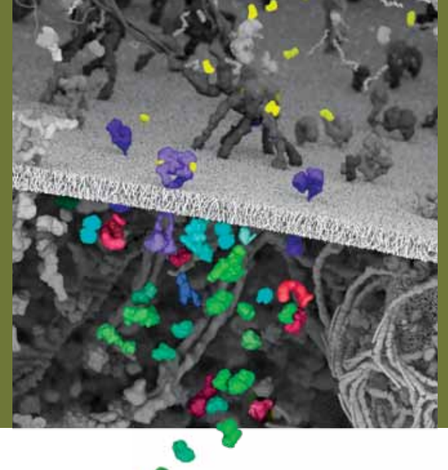
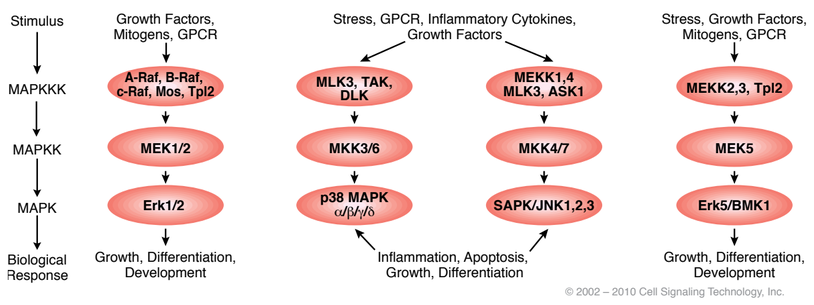
MAP Kinase Signaling

