MAPK PATHWAY

The MAPK pathway is activated by extracellular stimuli such as growth factors, cytokines, and stress signals. Pathway activation leads to the coordination of a variety of responses involving gene expression, proliferation, survival, apoptosis, metabolism, and differentiation. In mammals, there are five groups of MAPKs: the extracellular signal-regulated kinases (ERKs), the c-Jun amino-terminal kinases (JNKs), the p38 isoforms, ERKs 3 and 4, and ERK5 *(reviewed in* [1]*)*. ERK1 and ERK2 are part of the classical MAPK cascade and are activated by the upstream MAPK kinases (MAPKKs), MEK1 and MEK2. The MAPKK kinases (MAPKKK) for MEK1/2 include BRAF and Mos. ERK1/2 activation results mainly in transcription that promotes cell proliferation. The second group of MAPKs consists of the p38 isoforms which appear to be critical for immune function. The p38 isoforms are mainly activated by environmental stress and inflammatory cytokines via the MAPKKs, MEK3 and MEK6. Downstream targets of the p38 isoforms include transcription factors such as ATF1 and -2, NFkappaB, p53, and several MAPKactivated kinases (MKs). The third group of MAPKs consists of the JNKs (JNK1, -2, and -3) which are activated by the MAPKs, MEK4 and MEK7. In response to a variety of stimuli, JNKs phosphorylate transcription factors such as c-Jun, ATF-2, JunD, and STAT3. The fourth group includes the atypical MAPKs, ERK3 and ERK4. The physiological role of ERK3 and ERK4 is not completely understood, but studies suggest a prominent role in development. The best known substrate for ERK3 and -4 is PRAK (MK5)[2]. The last module of the MAPK kinase cascade involves ERK5. ERK5 has been found to play an important role in cardiovascular development and neural differentiation. It is activated by the MAPKK, MEK5. Activated ERK5 phosphorylates substrates such as myocyte enhancer factor 2 (MEF2) and Nur77[3].

References

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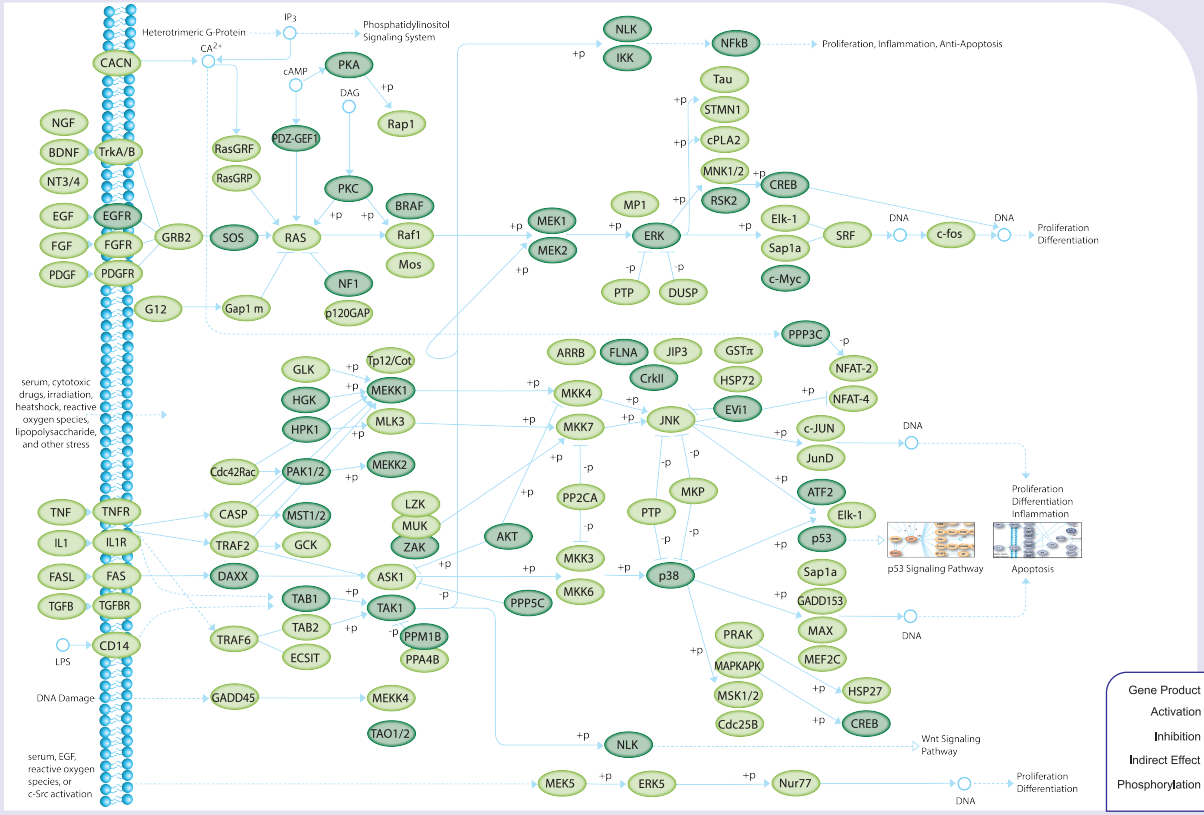
2. S. Kant et al., *J Biol Chem.* 281, 35511-35519 (2006).
3. S. Nishimoto and E. Nishida, *EMBO* Rep. 7, 782-786 (2006).



The mitogen activated protein kinase (MAPK) signal transduction cascade plays a key role in transmitting signals for cell proliferation, differentiation, organismal development, inflammation, cell survival and apoptosis, and the stress response.

The MAPK signaling cascade can be illustrated as three modules: the classical MAP signaling cascade involving Ras/Raf/MEK/ERK; the JNK and p38 pathway; and the ERK5 pathway. In response to extracellular growth factors, cytokines, or stress signals, ERK, JNK, p38, and ERK5 are activated by upstream MAPK kinases (MAPKK) which are themselves activated by MAPKK kinases (MAPKKK). The major substrates of MAPK signaling are MAPK-activated kinases (MKs) and transcription factors such as c-Jun, c-Myc, Max, CREB, p53, and ATF-2. The activation of MKs and transcription results in downstream cellular responses which include proliferation, inflammation, apoptosis, survival, p53 signaling, and wnt signaling. (Figure adapted from the KEGG Pathway Database www.genome.jp/kegg/pathway/hsa/hsa04150.html)

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