## Phylogeny

MAPK6/ERK3 is classified within the CMGC group of protein kinases, alongside CDK, GSK3, and CLK families (unknownauthors2015identificationofnovel pages 13-16, cheng1996erk3isa pages 7-8, widmann1999mitogenactivatedproteinkinase pages 1-2). It is an atypical member of the mitogen-activated protein kinase (MAPK) family, forming a distinct subgroup with its close homolog ERK4 (coulombe2007atypicalmitogenactivatedprotein pages 2-4, unknownauthors2015identificationofnovel pages 13-16). This ERK3/ERK4 subfamily resides on a separate evolutionary branch from conventional MAPKs like ERK1/2, p38, JNK, and ERK5, and is thought to have arisen from a gene duplication event of a common ancestor (coulombe2007atypicalmitogenactivatedprotein pages 2-4, schumacher2004scaffoldingbyerk3 pages 10-10, cheng1996erk3isa pages 7-8). This classification is consistent with the kinome analysis by Manning et al. (coulombe2007atypicalmitogenactivatedprotein pages 2-4, krens2006functionsofthe pages 7-7). While it shares approximately 42-50% amino acid identity with ERK1 in the kinase domain, its unique structural motifs and evolutionary lineage confirm its status as an atypical MAPK (bogoyevitch2004countingonmitogenactivated pages 2-3, coulombe2007atypicalmitogenactivatedprotein pages 2-4, unknownauthors2015identificationofnovel pages 19-23).

MAPK6 orthologs are conserved in vertebrates, with orthologs identified in human, mouse, rat, *Xenopus*, and zebrafish, and predicted genes in chicken (krens2006functionsofthe pages 1-3, krens2006functionsofthe pages 4-4). The gene is restricted to chordates/vertebrates and is absent in invertebrates and plants (coulombe2007atypicalmitogenactivatedprotein pages 2-4, pearson2001mitogenactivatedprotein(map) pages 5-6).

## Reaction Catalyzed

ATP + [a protein-serine/threonine] = ADP + [a protein-serine/threonine] phosphate (chen2001mapkinases. pages 2-3, unknownauthors2015identificationofnovel pages 19-23).

## Cofactor Requirements

As a serine/threonine kinase within the MAPK family, catalytic activity requires a divalent cation, primarily Mg²⁺ (chen2001mapkinases. pages 2-3, unknownauthors2015identificationofnovel pages 19-23).

## Substrate Specificity

A large-scale study of the human serine/threonine kinome determined the optimal substrate motifs for 303 kinases, including MAPK6 (johnson2023anatlasof pages 1-2). However, the specific consensus substrate motif and amino acid preferences for MAPK6 are not detailed in the provided context (johnson2023anatlasof pages 1-2).

## Structure

The human MAPK6/ERK3 protein is composed of 721 amino acids (~100 kDa) and features three primary domains: an N-terminal kinase domain, a highly conserved C34 domain that serves as a docking region, and an unusually long and flexible C-terminal tail of approximately 178-400 amino acids (elkhadragy2024roleofthe pages 1-2, unknownauthors2015identificationofnovel pages 19-23, bogoyevitch2004countingonmitogenactivated pages 2-3, dahm2024atypicalmapksin pages 3-4). The C-terminal tail is not resolved in the experimental X-ray crystal structure (PDB ID: 6YKY) and is predicted by AlphaFold to be intrinsically disordered, with low confidence scores (dahm2024atypicalmapksin pages 3-4).

The kinase domain contains several unique features that distinguish it from conventional MAPKs. The activation loop contains a Ser-Glu-Gly (S-E-G) motif with a single phospho-acceptor site (Ser189), replacing the canonical Thr-X-Tyr (T-X-Y) motif (bogoyevitch2004countingonmitogenactivated pages 2-3, coulombe2007atypicalmitogenactivatedprotein pages 2-4, elkhadragy2024roleofthe pages 1-2). In kinase subdomain VIII, a Ser-Pro-Arg (S-P-R) motif replaces the conserved Ala-Pro-Glu (A-P-E) motif; ERK3 is the only human kinase with an arginine at this position, which likely plays a structural role in stabilizing the C-terminal lobe (unknownauthors2015identificationofnovel pages 19-23, coulombe2007atypicalmitogenactivatedprotein pages 2-4, cheng1996erk3isa pages 1-2). Although ERK3 contains a C-helix and hydrophobic spine, these elements show atypical features that may underlie its distinct regulatory mechanisms (dahm2024atypicalmapksin pages 1-3).