Reference Materials from Cell Signaling Technology



Mitogen-Activated Protein Kinase Cascades



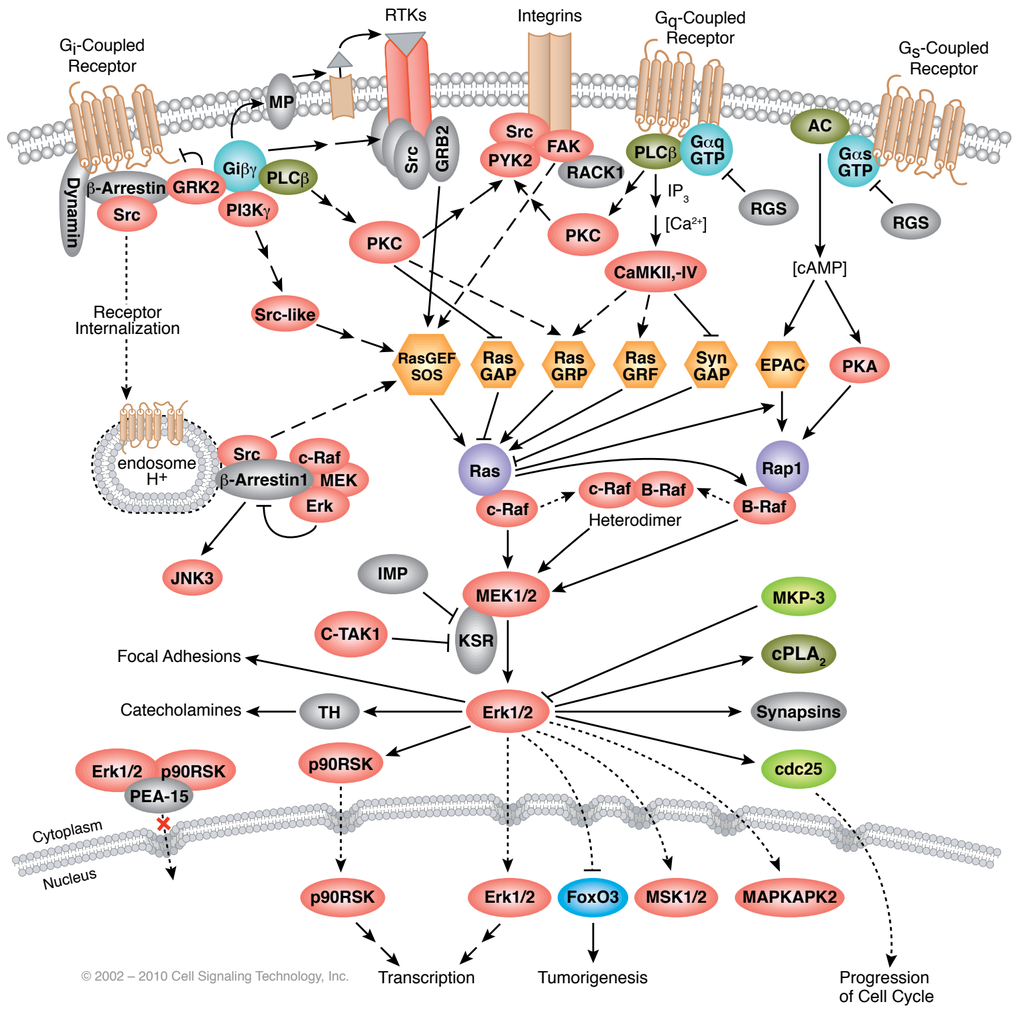
Our Commitment to You

As a company driven by science, our goal is to accelerate biomedical research by developing a "research tool box" that enables researchers to monitor and measure protein activity. We strive to meet contemporary and future research challenges by creating the highest quality, most specific and thoroughly validated antibodies and related reagents.

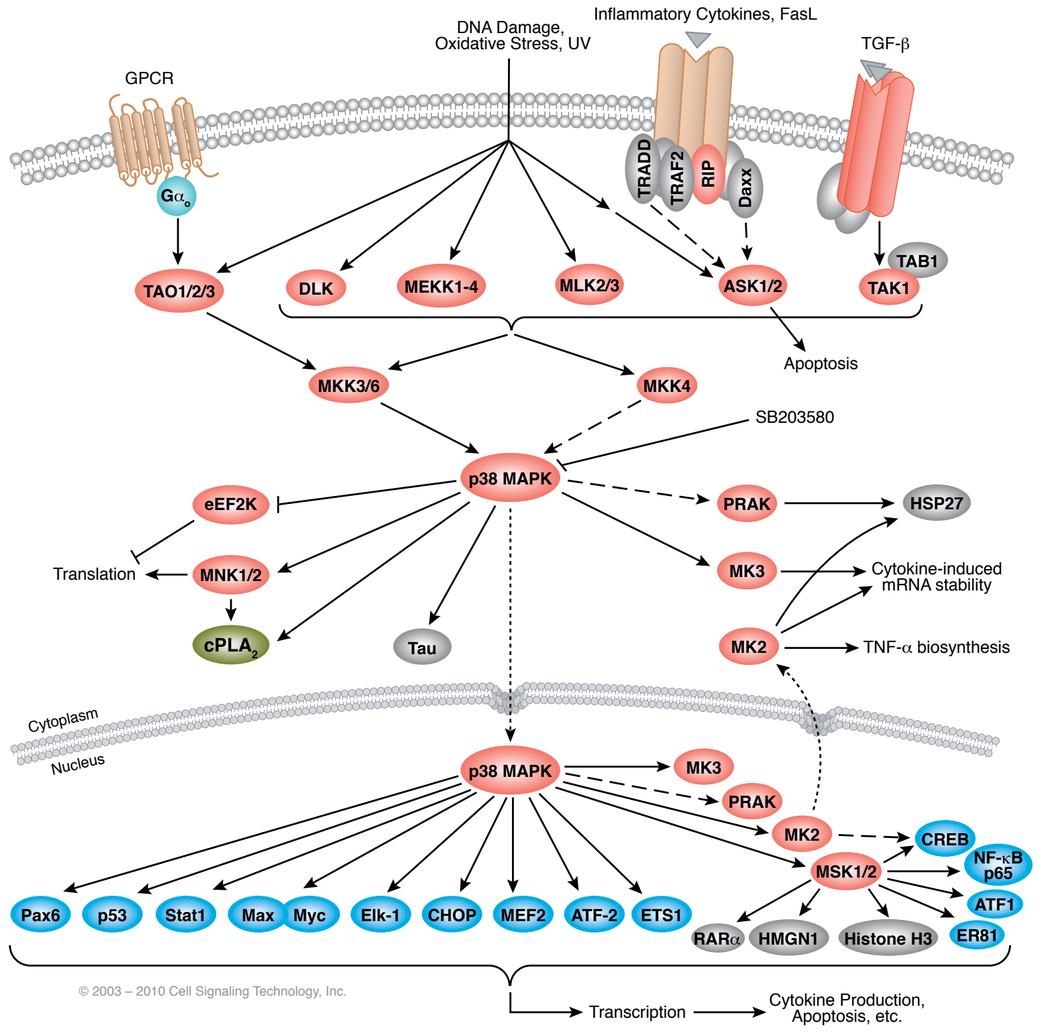
As a committed member of the research community, we practice responsible and sustainable business methods and invest heavily in research and development. We also encourage thoughtful use of our limited natural resources by highlighting environmental issues in our catalog and by promoting conservation and recycling.

