

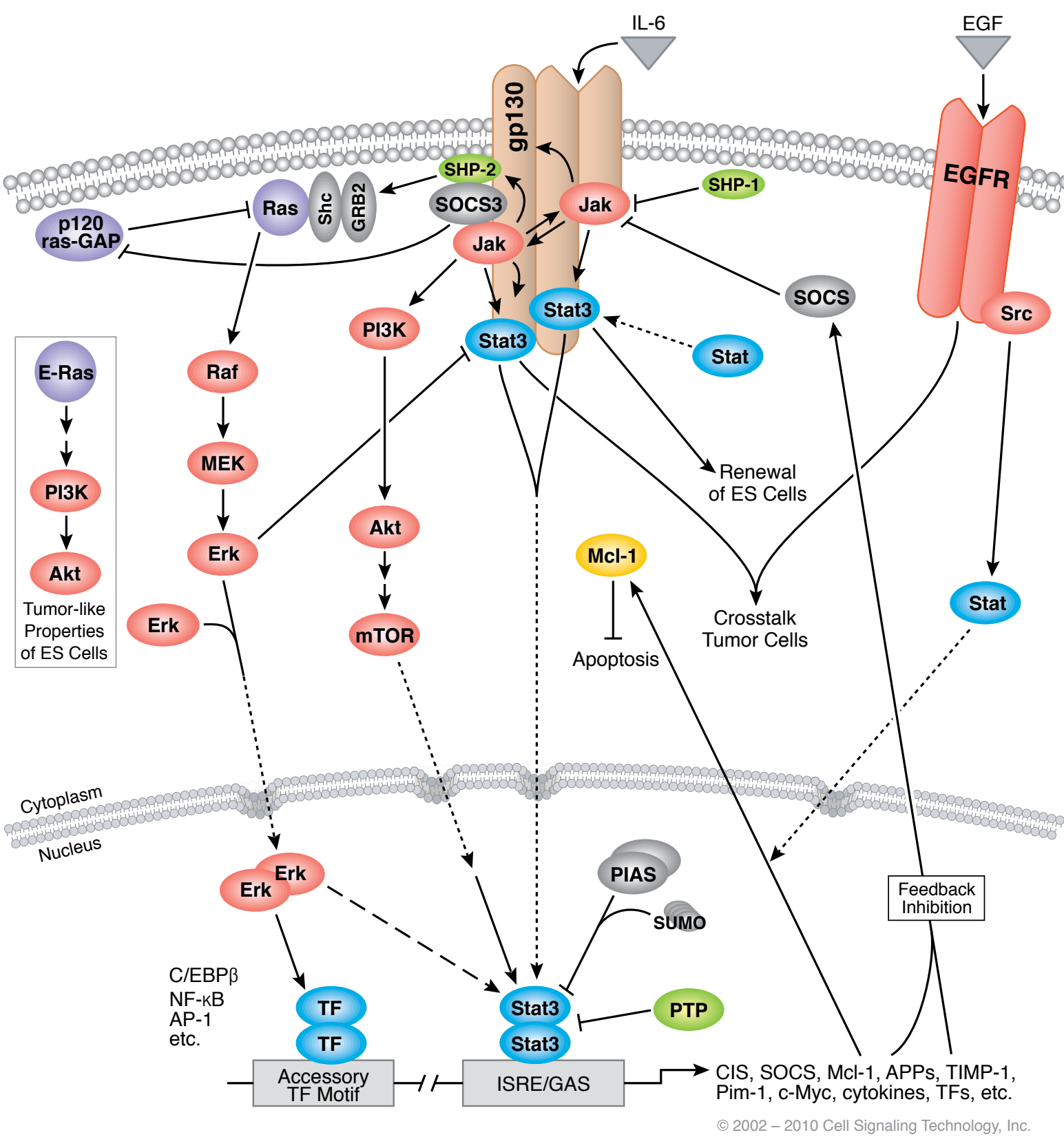
Immunology Signaling Pathways

from Cell Signaling Technology

