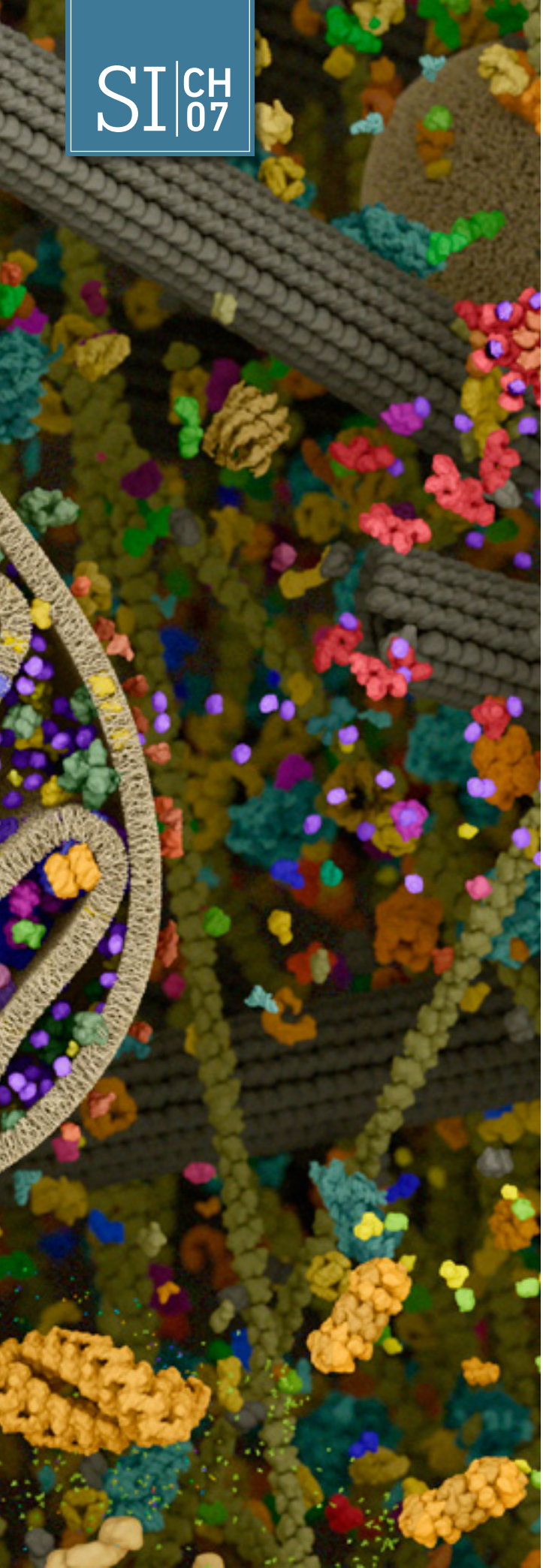
SI CH 07



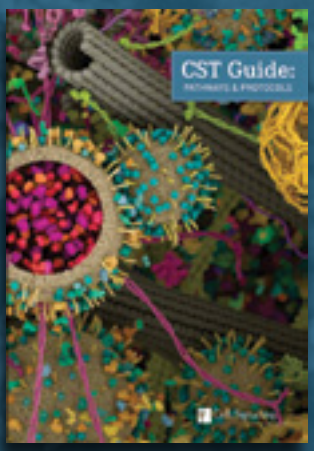
Immunology and Inflammation

An excerpt from the first edition of the
CST Guide: Pathways & Protocols

Cell Signaling TECHNOLOGY®

First Edition

CST Guide



GUIDE COVER PHOTO:

Cellular Landscape:

Vesicle Trafficking

Multiple levels shown of key pathways and structures involved in ER and Golgi-mediated trafficking and protein processing, including post-translational modifications.

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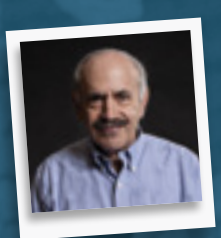

"...the time has come for us... to puzzle out, one protein at a time, how signals are really processed inside cells to create the marvelously functioning apparatus – the eukaryotic cell."

Dr. Robert A. Weinberg

Daniel K. Ludwig Professor for Cancer Research, MIT

Diagram & Table Keys

Pathway Diagram Key

The pathway diagrams found in this guide and on our website have been assembled by CST scientists and outside experts to provide succinct and current overviews of selected signaling pathways.

Direct Stimulatory Modification	Deacetylase
Direct Inhibitory Modification	Ribosomal subunit
Multistep Stimulatory Modification	TIM-3
Multistep Inhibitory Modification	Galectin-9
Tentative Stimulatory Modification	B7-H3
Tentative Inhibitory Modification	B7-H4
Separation of Subunits	CTLA-4
Joining of Subunits	CD80, 86
Translocation	PD-1
Transcriptional Stimulatory	PD-L1
Transcriptional Inhibitory	TCR
Kinase	MHC
Phosphatase	ICOS
Transcription Factor	ICOSL
Caspase	OX40
Receptor	OX40L
Enzyme	CD40
pro-apoptotic	CD40L
pro-survival	CD27
GAP/GEF	CD70
GTPase	CD137
G-protein	CD137L
Acetylase	CD28

Applications Key

While all of our antibodies are rigorously tested in a number of relevant applications, some products are more suitable for a specific application. This information is summarized in various lists and tables found throughout this guide.

