (2007). Targeting the Raf-MEK-ERK mitogen-activated protein kinase cascade for the treatment of cancer. Oncogene, 26, 3291-3310. https://doi.org/10.1038/sj.onc.1210422

Samadani, R., Zhang, J., Brophy, A., Oashi, T., Priyakumar, U. D., Raman, E. P., … Shapiro, P. (2015). Small-molecule inhibitors of ERK-mediated immediate early gene expression and proliferation of melanoma cells expressing mutated BRAF. Biochemical Journal, 467, 425-438. https://doi.org/10.1042/BJ20131571

Theodosiou, A., & Ashworth, A. (2002). MAP kinase phosphatases. Genome Biology, 3, reviews3009.1-3009.10. https://doi.org/10.1186/gb-2002-3-7-reviews3009