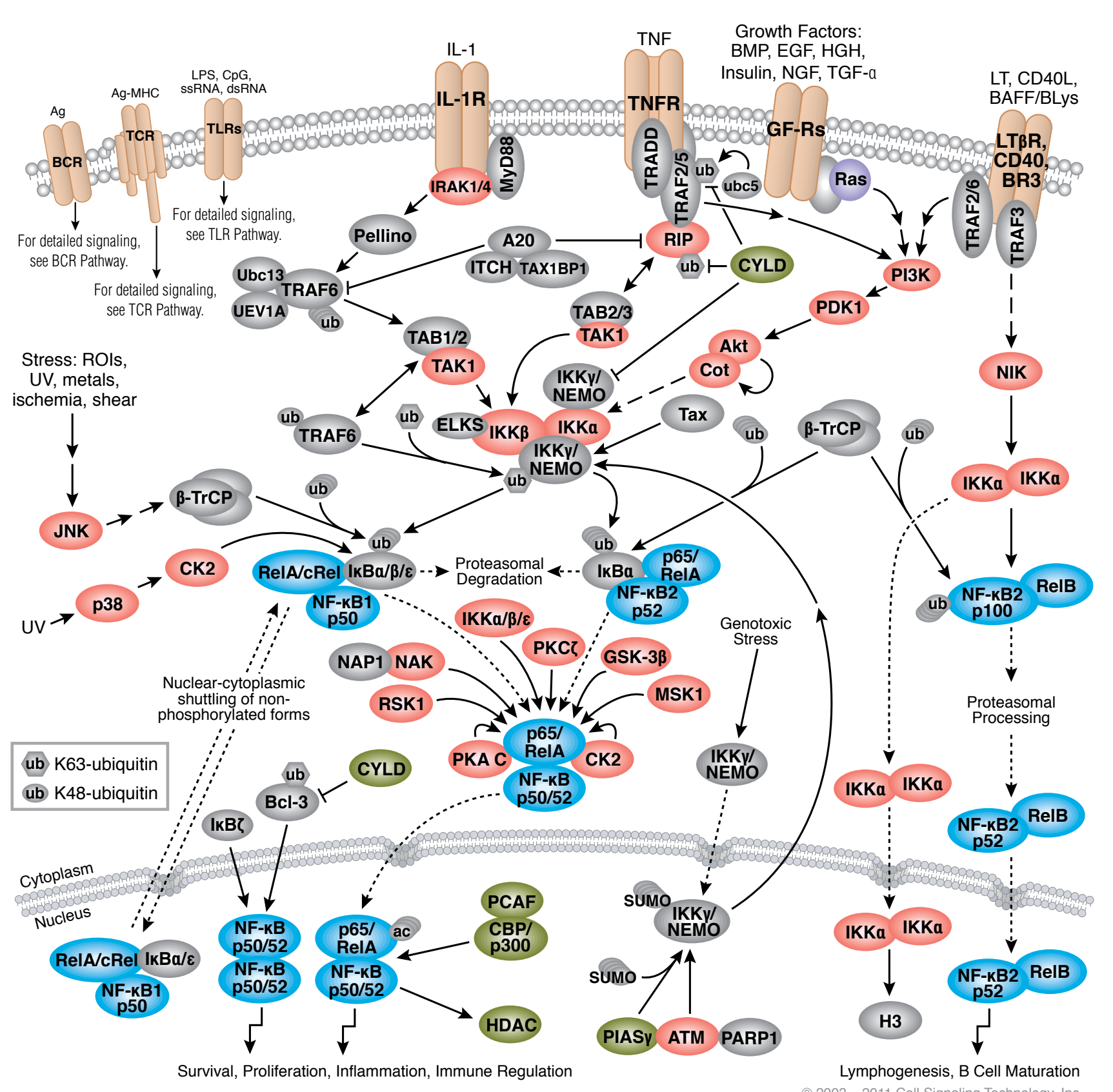
UNPARALLELED PRODUCT QUALITY, VALIDATION, AND TECHNICAL SUPPORT