WB	Western Blotting	**ChIP**	Chromatin Immunoprecipitation
IP	Immunoprecipitation	**-IC**	Immunocytochemistry
IHC	Immunohistochemistry	**-P**	Paraffin
IF	Immunofluorescence	**-F**	Frozen
F	Flow Cytometry	**E-P**	Peptide ELISA

Immunology and Inflammation

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Cell Signaling
TECHNOLOGY®

07

Immunology and Inflammation

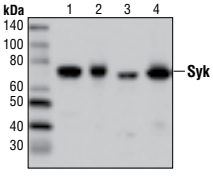
B Cell and T Cell Receptor Signaling and Adaptive Immunity

B and T lymphocytes mediate the humoral and cell-mediated immune responses, respectively, which make up the adaptive arm of the immune system. B cells mature in the bone marrow and differentiate into antibody-secreting plasma cells. In contrast, T cells are thymus-derived and, as effector cells, orchestrate cell-mediated immunity.

The B cell receptor (BCR) is composed of a membrane-bound antibody (immunoglobulin or Ig) flanked by Igα/Igβ (CD79A/CD79B) heterodimers. When membrane Ig binds antigen, the CD79 heterodimer transduces signals through its cytoplasmic immunoreceptor tyrosine-based activation motif (ITAM) domains. The T cell receptor (TCR) consists of a membrane-bound αβ heterodimer (TCRαβ), four CD3 chains (two CD3ε, one CD3γ, one CD3δ), and a ζ–chain homodimer. The TCRαβ dimer recognizes antigenic peptides, while the associated signaling chains transduce signals with their cytoplasmic ITAM domains. Thus, the lymphocyte antigen receptors use similar models of membrane-bound antigen receptors linked to signal-transducing accessory chains.

Signaling through the BCR and TCR involves activation of a number of Src family tyrosine kinases (Blk, Fyn, and Lyn in B cells and Fyn and Lck in T cells), which are responsible for phosphorylation of the receptor-associated ITAM motifs. Phosphorylated ITAMs act as docking sites for Syk family tyrosine kinases (Syk in B cells and Zap-70 in T cells). Activated Syk kinases amplify signals through phosphorylation of downstream adaptor proteins, thereby initiating a cascade of intracellular signaling molecules. In addition to mediating cell activation, lymphocyte receptor signaling drives B and T cell development, differentiation, proliferation, and survival.

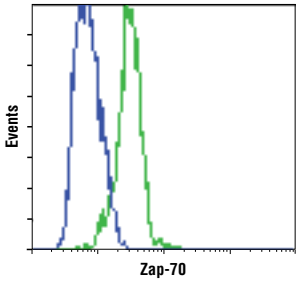
Syk is expressed in B cells and other cell lines.



Syk (D3Z1E) XP® Rabbit mAb #13198: WB analysis of extracts from various cell lines using #13198.

Lanes
1. SW620
2. SR
3. A20
4. YB2/0

Zap-70 is expressed in T cells.



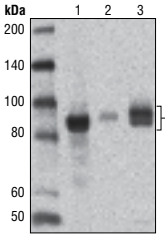
Zap-70 (D1C10E) XP® Rabbit mAb (Alexa Fluor® 488 Conjugate) #9473: Flow cytometric analysis of Ramos (B cells; blue) and Jurkat (T cells; green) cells using #9473.

TLR Signaling and Innate Immunity

The innate arm of the immune system consists of a host of immune cells and resistance mechanisms that act as the first line of defense against invading pathogens. The toll-like receptors (TLRs) are a family of evolutionarily conserved pattern recognition receptors (PRRs) that recognize the pathogen-associated molecular patterns (PAMPs) found in microbial pathogens. TLR1, 2, 4, 5, and 6 are expressed at the cell surface, while TLR3, 7, 8, and 9 have been shown to localize to intracellular vesicles. Activation of TLRs through ligand binding triggers a signaling cascade involving a variety of intracellular signaling adaptors including MyD88, IRAKs, and TRAF6. TLR signaling leads to the activation of the MAP kinase, NF-κB, and IRF signaling pathways, which mediate inflammation through the production of inflammatory cytokines, type I IFN, chemokines, and antimicrobial peptides. TLR signaling in innate immune cells, particularly dendritic cells, leads to their activation and subsequent induction of adaptive immune responses.

TLR2 expression in mouse macrophages and dendritic cells

Toll-like Receptor 2 (E1J2W) Rabbit mAb (Mouse Specific) #13744: WB analysis of extracts from Raw 264.7 cells, mouse bone marrow-derived macrophages (BMDM), and mouse bone marrow-derived dendritic cells (BMDC) using #13744.



