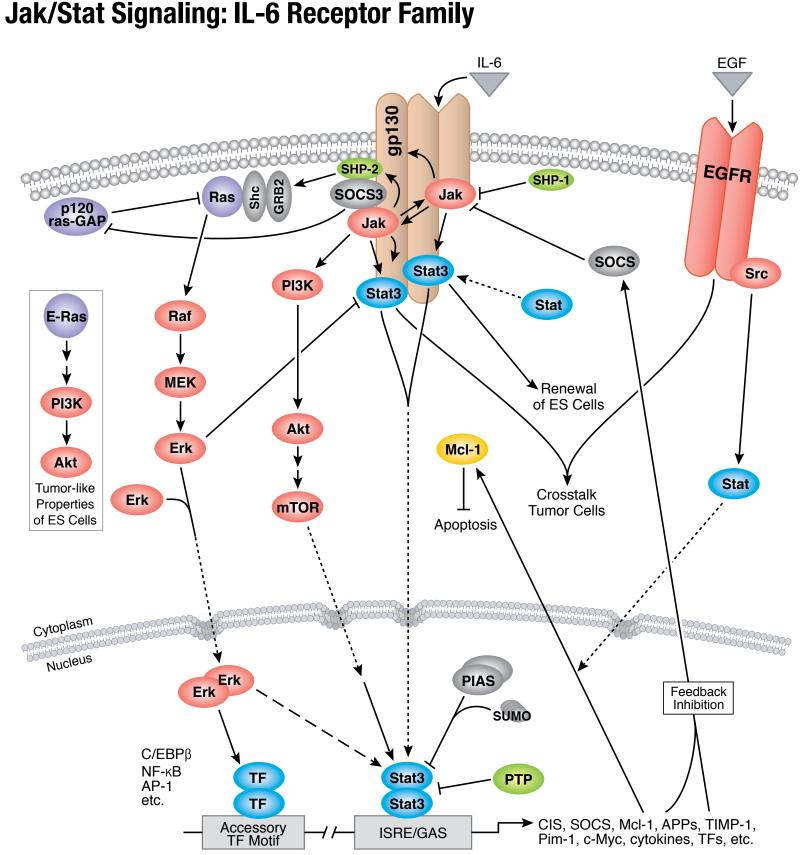
Immunology Signaling Pathways

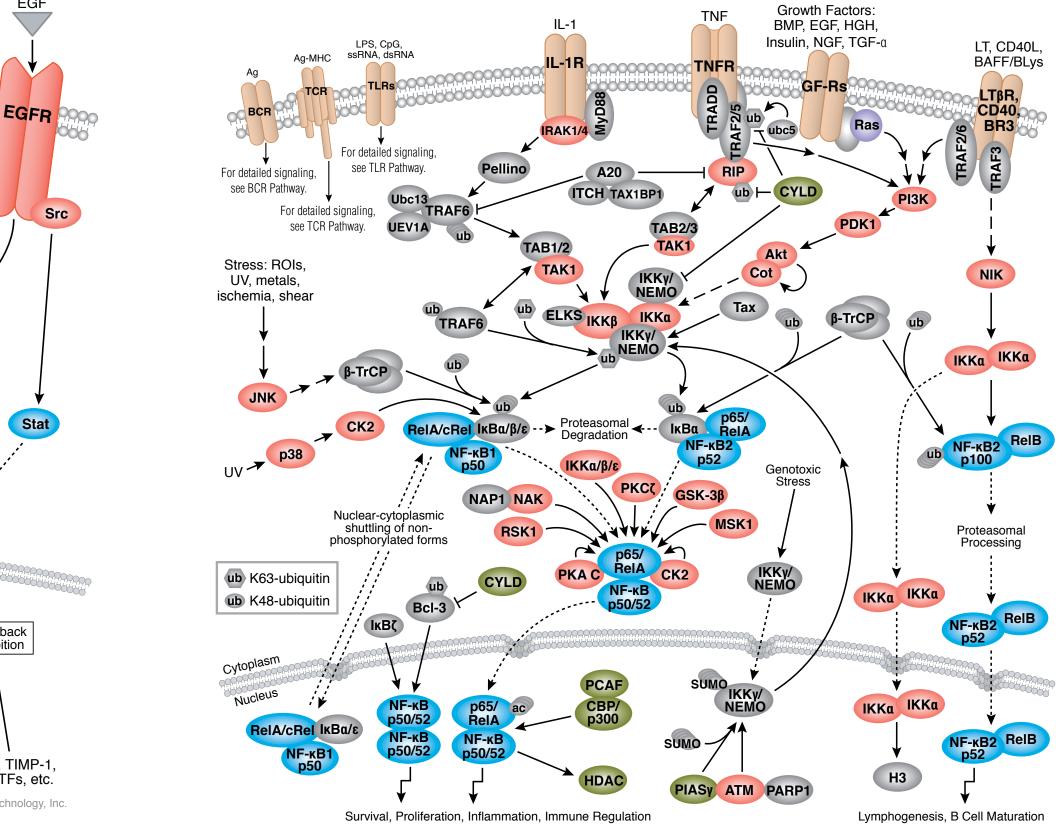
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April 2012