April 2012

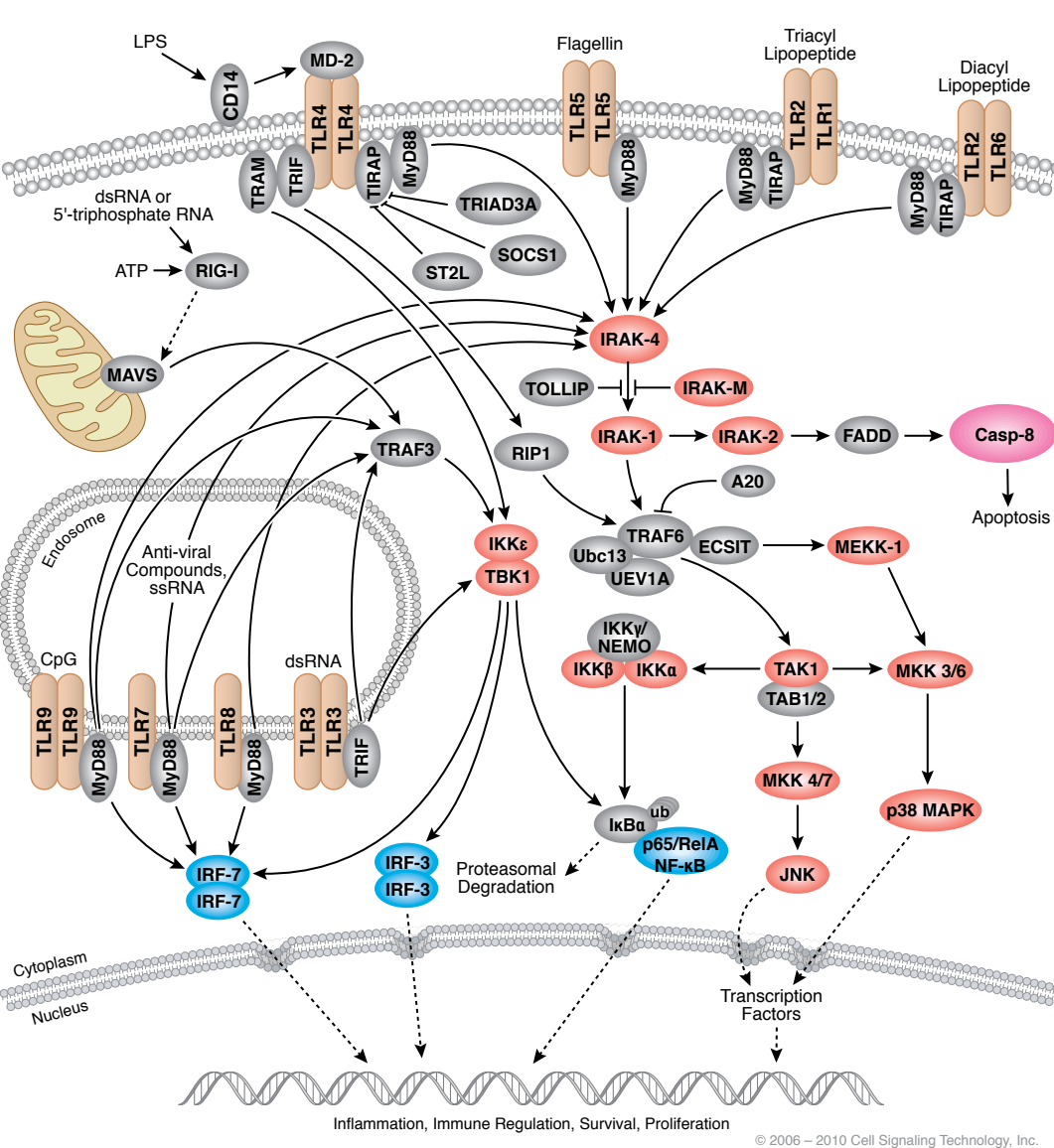
Jak/Stat Signaling: IL-6 Receptor Family