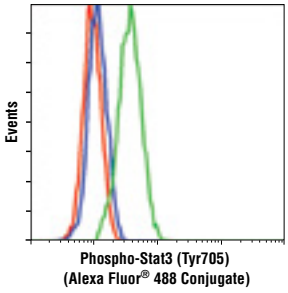
Lanes
1. Raw 264.7
2. BMDM
3. BMDC

Jak/Stat Signaling

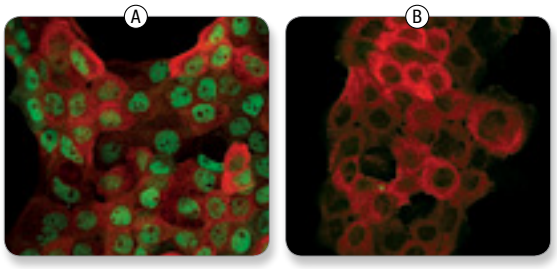
The Jak/Stat signaling pathway is utilized by a large number of cytokines, growth factors, and hormones upon binding to their specific receptors. Receptor-mediated tyrosine phosphorylation of Jak family members triggers phosphorylation of Stat proteins, resulting in their nuclear translocation, binding to specific DNA elements, and subsequent activation of transcription. The remarkable range and specificity of responses regulated by the Stats is determined, in part, by the tissue-specific expression of different cytokine receptors, Jaks, and Stats, as well as by the combinatorial coupling of various Stat members to different receptors. Stat1 is activated in response to a large number of ligands and is essential for responsiveness to IFN-α and IFN-γ. Stat3 is constitutively activated in a number of human tumors and possesses both oncogenic potential and antiapoptotic activities. Stat4 has been most extensively investigated as a mediator of IL-12 responses. Stat5 is activated in response to a wide variety of ligands including IL-2, GM-CSF, growth hormone, and prolactin.

Cytokine stimulation results in phosphorylation of Stat3 at Tyr705.

Phospho-Stat3 (Tyr705) (D3A7) XP® Rabbit mAb (Alexa Fluor® 488 Conjugate) #4323: Flow cytometric analysis of Jurkat cells, untreated (blue) or IFN-α treated (green), using #4323 compared to isotype control antibody (red).



Growth factor stimulation results in phosphorylation of Stat5 at Tyr694.



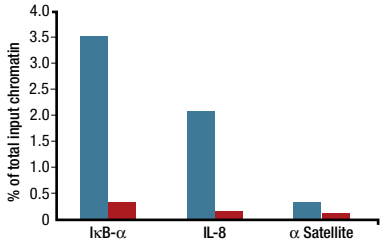
Phospho-Stat5 (Tyr694) (D47E7) XP® Rabbit mAb #4322: Confocal IF analysis of A-431 cells, treated with Human Epidermal Growth Factor (hEGF) #8916 **(A)** or untreated **(B)**, using #4322 (green) and Pan-Keratin (C11) Mouse mAb #4545 (red).

NF-κB Signaling

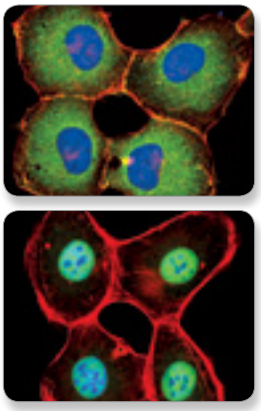
Transcription factors of the nuclear factor κB (NF-κB)/Rel family play a pivotal role in inflammatory and immune responses. There are five family members in mammals: RelA, c-Rel, RelB, NF-κB1 (p105/p50), and NF-κB2 (p100/p52). Both p105 and p100 are co-translationally processed by the proteasome to produce p50 and p52, respectively. Rel proteins bind p50 and p52 to form dimeric complexes that bind DNA and regulate transcription. In unstimulated cells, NF-κB is sequestered in the cytoplasm by IκB inhibitory proteins. NF-κB-activating agents can induce the phosphorylation of IκB proteins, targeting them for rapid degradation through the ubiquitin-proteasome pathway and releasing NF-κB to enter the nucleus where it regulates gene expression. NIK and IKKα (IKK1) regulate the phosphorylation and processing of NF-κB2 (p100) to produce p52, which translocates to the nucleus.

NF-κB1 p105/p50 associates with promoters for IκBα and IL-8, but not with α satellite repeat element.

NF-κB1 p105/p50 (D4P4D) Rabbit mAb #13586: Chromatin IPs were performed with cross-linked chromatin from 4 x 10^6 HeLa cells treated with Human Tumor Necrosis Factor-α (hTNF-α) #8902 (30 ng/ml, 1 hr) and either 10 µl of #13586 or 2 µl of Normal Rabbit IgG #2729 using SimpleChIP® Enzymatic Chromatin IP Kit (Magnetic Beads) #9003. The enriched DNA was quantified by real-time PCR using SimpleChIP® Human IκBα Promoter Primers #5552, human IL-8 promoter primers, and SimpleChIP® Human α Satellite Repeat Primers #4486. The amount of immunoprecipitated DNA in each sample is represented as a percent of the total input chromatin.

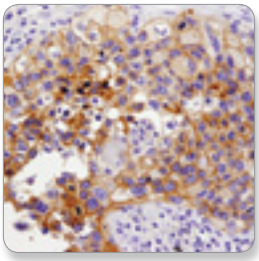


TNF-α treatment results in translocation of NF-κB p65 (RelA) to the nucleus.



NF-κB p65 (D14E12) XP® Rabbit mAb #8242: Confocal IF analysis of HT-1080 cells, untreated (top) or treated with hTNF-α #8902 (20 ng/ml, 20 min) (bottom), using #8242 (green). Actin filaments were labeled with DY-554 phalloidin (red). Blue pseudocolor = DRAQ5® #4084 (fluorescent DNA dye).

PD-L1 is expressed in lung carcinoma.



PD-L1 (E1L3N®) XP® Rabbit mAb #13684: IHC analysis of paraffin-embedded human lung carcinoma using #13684.

Immune Checkpoints

Activation of T lymphocytes by antigen-presenting cells (APCs) requires engagement of the T cell receptor with MHC class I or II molecules and co-stimulatory signals generated from CD28 (on T cells) binding to CD80 or CD86 (on APCs). However, under certain circumstances, such as maintaining self-tolerance or preventing collateral tissue damage, T cell engagement is coupled with inhibitory signals that repress T cell activation and response, known as immune checkpoints. Immune checkpoint proteins such as PD-1 and CTLA-4, which are commonly upregulated in infiltrating T cells, bind their corresponding ligands, PD-L1 and CD80/86 respectively, which are upregulated in cancer cells as a means to evade immune detection and downregulate T cell response. Activating antitumor immunity through the blockade of immune checkpoint proteins has become a promising therapeutic strategy for the treatment of cancer.