## Regulation

MAPK6/ERK3 regulation occurs primarily at the level of protein stability, which is governed by multiple post-translational modifications (PTMs), rather than through a canonical upstream kinase cascade (krens2006functionsofthe pages 1-3, schumacher2004scaffoldingbyerk3 pages 1-2, elkhadragy2024roleofthe pages 1-2).

Phosphorylation at Ser189 in the activation loop is a key regulatory event. In resting cells, Ser189 is constitutively phosphorylated via both autophosphorylation (in *cis*), which requires the C34 domain, and phosphorylation in *trans* by group I p21-activated kinases (PAK1/2/3) (elkhadragy2024roleofthe pages 7-9, unknownauthors2015identificationofnovel pages 19-23, deleris2011activationloopphosphorylation pages 1-2). PKC-h may also phosphorylate this site (bogoyevitch2004countingonmitogenactivated pages 2-3). Phosphatases Cdc14A/B and DUSP2 dephosphorylate ERK3, modulating its activity (elkhadragy2024roleofthe pages 7-9). Additional phosphorylation at C-terminal sites by CyclinB-Cdk1 stabilizes the protein (elkhadragy2024roleofthe pages 7-9).

ERK3 is an unstable protein with a short half-life, undergoing rapid degradation via the ubiquitin-proteasome pathway (bogoyevitch2004countingonmitogenactivated pages 2-3, unknownauthors2015identificationofnovel pages 19-23). Ubiquitination at its N-terminus promotes degradation, a process that is reversed by the deubiquitinase USP20 (elkhadragy2024roleofthe pages 7-9). Protein stability is also increased by hydroxylation by PHD3 and by its interaction with the substrate MK5 (elkhadragy2024roleofthe pages 7-9, unknownauthors2015identificationofnovel pages 19-23).

## Function

MAPK6/ERK3 is ubiquitously expressed in vertebrates, with highest mRNA levels in adult skeletal muscle and brain (elkhadragy2024roleofthe pages 1-2). Its expression increases during early murine embryogenesis (bogoyevitch2004countingonmitogenactivated pages 2-3). The protein is constitutively nuclear but can also be found in the cytoplasm, at the plasma membrane, and in the Golgi/ER, and it undergoes CRM1-mediated nuclear export (cheng1996erk3isa pages 7-8, bogoyevitch2004countingonmitogenactivated pages 2-3, elkhadragy2024roleofthe pages 11-13).

The only known physiological substrate is MAPK-activated protein kinase 5 (MK5), which ERK3 phosphorylates at Thr182, leading to MK5 activation (elkhadragy2024roleofthe pages 2-4, deleris2011activationloopphosphorylation pages 1-2). The ERK3/MK5 interaction is reciprocal and forms a signaling module; MK5 also phosphorylates and stabilizes the ERK3 protein (unknownauthors2015identificationofnovel pages 19-23, schumacher2004scaffoldingbyerk3 pages 1-2). Other substrates include steroid receptor co-activator 3 (SRC-3) at Ser857 (unknownauthors2015identificationofnovel pages 19-23). Additional interacting partners include Rab31, Cdc42, Rac1, Cdk1, Cdc14A/B, and the transcription factor HNF4G (elkhadragy2024roleofthe pages 11-13, elkhadragy2024roleofthe pages 7-9).

ERK3 participates in diverse biological roles, including fetal growth, lung maturation, neuronal morphogenesis, T-cell development, angiogenesis, inflammation, and metabolism (unknownauthors2015identificationofnovel pages 19-23, elkhadragy2024roleofthe pages 1-2, elkhadragy2024roleofthe pages 2-4).

## Inhibitors

Few bona fide inhibitors of ERK3 have been described (elkhadragy2024roleofthe pages 1-2). Recently developed inhibitors serve as tools for research (elkhadragy2024roleofthe pages 11-13).

## Other Comments

MAPK6/ERK3 has dual and context-dependent roles in cancer, where it can regulate cell proliferation, migration, invasion, and chemoresistance (elkhadragy2024roleofthe pages 1-2, elkhadragy2024roleofthe pages 7-9). Cancer-associated mutations, such as L290P/V, result in increased cytosolic localization and enhanced cell migratory and invasive properties (elkhadragy2024roleofthe pages 11-13). It has also been implicated in non-malignant conditions such as autoimmune uveoretinitis, obesity, and ischemia/reperfusion injury (elkhadragy2024roleofthe pages 2-4).

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