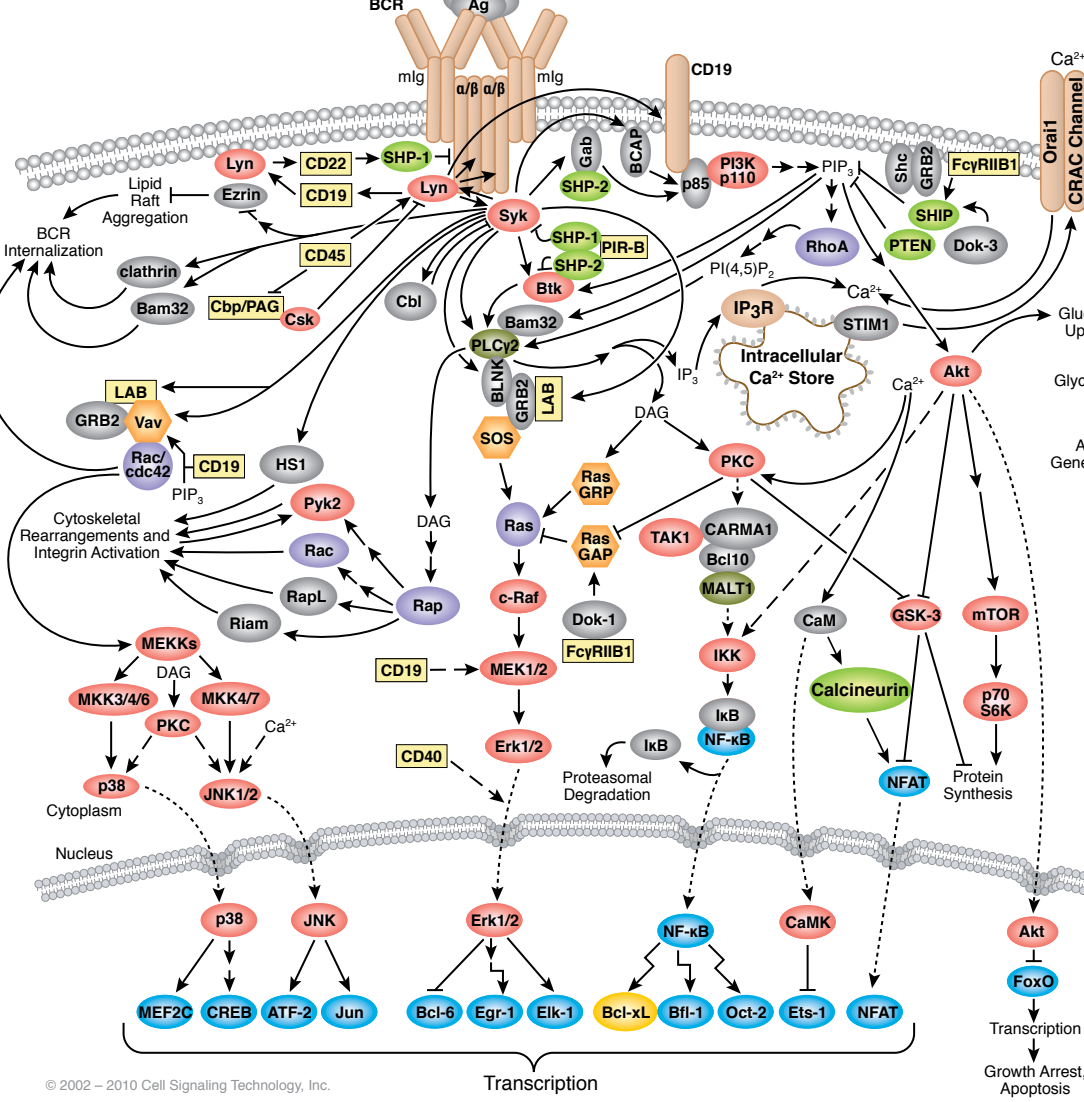
NF-κB Signaling



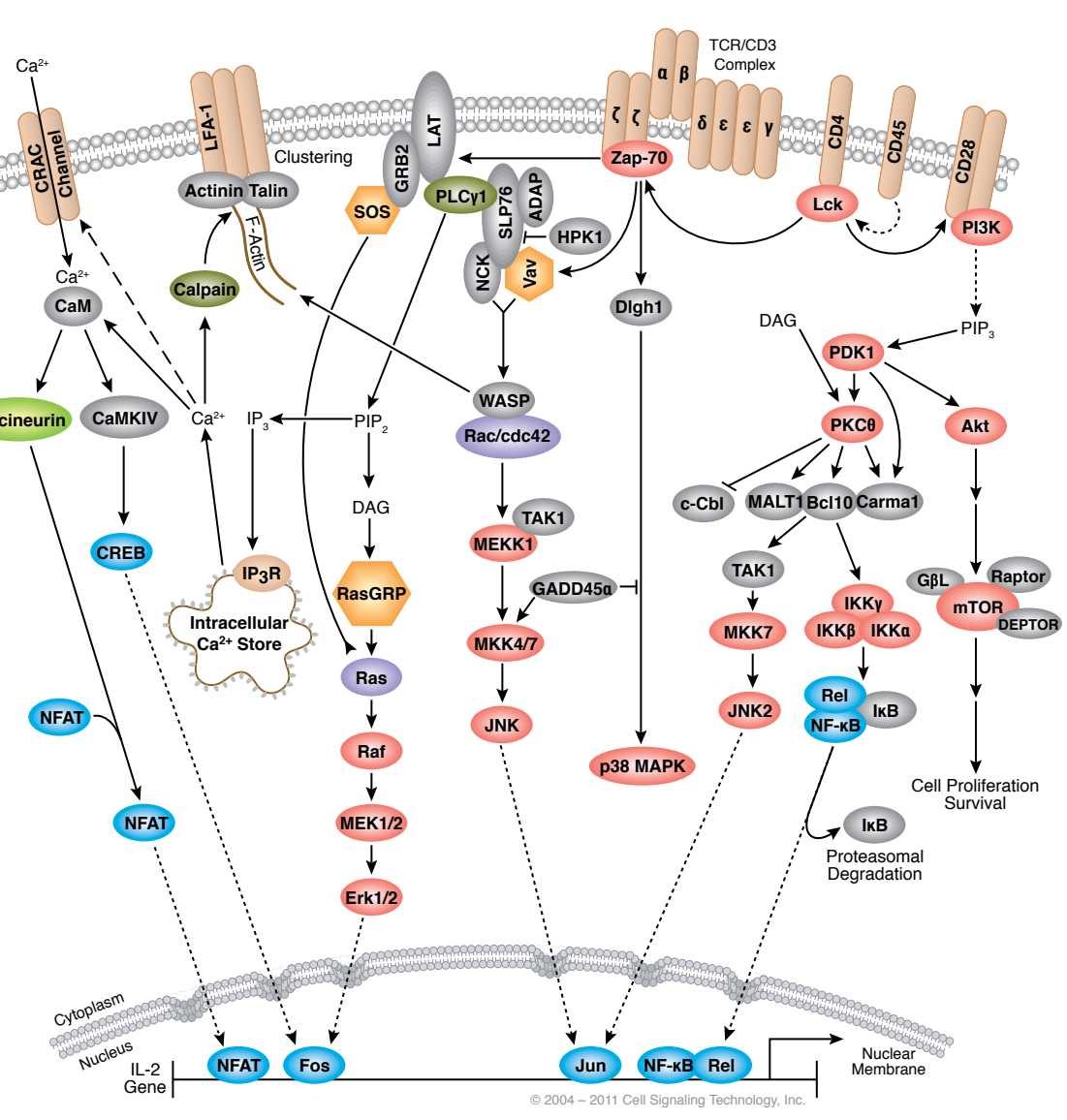
Toll-like Receptor Signaling



B Cell Receptor Signaling



T Cell Receptor Signaling



Jak/Stat Signaling: IL-6 Receptor Family

Pathway Description: Nuclear factor-κB (NF-κB) proteins include NF-κB2 p52/p100, NF-κB1 p50/p105, c-Rel, RelA/p65, and RelB. These proteins function as dimeric transcription factors that control genes regulating a broad range of biological processes including innate and adaptive immunity, inflammation, stress responses, B cell development, and lymphoid organogenesis. In the classical (or canonical) pathway, NF-κB/Rel proteins are bound and inhibited by IκB proteins. Proinflammatory cytokines, LPS, growth factors, and antigen receptors activate an IKK complex (IKKα, IKKβ, and NEMO), which phosphorylates IκB proteins. Phosphorylation of IκB leads to its ubiquitination and proteasomal degradation, freeing NF-κB/Rel complexes. Active NF-κB/Rel complexes are further activated by phosphorylation and translocate to the nucleus where, either alone or in combination with other transcription factor families including AP-1, Ets, and Stat, they induce target gene expression. In the alternative (or noncanonical) NF-κB pathway, NF-κB2 p100/RelB complexes are inactive in the cytoplasm. Signaling through a subset of receptors including LTβR, CD40, and BR3 activates the kinase NIK, which in turn activates IKKα complexes that phosphorylate C-terminal residues in NF-κB2 p100. Phosphorylation of NF-κB2 p100 leads to its ubiquitination and proteasomal processing to NF-κB2 p52, creating transcriptionally competent NF-κB2 p52/RelB complexes that translocate to the nucleus and induce target gene expression. Only a subset of NF-κB agonists and target genes are shown here.