Select Reviews

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Commonly Studied Immunology and Inflammation Targets

These protein targets represent key nodes within immunology and inflammation signaling pathways and are commonly studied in immunology and inflammation research. Primary antibodies, antibody conjugates, and antibody sampler kits containing these targets are available from CST.

Listing as of September 2014. See our website for current product information.

- **M** Monoclonal Antibody
- **P** Polyclonal Antibody
- **E** PathScan® ELISA Kits
- **S** SignalSilence® siRNA
- **C** Antibody Conjugate

Target	M	P	E	S	C
A20/TNFAIP3	●	●			
ABIN-1		●		●	
ADAP		●			
AID	●				
AIM2	●	●			
Aiolos		●			
AML1	●	●			
Phospho-AML1 (Ser249)		●			
β2-microglobulin	●	●		●	
BACH2		●			
BAFF	●				
Basigin/EMMPRIN	●	●			
BATF	●				
BCL6	●	●			
Bcl10	●				
Blimp-1/PRDI-BF1	●				
Blk		●			
BLNK	●				
Phospho-BLNK (Tyr96)		●			
Btk	●				●
Phospho-Btk (Ser180)	●				
Phospho-Btk (Tyr223)		●			
CARD9		●			
CARD11	●	●			
Phospho-CARD11 (Ser652)		●			
CBFβ		●			
CCR2	●				
CD3ε	●				
CD4	●				
CD8	●				

Target	M	P	E	S	C
CD9	●				
CD10	●				
CD13	●				
CD19		●			
Phospho-CD19 (Tyr531)		●			
CD31 (PECAM-1)	●				
CD34	●				
CD44	●	●	●		●
CD45	●				
CD46	●				
CD79A	●	●			
Phospho-CD79A (Tyr182)		●			
CD82	●	●			
CIITA		●			
CISH	●				
CrkL	●				
Phospho-CrkL (Tyr207)		●			
Cytokine Receptor Common β-Chain		●			
Cox1	●	●			
Cox2	●	●	●		●
Cyclophilin A		●			
DAP12	●				
DC-SIGN	●	●			
Dectin-1		●			
E2A	●	●			
ERC1		●			
ERC1α		●			
ETO		●			
Evi-1	●	●			
Fgr		●			
FoxP3	●				

Target	M	P	E	S	C
Fyn		●		●	
Galectin-1/LGALS1	●	●			
Galectin-3/LGALS3		●			
GIMAP5		●			
GP130		●			
GRK6	●				
Helios		●			
HPK1		●			
HS1	●	●			
Phospho-HS1 (Tyr397)	●	●			●
IFI16		●			
IFIT1		●			
IFITM1		●			
IFITM2		●			
IFN-α	●				
IFN-γ	●				●
IGBP1	●				
Ikaros	●	●			
IκBα	●	●	●	●	
Phospho-IκBα (Ser32)	●		●		●
Phospho-IκBα (Ser32/Ser36)					●
IκBα (Amino-terminal Antigen)	●				●
IκBα (Carboxy-terminal Antigen)	●				
IκBβ	●	●			
Phospho-IκBε (Ser18/22)		●			
IκBζ		●			
IKKα	●	●	●	●	
Phospho-IKKα (Ser176)/IKKβ (Ser177)	●				

Target	M	P	E	S	C
Phospho-IKKα/β (Ser176/180)	●		●		
IKKβ	●	●		●	
Phospho-IKKβ (Ser177/181)			●		
IKKγ	●	●			
Phospho-IKKγ (Ser376)		●			
IKKε	●	●			
Phospho-IKKε (Ser172)	●				
IL-1β	●				
IL-1RA	●				
IL-2	●				
IL-2Rα	●	●			
IL-2Rβ		●			
Mouse IL-3 Neutralizing	●				
Human IL-4 Neutralizing	●				
IL-4	●				
IL-6	●				
IL10	●				
IL-17A	●				
Human IL-17A Neutralizing	●				
IL17R	●	●			
IDO		●			
IRAK1	●	●		●	●
Phospho-IRAK1 (Thr209)		●			
Phospho-IRAK1 (Thr387)		●			
IRAK2		●			
IRAK4		●			
Phospho-IRAK4 (Thr345/Ser346)	●				●
IRAK-M		●			
IRF-1	●				●
IRF-2		●			
IRF-3	●			●	
Phospho-IRF-3 (Ser396)	●				
IRF-4	●	●			
IRF-5	●	●			
IRF-6		●			
IRF-7	●	●		●	
Phospho-IRF-7 (Ser471/472)		●			
Phospho-IRF-7 (Ser477)	●				
IRF-8	●				
Itk	●				
Jak1	●	●			
Phospho-Jak1 (Tyr1022/1023)		●			
Jak2	●			●	●
Phospho-Jak2 (Tyr221)		●			
Phospho-Jak2 (Tyr1007)	●				
Phospho-Jak2 (Tyr1007/1008)	●	●			