These MAPK signaling reference materials were created by research scientists at Cell Signaling Technology and reviewed by the foremost scientists in the field. Visit www.cellsignal.com for additional reference materials and comprehensive validation data for over 4,000 antibodies and related reagents.

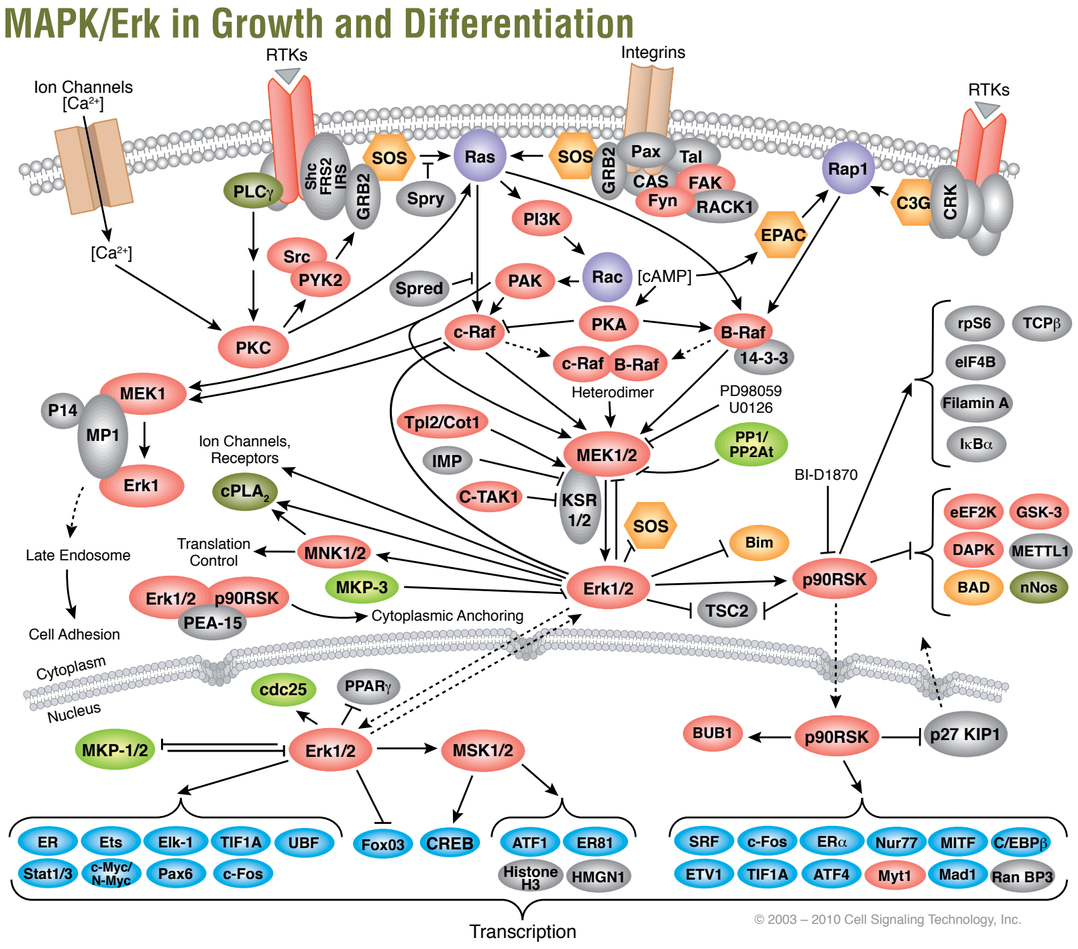
G Protein-coupled Receptors Signaling to MAPK/Erk