NF-κB Signaling

Pathway Description: Toll-like receptors (TLRs) recognize distinct pathogen-associated molecular patterns and play a critical role in innate immune responses. They participate in the first line of defense against invading pathogens and play a significant role in inflammation, immune cell regulation, survival, and proliferation. To date 11 members of the TLR family have been identified, of which TLR1, TLR2, TLR4, TLR5, and TLR6 are located on the cell surface and TLR3, TLR7, TLR8, and TLR9 are located in the endosomal/lysosomal compartment. The activation of the TLR signaling pathway originates from the cytoplasmic Toll/IL-1 receptor (TIR) domain that associates with a TIR domain-containing adaptor, MyD88. Upon stimulation with ligands, MyD88 recruits IL-1 receptor-associated kinase-4 (IRAK-4) to TLRs through interaction of the death domains of both molecules. IRAK-1 activated by phosphorylation then associates with TRAF6, finally leading to activation of MAP kinases (JNK, p38 MAPK) and NF-κB. Tollp and IRAK-M interact with IRAK-1 and negatively regulate the TLR-mediated signaling pathways. Additional modes of regulation for these pathways include TRIF-dependent induction of TRAF6 signaling by RPI1 and negative regulation of TRAP-mediated downstream signaling by ST2L, TRAF3A, and SOCS1. MyD88-independent pathways induce activation of IRF3 and expression of interferon-β. TIR domain-containing adaptors such as TRAF3, TRAF6, and TRAM regulate TLR-mediated signaling pathways by providing specificity for individual TLR signaling cascades.

Toll-like Receptor Signaling

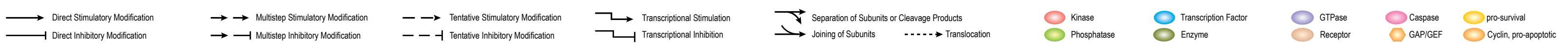