Target	M	P	E	S	C
Phospho-Jak2 (Tyr1008)	●				●
Jak3	●	●			
Phospho-Jak3 (Tyr980/Tyr981)	●				
Langerin		●			
LAT		●			
Phospho-LAT (Tyr171)		●			
Phospho-LAT (Tyr191)		●	●		
Lck	●	●			
Phospho-Lck (Tyr505)		●	●		
LGP2	●				
LITAF		●			
5-Lipoxygenase	●				
Phospho-5-Lipoxygenase (Ser271)		●			
Phospho-5-Lipoxygenase (Ser663)		●			
LRF/Pokemon		●			
Lsp1		●			
Lyn	●	●			
Phospho-Lyn (Tyr507)		●			
MALT1		●			
Mannose Receptor		●			
MAVS		●			
MCP-1 mouse		●			
MDA-5	●				
MEIS1/2		●			
Miz-1		●		●	
MNDA	●				●
MyD88	●	●			
Myeloperoxidase		●			
NALP1		●			
NDP52		●		●	
NFAT1	●	●			
NFAT2	●				
NFAT3	●				
NFAT4		●			
NF-κB p65	●		●	●	●
Phospho-NF-κB p65 (Ser468)		●			
Phospho-NF-κB p65 (Ser536)	●	●	●		●
Acetyl-NF-κB p65 (Lys310)	●	●			
Methyl-NF-κB p65 (Lys310)		●			
NF-κB p105		●			
Phospho-NF-κB p105 (Ser932)	●				
NF-κB p105/p50	●	●			
NF-κB2 p100/p52	●	●			
Phospho-NF-κB2 p100/p52 (Ser866/Ser870)		●			
NIK		●			
NLRC4	●				
NLRP3	●				
NLRX1		●			
Nod1		●			

Target	M	P	E	S	C
NOS (pan)		●			
iNOS	●	●	●		
NTAL/LAB	●	●			
Phospho-p40phox (Thr154)		●			
p47phox	●	●			
p67phox		●			
Pbx1		●			
PD-L1	●				
PIAS1	●				
PIAS3	●	●		●	
PIAS4	●				
Pim-1	●	●			
Pim-2	●				
Pim-3	●				
Pirin	●				
Prolactin Receptor	●				
PTPN22		●			
PU.1	●	●			●
RAG1	●				
RAGE		●			
RAGE 1	●	●			
RANK		●			
RANK Ligand		●			
RANTES		●			
c-Rel	●	●		●	
RelB	●	●			
Phospho-RelB (Ser552)	●	●			●
Rig-I	●	●			
RIP	●	●			
RIP2	●	●			
Phospho-RIP2 (Ser176)	●	●			
RIP3	●	●			
RIP4		●			
SAMHD1		●			
SARM1	●				
SDF1	●	●			
SH2D1A	●	●			
SHIP1	●	●			
Phospho-SHIP1 (Tyr1020)		●			
SHIP2	●	●			
Phospho-SHIP2 (Tyr986/Tyr987)		●			
Phospho-SHIP2 (Tyr1135)		●			
SHP-1	●				
Phospho-SHP-1 (Tyr564)	●				
SINTBAD	●				
SLP76		●			
Phospho-SLP76 (Ser376)		●			
SOCS1		●			
SOCS2		●			
SOCS3		●			
Stat1	●	●		●	
Phospho-Stat1 (Tyr701)	●		●		●

285

2012–2014 CITATIONS

CST antibodies for Phospho-Stat3 (Tyr705) have been cited over 285 times in high-impact, peer-reviewed publications from the global research community.

Select Citations:

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Schmidt, J.W. et al. (2014) Stat5 regulates the phosphatidylinositol 3-kinase/Akt1 pathway during mammary gland development and tumorigenesis. *Mol. Cell Biol.* 34, 1363–1377.

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Target	M	P	E	S	C
Phospho-Stat1 (Ser727)	●	●			
Stat2		●			
Phospho-Stat2 (Tyr690)		●			
Stat3	●	●	●	●	●
Phospho-Stat3 (Tyr705)	●	●	●		●
Phospho-Stat3 (Ser727)	●	●	●		
Acetyl-Stat3 (Lys685)		●			
Stat3α	●	●			
Stat4	●				
Phospho-Stat4 (Tyr693)	●	●			●
Stat5	●	●		●	●
Phospho-Stat5 (Tyr694)	●	●	●		●
Stat5a	●				
Stat6	●	●	●	●	
Phospho-Stat6 (Tyr641)	●	●	●		●
STING	●				
Syk	●	●			
Phospho-Syk (panTyr)			●		

Target	M	P	E	S	C
Phospho-Syk (Tyr323)		●			
Phospho-Syk (Tyr525/526)	●	●	●		●
TAL1		●			
TAP1		●			
TAP2		●			
T-bet/TBX21 (V365)	●	●			
TBK1/NAK	●	●			
Phospho-TBK1/ NAK (Ser172)	●				●
Tec		●			
THEMIS		●			
ThPOK	●				
TIRAP	●				
Toll-like Receptor 1		●			
Toll-like Receptor 2	●	●			
Toll-like Receptor 3	●			●	
Toll-like Receptor 4	●				
Toll-like Receptor 6	●				
Toll-like Receptor 7	●	●			
Toll-like Receptor 8	●				
Toll-like Receptor 9	●	●			
Human TNF-α Neutralizing	●				

Target	M	P	E	S	C
Mouse TNF-α Neutralizing	●				
TNF-α	●	●	●		●
TNF-R1	●			●	
Tollip		●			
Phospho-TPOR (Tyr626)	●				
TREX1		●			
TRIF		●			
TWEAK		●			
TWEAK Receptor/ Fn14		●			
Tyk2	●	●	●		
Phospho-Tyk2 (Tyr1054/1055)		●			
VCAM1		●			
Yes		●			
ZAP70	●		●		●
Phospho-ZAP70 (Tyr319)			●		
Phospho-Zap-70 (Tyr319)/Syk (Tyr352)	●	●			●
Phospho-ZAP70 (Tyr493)		●			

Jak and Cytokine Receptor Mutants

This table lists Jak and cytokine receptor mutations found in various cancers, along with corresponding publications.

