Sequence of pp42/MAP kinase, a serine/threonine kinase regulated by tyrosine phosphorylation

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Pp42/MAP kinase (refered to here as $p42^{mapk}$) becomes enzymatically activated within 5 minutes following addition to quiescent cells of various growth and metabolic agonists (1, 2). The activated form of $p42^{mapk}$ is phosphorylated on threonine and tyrosine and both phosphorylations are required for activity (3), suggesting the enzyme serves to integrate different signaling pathways.

We purified $p42^{mapk}$ to homogeneity, and determined the sequence of the tryptic peptide which contains both of the regulatory phosphorylations (4). This sequence was found to be similar to a previously published partial sequence of a cDNA (ERK1) for another mitogen-activated protein kinase (5). Using oligonucleotides based on this sequence information, we isolated from a mouse 3T3 library a full-length cDNA which encodes $p42^{mapk}$ (Figure 1). The sequence is 85% identical to the rat ERK1 sequence at the amino acid level. However, $P42^{mapk}$ is not the murine equivalent of rat ERK1, as we also have isolated a mouse 3T3 cDNA which is 97% identical to the published ERK1 sequence. Thus, there appears to be a family of kinases related to $p42^{mapk}$, as suggested by Northern analysis using ERK1 probes (5, 6). This is the first report of a full length sequence for one of these family members.

The $p42^{mapk}$ amino acid sequence is 50% identical to KSS1 (7) and FUS3 (8), two yeast kinases which also function in Go. Interestingly, the region in $p42^{mapk}$ which contains the regulatory phosphorylations is perfectly conserved in all four kinases, raising the possibility that both the function and the mechanisms of regulation have been evolutionarily conserved in this kinase family.

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MAPK         MAAAAAAGPEMVRGQVFDVGPRYTNLSYIGEGAYGMVCSAYDNLNKVRVAIK    52
ERK1   EPRGTAGVVPVVPGEV.V.K..P........Q.Q.........S....H.R.T.....
KSS1                    MA.TIT..IPSQ.KLVDL.......T....IHKPSGIK....  42
FUS3                    MPKRI.YNISSDFQLK.LL......V....THKPTGEI....  42

MAPK   KISPFEHQTYCQRTLREIKILLRFR-HENIIGINDIIRAPTIEQMKDVYIVQDLMETDL  109
ERK1   ................Q...G..-...V...R..L....L.A.R.............
KSS1   ..Q..SKKLFVT..I....L.RY.HE.....S.L.KV.PVS.DKLNA..L.EE.....  101
FUS3   ..E..DKPLFAL.........KH.K-.....T.FN.Q.PDSF.NFNE...I.E..Q...   99

MAPK   YKLLKTQ-----HLSNDHICYFLYQILRGLKYIHSANVLHRDLKPSNLLLNTTCDLKIC  164
ERK1   .....S.-----Q.....................................I........
KSS1   Q.VINN.NSGFST..D..VQ..T.....A..S....Q.I...I........SN....V.  160
FUS3   HRVIS..-----M..D...Q..I..T..AV.VL.GS..I..........I.SN....V.  154

MAPK   DFGLARVADPDHD-------HTGFLTEYVATRWYRAPEIMLNSKGYTKSIDIWSVGCIL  216
ERK1   .....I...E..-------.....................................
KSS1   ......CLASSS.---SRETLV..M..............TFQE..TAM....C....  216
FUS3   ......II.ESAADNSEPTGQQSGM.............V..T.AK.SRAM.V..C....  213

MAPK   AEMLSNRPIFPGKHYLDQLNHILGILGSP-SQEDLNCIINLKARNYLLSLPHKNKVPWN  272
ERK1   ..........................-.........M......Q...S.T..A.A
KSS1   ...V.GK.L...RD.HH..WL..EV..T.-.F..F.Q.KSKR.KE.IAN..MRPPL..E  274
FUS3   ..LFLR......RD.RH..LL.F..I.T.H.DN..R..ESPR..E.IK...MYPAA.LE  270

MAPK   RLFPNAD--SKALDLLDKMLTFNPHKRIEVEQALAHPYLEQYYDPSDEPIAEAP-----  319
ERK1   K...KS.--........R......N...T..E.............T...V..E.-----
KSS1   TVWSKT.LNPDMI.......Q...D...SAAE..R....AM.H......EYPPLNLDDE  332
FUS3   KM..RVN--P.GI...QR..V.D.A...TAKE..E....QT.H..N...EG.PIPPSF-  321

MAPK   -------FKFDMELDDLPKEKLKELIFEETARFQPGYRS                     358
ERK1   --------.T...........R......Q........APEAP
KSS1   FWKLDNKIMRPE.EEEV.I.M..DMLYD.LMKTME                          368
FUS3   -------.E..HHKEA.TTKD..K..WN.IFS                             353
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Figure 1. Amino acid sequence of $p42^{mapk}$, and comparison with related kinases. conserved amino acids are marked with (.), gaps with (–) and the phosphorylation sites with (*).

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