Pathway Description: The B cell antigen receptor (BCR) is composed of membrane immunoglobulin (mIg) molecules and associated Igα/Igβ (CD79a/CD79b) heterodimers (αβ). The mIg subunits bind antigen, resulting in receptor aggregation, while the αβ subunits transduce signals to the cell interior. BCR aggregation rapidly activates the Src family tyrosine kinases Lyn, Btk, and Fyn as well as the Syk and Blk tyrosine kinases. This initiates the formation of a "signalingosome" composed of the BCR, the aforementioned tyrosine kinases, adaptor proteins such as CD19 and BLNK, and signaling enzymes such as PLCγ2, PI3K, and Vav. Signals emanating from the signalingosome activate multiple signaling cascades that involve kinases, GTPases, and transcription factors. This results in changes in cell metabolism, gene expression, and cytoskeletal organization. The complexity of BCR signaling permits many distinct outcomes, including survival, tolerance (energy) or apoptosis, proliferation, and differentiation into antibody-producing cells or memory B cells. The outcome of the response is determined by the maturation state of the cell, the nature of the antigen, the magnitude and duration of BCR signaling, and signals from other receptors such as CD40 and BAFF-R. Many other transmembrane proteins, some of which are receptors, modulate specific elements of BCR signaling. A few of these, including CD45, CD19, CD22, PIR-B, and FcγRIIB1 (CD32), are indicated above in yellow. The magnitude and duration of BCR signaling are limited by negative feedback loops including those involving the Lyn/CD22/SHP-1 pathway, the Cdc42 pathway, SHIP, Cbl, Dok-3, FcγRIIB1, PIR-B, and internalization of the BCR. Please refer to the diagrams for the PI3K/Akt signaling pathway, the NF-κB signaling pathway, and the regulation of actin dynamics for more details about these pathways.