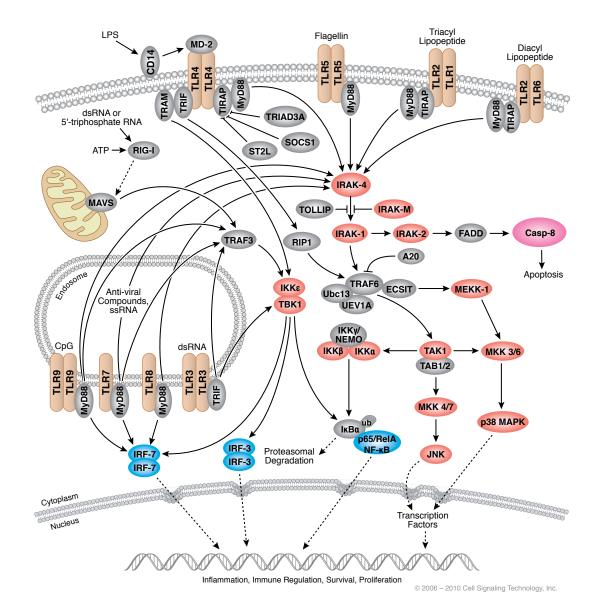


NF-kB Signaling



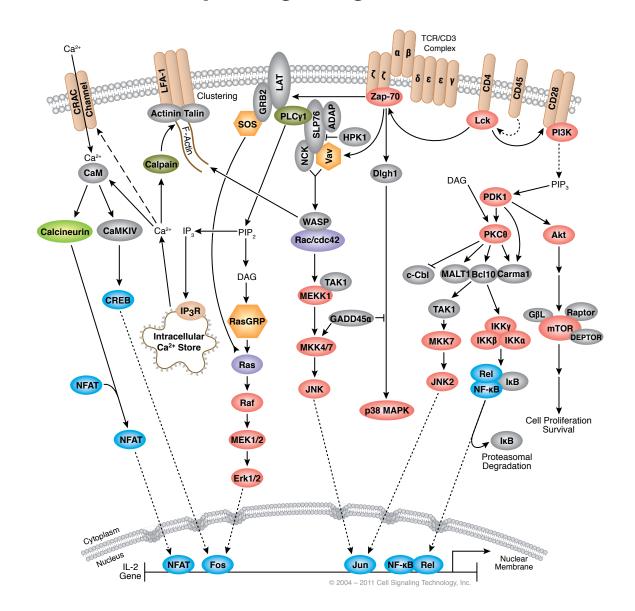
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Toll-like Receptor Signaling



B Cell Receptor Signaling CD19 2000000000000000 ___Lyn Lipid Raft H Ezrin SHP-2 CD19 ← Aggregation BCR PTEN Dok-3 RhoA LSHP-2 PI(4.5)F Btk Cbl Bam32 Cbp/PA STIM1 Uptake Intracellular Akt Ca²⁺ Store Ca Glycolysi LAB GRB2 Var ATP Rac/ cdc42 Generation - CD19 Cvtoskelet TAK1 CARMA1 earrangements a Integrin Activation MALT mTOR Dok-1 GSK-3 CaM ¥ ⊮∕ MEKKs IKK **CD19** 🖌 DẠG 🔪 MEK1/2 MKK3/4/6 WKK4/7 PKC IKB Erk1/2 CD40 F *** Proteasomal NFAT p38 **JNK1/2** Degradatio Cvtoplasm IEF2C CREB ATF-2 Jun Bcl-6 Egr-1 Elk-1 Bcl-xL Bfl-1 Oct-2 Ets-1 Transcription © 2002 - 2010 Cell Signaling Technology, Inc

T Cell Receptor Signaling



Jak/Stat Signaling: IL-6 Receptor Family

Pathway Description: Jaks and Stats are critical components of many cytokine receptor systems, regulating growth, survival, differentiation, and pathogen resistance. An example of these pathways is shown for the IL-6 (or gp130) family of receptors, which co-regulate B cell differentiation, plasmacytogenesis and the acute phase reaction. Cytokine binding induces receptor dimerization, activating the associated Jaks, which phosphorylate themselves and the receptor. The phosphorylated sites on the receptor and Jaks serve as docking sites for the SH2-containing Stats such as Stat3, and for SH2-containing proteins and adaptors that link the receptor to MAP kinase, PI3K/Akt, and other cellular pathways.

Receptor-bound Stats phosphorylated by Jaks dimerize and translocate into the nucleus to regulate target gene transcription. Members of the suppressor of cytokine signaling (SOCS) protein family dampen receptor signaling via homologous or heterologous feedback regulation. Jaks or Stats can also participate in signaling through other receptor classes, as outlined in the Jak/Stat Utilization Table.