Jak Mutants	Cytokine Receptor	Disease	References
Jak2 V617F	EpoR, TpoR (MPL), G-CSFR	Myeloproliferative neoplasms (MNPs), PV, ET, PMF	1–5
Jak2 K539L, exon 12 mutants	EpoR	MNP: PV	6
Jak2 T875N	Undetermined	AML (AMKL)	7
Jak3 A572V	Undetermined	AML (AMKL) (cell lines)	8
Jak1 V658F, Jak1 A634D, R879H, R724S	IL2R, IL9R, other undetermined	T-ALL	9,10
Jak1 R683G/S Jak2 DIREED	TLSPR	Pediatric and Down syndrome ALL	11–15
Jak2 V617I, Jak2 R564Q, Jak2 S755R/ R938Q	TpoR (MPL)	Hereditary thrombocytosis	16–18

Receptor Mutants	Cytokine Receptor	Disease	References
TpoR W515L/K/A	Jak2	MPNs: ET, PMF	19–21
TpoR S505N			22
TpoR S487A			23
TLSPR F232S / TLSPR translocations	Jak2 R683 mutants	Pediatric and Down syndrome ALL	13, 24–26

References: (1) James, C. et al. (2005) *Nature* 434, 1144–1148. • (2) Baxter, E.J. et al. (2005) *Lancet* 365, 1054–1061. • (3) Kralovics, R. et al. (2005) *N. Engl. J. Med.* 352, 1779–1790. • (4) Levine, R.L. et al. (2005) *Cancer Cell* 7, 387–397. • (5) Vainchenker, W. et al. (2008) *Semin. Cell Dev. Biol.* 19, 385–393. • (6) Scott, L.M. et al. (2007) *N. Engl. J. Med.* 356, 459–468. • (7) Mercher, T. et al. (2006) *Blood* 108, 2770–2779. • (8) Walters, D.K. et al. (2006) *Cancer Cell* 10, 65–75. • (9) Flex, E. et al. (2008) *J. Exp. Med.* 205, 751–758. • (10) Jeong, E.G. et al. (2008) *Clin. Cancer Res.* 14, 3716–3721. • (11) Malinge, S. et al. (2007) *Blood* 109, 2202–2204. • (12) Mullighan, C.G. et al. (2009) *Proc. Natl. Acad. Sci. USA* 106, 9414–9418. • (13) Mullighan, C.G. et al. (2009) *Nat. Genet.* 41, 1243–1246. • (14) Bercovich, D., et al. (2008) *Lancet* 372, 1484–1492. • (15) Kearney, L. et al. (2009) *Blood* 113, 646–648. • (16) Mead, A.J. et al. (2013) *Blood* 121, 4156–4165. • (17) Etheridge, S.L. et al. (2014) *Blood* 123, 1059–1068. • (18) Marty, C. et al. (2014) *Blood* 123, 1372–1383. • (19) Pikman, Y. et al. (2006) *PLoS Med.* 3, e270. • (20) Pardanani, A.D. et al. (2006) *Blood* 108, 3472–3476. • (21) Pecquet, C. et al. (2010) *Blood* 115, 1037–1048. • (22) Ding, J. et al. (2004) *Blood* 103, 4198–4200. • (23) Malinge, S. et al. (2008) *Blood* 112, 4220–4226. • (24) Russell, L.J. et al. (2009) *Blood* 114, 2688–2698. • (25) Chapiro, E. et al. (2010) *Leukemia* 24, 642–645. • (26) Hertzberg, L. et al. (2010) *Blood* 115, 1006–1017.

Jak/Stat Utilization

This table lists the combinatorial use of tyrosine kinases and Stat proteins in cytokine/growth factor signaling.