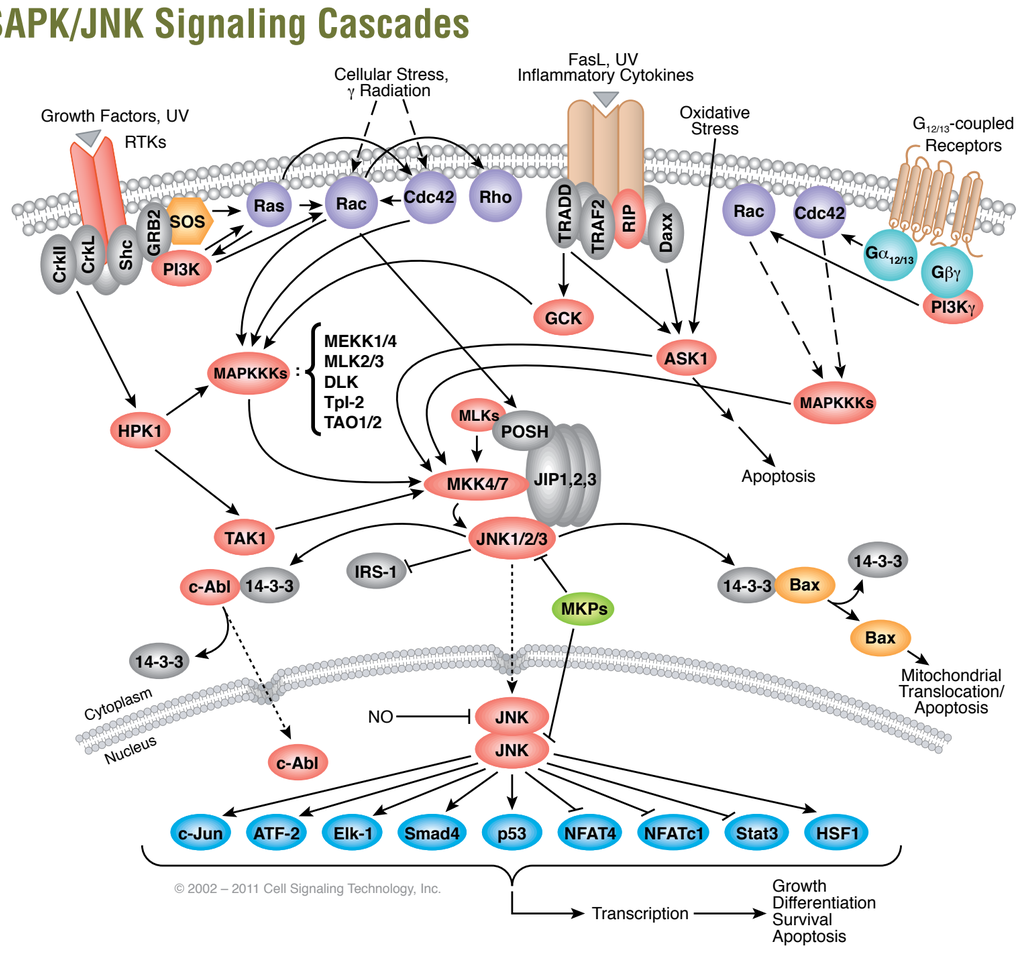
Signaling Pathways Activating p38 MAPK



MAPK/Erk in Growth and Differentiation



SAPK/JNK Signaling Cascades



Direct Stimulatory Modification
Direct Inhibitory Modification
Multistep Stimulatory Modification
Multistep Inhibitory Modification
Tentative Stimulatory Modification
Tentative Inhibitory Modification
Transcriptional Stimulation
Transcriptional Inhibition
Separation of Subunits or Cleavage Products
Joining of Subunits
Translocation
Kinase
Phosphatase
Transcription Factor
Enzyme
GTPase
G-protein
Receptor