Deregulated signaling of IL-6 is seen in the pathogenesis of autoimmune diseases, inflammation, and cancers such as multiple myeloma and prostate cancer. Stat3 can act as an oncogene and is constitutively active in many cancers. In prostate cancer and multiple myeloma, signaling from the IL-6R involves cross talk with Epidemal Growth Factor Receptor (EGFR) family members. IL-6 also induces anti-apoptotic signals, which may contribute to oncogenesis. One target gene is a Bcl-2 family member, Mcl-1.

Janus kinase mutations are major molecular events in human hematological malignancies. A unique somatic mutation in the Jak2 pseudokinase domain (V617F) occurs in >90% of polycythemia vera patients, and in a large proportion of essential thrombocythemia and idiopathic myelofibro-sis patients. This mutation results in the pathologic activation Jak2 kinase, which leads to malignant transformation of hematopoietic progenitors. Several Jak3 pseudokinase domain mutations, present in some patients with acute megakaryoblastic leukemia, also render Jak3 constitutively active. Somatic acquired gain-of-function mutations in Jak1 have been discovered in approximately 20% of adult T-cell acute lymphoblastic leukemia.

Somatic activating mutations in Jak1, Jak2, and Jak3 have been identified in pediatric acute lymphoblastic leukemia (ALL) patients. Jak2 mutations have been detected around pseudokinase domain R683 (R683G or AIREED) in Down syndrome and pediatric B-ALL patients, where they are also associated with translocations or mutations (F232C) in the CRLF2 gene, which codes for the thymic stromal lymphopoietin receptor (TLSP) receptor. Although TLSP was thought to signal via other Jaks, it appears that mutant Jak2 and TLSPR cooperate to promote oncogenesis in a fraction of pediatric ALL

NF-kB Signaling

Pathway Description: Nuclear factor-KB (NF-KB)/Rel proteins include NF-KB2 p52/ p100, NF-kB1 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-ĸB/ Rel proteins are bound and inhibited by IkB proteins. Proinflammatory cytokines, LPS, growth factors, and antigen receptors activate an IKK complex (IKKB, IKKa, and NEMO), which phosphorylates IkB proteins. Phosphorylation of IkB leads to its ubiquitination and proteasomal degradation, freeing NF-KB/Rel complexes. Active NF-KB/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-KB pathway, NF-kB2 p100/RelB complexes are inactive in the cytoplasm. Signaling through a subset of receptors including LT β R, CD40, and BR3 activates the kinase NIK, which in turn activates IKK α complexes that phosphorylate C-terminal residues in NF- κ B2 p100. Phosphorylation of NF-KB2 p100 leads to its ubiquitination and proteasomal processing to NF- κ B2 p52, creating transcriptionally competent NF- κ B 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.

Toll-like Receptor 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 localized to 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-kB. Tollip 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 RIP1 and negative regulation of TIRAP mediated downstream signaling by ST2L, TRIAD3A, and SOCS1. MyD88-independent pathways induce activation of IRF3 and expression of interferon-β. TIR-domain containing adaptors such as TIRAP, TRIF, and TRAM regulate TLR-mediated signaling pathways by providing specificity for individual TLR signaling cascades.

B Cell Receptor Signaling

Pathway Description: The B-cell antigen receptor (BCR) is composed of membrane immunoglobulin (mlg) molecules and associated Iga/IgB (CD79a/CD79b) heterodimers (α/β). The mlg subunits bind antigen, resulting in receptor aggregation, while the α/β subunits transduce signals to the cell interior. BCR aggregation rapidly activates the Src family kinases Lyn, Blk, and Fyn as well as the Syk and Btk tyrosine kinases. This initiates the formation of a 'signalosome' composed of the BCR, the aforementioned tyrosine kinases, adaptor proteins such as CD19 and BLNK, and signaling enzymes such as PLCy2, PI3K, and Vav. Signals emanating from the signalosome 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 (anergy) 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 FcyRIIB1 (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 Cbp/Csk pathway, SHIP, Cbl, Dok-1, Dok-3, FcyRIIB1, PIR-B, and internalization of the BCR. Please refer to the diagrams for the Pl3K/Akt signaling pathway, the NF-κB signaling pathway, and the regulation of actin dynamics for more details about these pathways.

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. ζ-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 v1 (PLCv1) by Itk results in the hydrolysis of phosphatidylinositol 4,5-bisphosphate (PIP,) to produce the second messengers diacylglycerol (DAG) and inositol trisphosphate (IP₂). DAG activates PKC0 and the MAPK/Erk pathways, both promoting transcription factor NF- κ B 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.

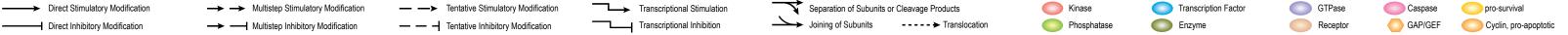
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Transcriptional Stimulation

Transcription Factor



GTPase









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