B Cell Receptor Signaling

Pathway Description: T cell receptor (TCR) activation promotes a number of signaling cascades that ultimately determine cell fate through regulating cytokine production, cell survival, proliferation, and differentiation. An early event in TCR activation is phosphorylation of immunoreceptor tyrosine-base activation motifs (ITAMs) on the cytosolic side of the TCR/CD3 complex by lymphocyte protein-tyrosine kinase (Lck). The CD45 receptor tyrosine phosphatase modulates the phosphorylation and activation of Lck and other Src family tyrosine kinases. C-chain associated protein kinase (Zap-70) is recruited to the TCR/CD3 complex where it becomes activated, promoting recruitment and phosphorylation of downstream adaptor or scaffold proteins. Phosphorylation of SLP-76 by Zap-70 promotes recruitment of Vav (a guanine nucleotide exchange factor), the adaptor proteins NCK and GADS, and an inducible T cell kinase (ITK). Phosphorylation of phospholipase C γ1 (PLCγ1) by Itk results in the hydrolysis of phosphatidylinositol 4,5-bisphosphate (PIP2) to produce the second messengers diacylglycerol (DAG) and inositol trisphosphate (IP3). DAG activates PKCθ and the MAPK/Erk pathways, both promoting transcription factor NF-κB activation. IP3 triggers the release of Ca²⁺ from the ER, which promotes the entry of extracellular Ca²⁺ into cells through calcium release-activated Ca²⁺ (CRAC) channels. Calcium bound calmodulin (Ca²⁺/CaM) activates the phosphatase calcineurin, which promotes IL-2 gene transcription through the transcription factor NFAT. Feedback regulation at several points within these pathways allows for different outcomes, depending on the cell type and environment. The incorporation of signals from additional cell surface receptors (such as CD28 or LFA-1) further regulates cellular response.

T Cell Receptor Signaling

Pathway Description: T cell receptor (TCR) activation promotes a number of signaling cascades that ultimately determine cell fate through regulating cytokine production, cell survival, proliferation, and differentiation. An early event in TCR activation is phosphorylation of immunoreceptor tyrosine-base activation motifs (ITAMs) on the cytosolic side of the TCR/CD3 complex by lymphocyte protein-tyrosine kinase (Lck). The CD45 receptor tyrosine phosphatase modulates the phosphorylation and activation of Lck and other Src family tyrosine kinases. C-chain associated protein kinase (Zap-70) is recruited to the TCR/CD3 complex where it becomes activated, promoting recruitment and phosphorylation of downstream adaptor or scaffold proteins. Phosphorylation of SLP-76 by Zap-70 promotes recruitment of Vav (a guanine nucleotide exchange factor), the adaptor proteins NCK and GADS, and an inducible T cell kinase (ITK). Phosphorylation of phospholipase C γ1 (PLCγ1) by Itk results in the hydrolysis of phosphatidylinositol 4,5-bisphosphate (PIP2) to produce the second messengers diacylglycerol (DAG) and inositol trisphosphate (IP3). DAG activates PKCθ and the MAPK/Erk pathways, both promoting transcription factor NF-κB activation. IP3 triggers the release of Ca²⁺ from the ER, which promotes the entry of extracellular Ca²⁺ into cells through calcium release-activated Ca²⁺ (CRAC) channels. Calcium bound calmodulin (Ca²⁺/CaM) activates the phosphatase calcineurin, which promotes IL-2 gene transcription through the transcription factor NFAT. Feedback regulation at several points within these pathways allows for different outcomes, depending on the cell type and environment. The incorporation of signals from additional cell surface receptors (such as CD28 or LFA-1) further regulates cellular response.



Antibodies and Related Reagents for signal transduction research