Ligand	Receptor	Jak-Kinase	Other Tyrosine Kinases	Stat Family Members
IL-6	IL-6Rα+gp130	Jak1,2, Tyk2	Hck	Stat1, Stat3
IL-11	IL-11R+gp130	Jak1,2, Tyk2	Src, Yes	Stat3
CNTF, CT-1, LIF, OSM	CNTFR+gp130, CT-1R+gp130, LIFR+gp130, OSMR+gp130	Jak1,2, Tyk2	Src family	Predominant: Stat3 Secondary: Stat1,5
G-CSF	G-CSFR	Jak2, Tyk2	Lyn	Stat3
IL-12 (p40+p35)	IL-12Rβ1+IL-12Rβ2	Jak2, Tyk2	Lck	Stat4
Leptin	LeptinR	Jak2	Not determined	Stat3,5,6
IL-3	IL-3Rα+βc	Jak2	Fyn, Hck, Lyn	Stat3,5,6
IL-5	IL-5R+βc	Jak2	Btk	Stat3,5,6
GM-CSF	GM-CSFR+βc	Jak2	Hck, Lyn	Stat3,5
Angiotensin	GPCR	Jak2, Tyk2		Stat1,2,3
Serotonin	GPCR	Jak2		Stat3
α-Thrombin	GPCR	Jak2		Stat1,3
Chemokines	CXCR4	Jak2,3		
IL-2	IL-2Rα+IL-2Rb+γc	Jak1,2,3	Fyn, Hck, Lck, Syk, Tec	Stat3,5
IL-4	IL-4Rα+γcR or IL-4Rα+IL-13Rα1	Jak1,3	Lck, Tec	Stat6
IL-7	IL-7R+γc	Jak1,3	Lyn	Stat3,5
IL-9	IL-9R+γc	Jak1,3	Not determined	Stat1,3,5
IL-13	IL-13Rα1+ IL-4Rα	Jak1,2, Tyk2	Ctk	Stat6
IL-15	IL-15Rα+IL-2Rβ+γc	Jak1,3	Lck	Stat3,5
IL-19	IL-20Rα+IL-20Rβ	Jak1, ?		Stat3
IL-20	IL-20Rα+IL-20Rβ, IL-22R+IL-20Rβ	Jak1, ?		Stat3
IL-21	IL-21R+γc	Jak1,3		Stat1,3,5
IL-22	IL-22R+IL-10Rβ	Jak1, Tyk2		Stat1,3,5
IL-23 (p40+p19)	IL-12Rβ1+IL-23R	Jak2	Tyk2	Stat4
IL-24	same as IL-20	Jak1, ?		Stat3
IL-26	IL-20Rα+IL-10Rβ	Jak1, Tyk2		Stat3
IL-27 (EBI3+p28)	gp130+WSX1	Jak1,2, Tyk2		Stat1,2,3,4,5
IL-28A, IL-28B, IL-29	IL-28R+IL-10Rβ	Jak1, Tyk2		Stat1,2,3,4,5
IL-31	IL-31Rα+OSMR	Jak1,2, Tyk2		Stat1,3,5
IL-35 (p35+EBI3)	gp130+WSX1	Jak1,2, Tyk2		Stat1,3,5
GH	GHR	Jak2	Src family	Stat3,5 (mainly Stat5a)
Tpo	TpoR (c-Mpl)	Jak2, Tyk2	Lyn	Stat1,3,5
Epo, Pro	EpoR, ProlactinR	Jak2	Src Family	Stat5 (mainly Stat5a)
Interferon (IFNα/β)	IFNAR1+IFNAR2	Jak1, Tyk2	Lck	Predominant: Stat1,2 Secondary: Stat3,4,5
IFN-γ	IFN-gR1+IFN-γR2	Jak1, Jak2	Hck, Lyn	Stat1
IL-10	IL-10Rα+ IL-10Rβ	Jak1, Tyk2	Not determined	Stat1,3,5
TLSP	TLSPR and IL-7R	Jak1, possibly Jak2	Not determined	Stat3,5
EGF	EGFR	Jak1	EGFR, Src	Stat1,3,5
PDGF	PDGFR	Jak1,2	PDGFR, Src	Stat1,3,5

We would like to thank Prof. Stefan Constantinescu, Ludwig Institute for Cancer Research, Brussels, Belgium for contributing to this table.

Protein Kinases: Introduction

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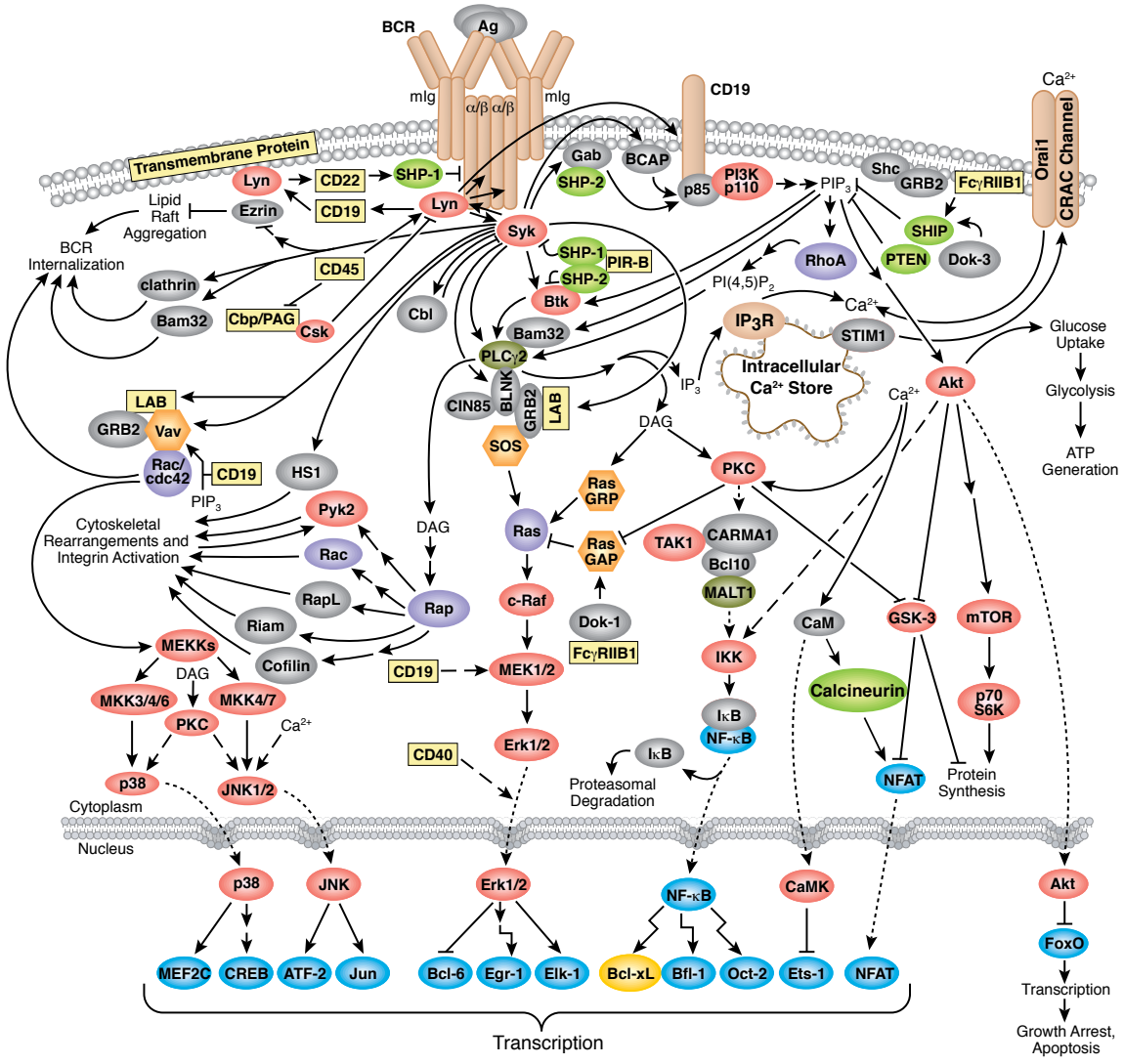
B Cell Receptor Signaling



