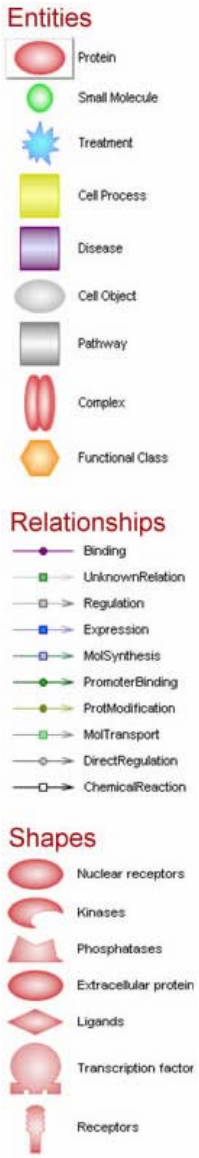
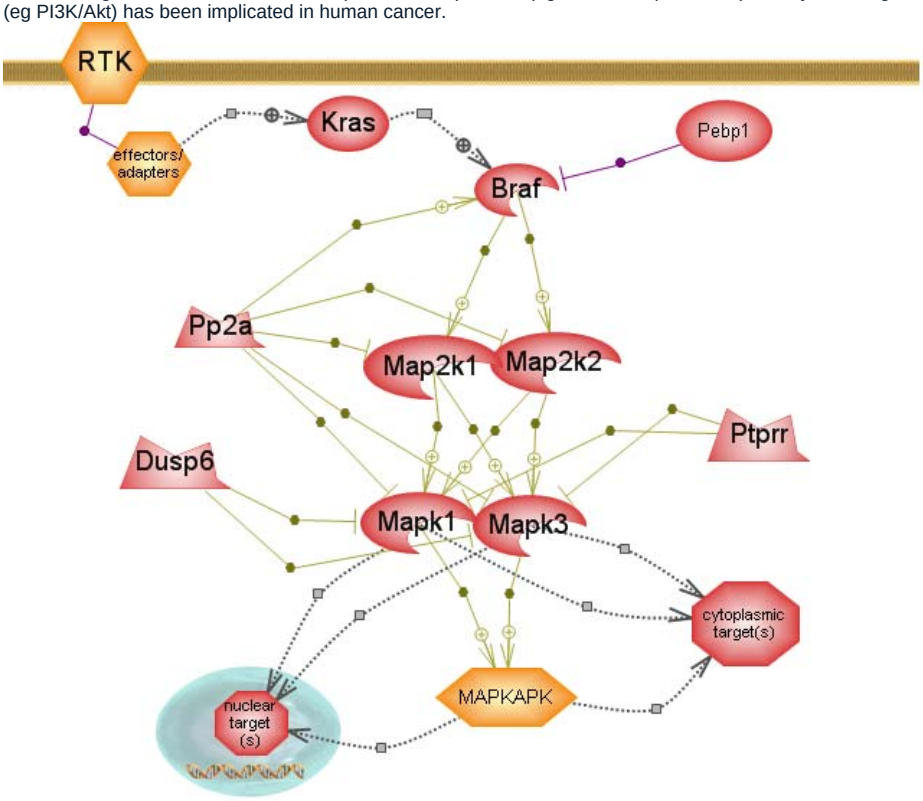
The extracellular signal-regulated RAF/MEK/ERK signaling pathway



Description

The extracellular signal regulated MAP kinase pathway (Raf/Mek/Erk) couples signals reverberating from activated cell surface receptors via their downstream effectors, to many cytoplasmic and nuclear targets. Raf/Mek/Erk displays the characteristic three-tier core cascade MAPK architecture. The downstream and effector MAPK tier (here Erk represented by Mapk1 and 3) is activated by phosphorylation of threonine and tyrosine residues within the conserved TEY motif in the activation loop by dual specificity kinases of the middle MAP2K tier (here Mek represented by Map2k1 and 2), in turn activated by the upstream MAP3K tier (here Raf). While the Raf proteins are the main MAP3Ks, other MAP3Ks can activate this and other MAPK signaling (e.g. Map3k1/Mekk1 also acting as a MAP3K for JNK pathway). Downstream of growth factors activated receptor tyrosine kinases, various effectors and adapters lead to activation of small monomeric G proteins of the Ras family. Activated Ras bind to and recruit the Raf proteins to the plasma membrane where through a series of phosphorylation, dephosphorylation and other events they get activated. Of the several members of Ras, Kras appears to be a more potent inducer of the Raf/Mek/Erk cascade. The three mammalian Raf proteins – Araf, Braf and Raf1/Craf are serine/threonine kinases whose primary targets are the Map2k1/Mek1 and Map2k2/Mek2 members of the MAP2K tier. Mapk1/Erk2 and Mapk3/Erk1 are serine/threonine kinases whose targets transcription factors, cytoplasmic proteins as well as other kinases referred to as MAPKAPK that further transmit the signal. Phosphorylated MAPKs are the targets of many phosphatases such as Pp2a – a serine/threonine phosphatase, Ptprr (known as PTP-SL) – a tyrosine phosphatase, or by members of the dual specificity phosphatases of the MKP/Dusp family, eg. Dusp6. Pp2a also dephosphorylates and downregulates the activity of Mek while dephosphorylation of Raf helps rescue it from an inactive state and leads to its activation. Raf is negatively regulated by phosphorylation within the regulatory domain, eg. Akt, or through the interaction with Pebp1/Rkip that inhibits its kinase activity. The MAPKs can also provide feedback regulatory loops to the upstream components of the pathway. Scaffold proteins, eg. Ksr1, help organize the core modules and shape their activity. Raf/Mek/Erk pathway regulates processes such as proliferation, differentiation and many others. Deregulation of the pathway either through mutations in the core or upstream components (eg B-Raf, Ras) or other pathways that regulate it (eg PI3K/Akt) has been implicated in human cancer.



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