Mitogen-Activated Protein Kinase Cascades
Mitogen-activated protein kinases (MAPK) are a family of Ser/Thr protein kinases widely conserved among eukaryotes and are involved in many cellular programs such as cell proliferation, cell differentiation, cell movement and cell death. MAPK signaling cascades are organized hierarchically into three-tiered modules. MAPKs are phosphorylated and activated by MAPK-kinases (MAPKKs), which in turn are phosphorylated and activated by MAPKK-kinases (MAPKKKs). The MAPKKKs are in turn activated by interaction with the family of small GTPases and/or other protein kinases, connecting the MAPK module to cell surface receptors or external stimuli.

G Protein-coupled Receptors Signaling to MAPK/Erk
G protein-coupled receptors (GPCRs) are activated by a wide variety of external stimuli. Upon receptor activation, the G protein exchanges GDP for GTP, causing the dissociation of the GTP-bound α and β/γ subunits and triggering diverse signaling cascades. Receptors coupled to different heterotrimeric G protein subtypes can utilize different scaffolds to activate the small G protein/MAPK cascade, employing at least three different classes of Tyr kinases. Src family kinases are recruited following activation of PI3Kγ by β/γ subunits. They are also recruited by receptor internalization, cross-activation of receptor Tyr kinases, or by signaling through an integrin scaffold involving Pyk2 and/or FAK. GPCRs can also employ PLCβ to mediate activation of PKC and CaMKII, which can have either stimulatory or inhibitory consequences for the downstream MAPK pathway.

Signaling Pathways Activating p38 MAPK
p38 MAPKs (α, β, γ, and δ) are members of the MAPK family that are activated by a variety of environmental stresses and inflammatory cytokines. As with other MAPK cascades, the membrane-proximal component is a MAPKKK, typically a MEKK or a mixed lineage kinase (MLK). The MAPKKK phosphorylates and activates MKK3/6, the p38 MAPK kinases. MKK3/6 can also be activated directly by ASK1, which is stimulated by apoptotic stimuli. p38 MAPK is involved in regulation of HSP27 and MK2 (MAPKAPK-2), MK3 (MAPKAPK-3) and several transcription factors including ATF-2, Stat1, the Max/Myc complex, MEF-2, Elk-1 and indirectly CREB via activation of MSK1.

MAPK/Erk in Growth and Differentiation
The MAPK/Erk signaling cascade is activated by a wide variety of receptors involved in growth and differentiation including receptor tyrosine kinases (RTKs), integrins, and ion channels. The specific components of the cascade vary greatly among different stimuli, but the architecture of the pathway usually includes a set of adaptors (Shc, GRB2, Crk, etc.) linking the receptor to a guanine nucleotide exchange factor (SOS, C3G, etc.) transducing the signal to small GTP binding proteins (Ras, Rap1), which in turn activate the core unit of the cascade composed of a MAPKKK (Raf), a MAPKK (MEK1/2), and MAPK (Erk). An activated Erk dimer can regulate targets in the cytosol and also translocate to the nucleus where it phosphorylates a variety of transcription factors regulating gene expression.

SAPK/JNK Signaling Cascades
Stress-activated protein kinases (SAPK)/Jun amino-terminal kinases (JNK) are members of the MAPK family and are activated by a variety of environmental stresses, inflammatory cytokines, growth factors and GPCR agonists. Stress signals are delivered to this cascade by small GTPases of the Rho family (Rac, Rho, cdc42). As with the other MAPKs, the membrane proximal kinase is a MAPKKK, typically MEKK1–4, or a member of the mixed lineage kinases (MLK) that phosphorylates and activates MKK4 (SEK) or MKK7, the SAPK/JNK kinases. Alternatively, MKK4/7 can be activated by a member of the germinal center kinase (GCK) family in a GTPase-independent manner. SAPK/JNK translocates to the nucleus where it can regulate the activity of multiple transcription factors.

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