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Editorial

Constriction of the p44/p42 MAP Kinase Pathway

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EDITORIAL NOTE

Each pathway explorer antibody minipack contains three related antibodies as part of a signaling cataract or a mixture of total and phosphorylated forms of key signaling targets. Each of the antibodies is 30 percent of the original pack size. Erk (Extracellular signal-related kinase) is a family of two, highly homologous proteins denoted as Erk1 i.e. p44, MAPK3 and Erk2 i.e. p42, MAPK1 that together function in the similar pathway. The two proteins are often referred to together as Erk1/2 or p44/p42 MAP kinase.

The Erk pathway is measured the classical, canonical MAPK (Mitogen-Activated Protein Kinase) signaling pathway. It is an evolutionarily preserved pathway that controls and is a critical regulator of the growth and survival through the promotion of cell proliferation and the prevention of apoptosis. Erk is involved in the control of many fundamental cellular procedures including cell proliferation, survival, differentiation, apoptosis, motility and metabolism. Erk is activated by growth factor stimulation of receptor tyrosine kinases (RTKs), GPCR, and/or integrin stimulation.

This activates the Ras-Raf-MEK-Erk pathway that results in the phosphorylation/activation of Erk1/2. The Raf proteins (A-Raf, B-Raf, Raf-1/c-Raf) are Ser/Thr kinases with homology to the PKC family, covering an N-terminal regulatory domain and a C-terminal catalytic domain. Raf (MAP Kinase Kinase Kinase) is the top kinase in the canonical MAPK pathway. Members of the Raf family bind to activated Ras. Ras, in its GTP-bound active state, activates the kinase activity of Raf. This results in Raf translocation to the plasma membrane and activation.

Once triggered, Raf then binds to and activates MEK by phosphorylating it on the two residue motif. It is supposed that B-Raf strength be the main activator of MEK and that Raf-1 has a role in protection against apoptosis; a process that does not require either its kinase activity or its activation of MEK. The regulation of a large number of cellular processes is dependent upon the activation state of ERK, so the controlling of this pathway could have profound effects on various diseases. Activation of Raf-1 involves phosphorylation of Ser338/339 and Tyr340/341. Activating mutations of B-Raf that disrupt its auto-inhibition loop have been implicated in a number of cancers, counting melanoma and colon cancer.

MAP Kinase/Erk Kinase (MEK), alternatively known as MKK, is a true dual-specificity kinase, in that it phosphorylates the MAP kinases (Erk1/2; p44/p42)) on both the Thr and Tyr of the activation motif TEY. In vitro, the tyrosine phosphorylation is favored, whereas in vivo both phosphorylation events appear to occur simultaneously. This proposes that an additional factor is current in cells to facilitate the reaction. MEK1 and MEK2 are triggered by phosphorylation of two serine residues (Ser218/222 in MEK1 and Ser222/226 in MEK2), which are substrates for the Raf family of kinases. Mutation of the phosphorylation sites from Ser to Asp creates a protein with constitutive kinase activity, which when spoken in cells is able to cause transformation. Involved in the transduction of mitogenic signals from the cell membrane to the nucleus. Part of the Ras-dependent signaling pathway from receptors to the nucleus. Protects cells from apoptosis arbitrated by STK3.

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