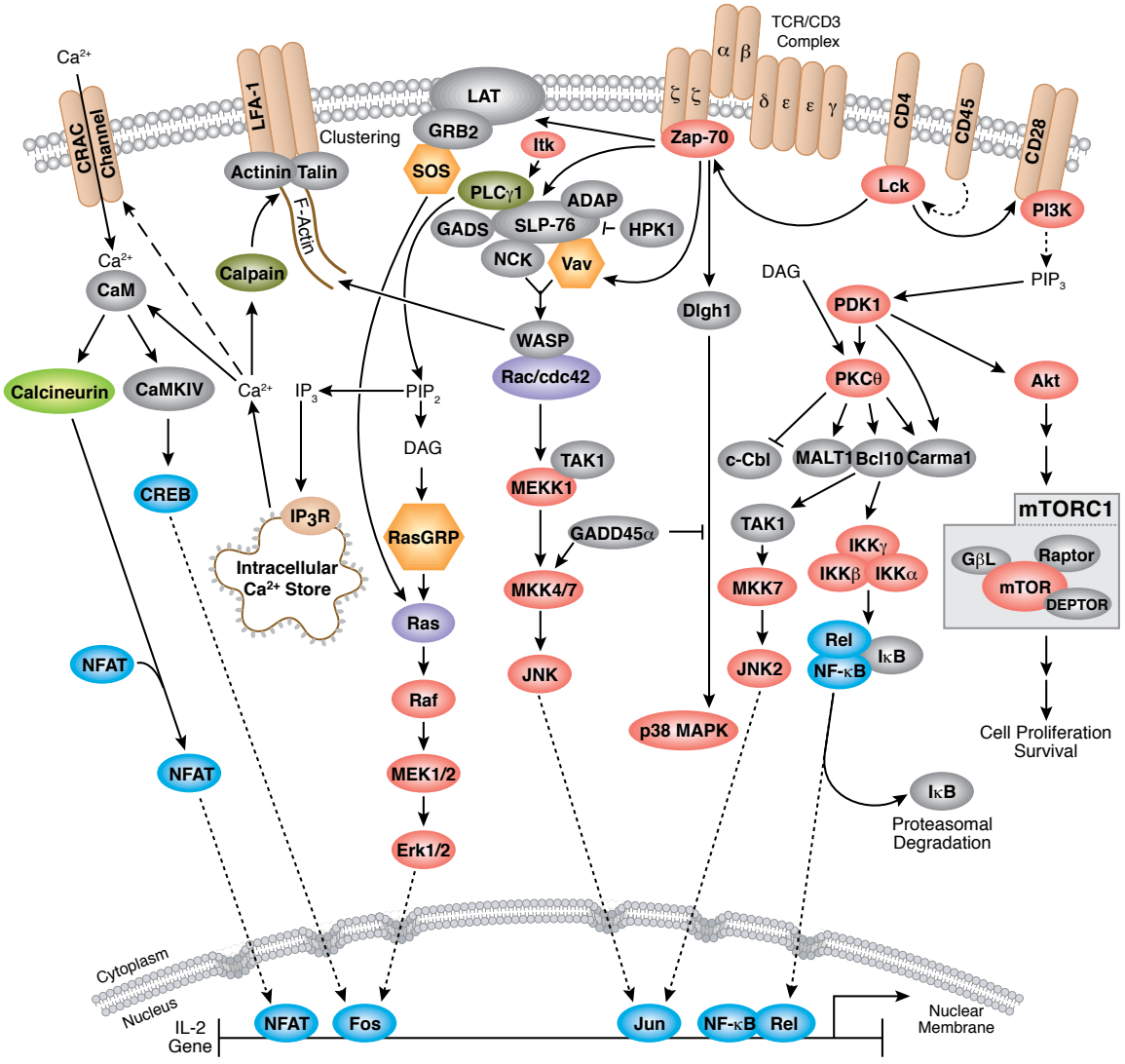
The B cell antigen receptor (BCR) is composed of membrane immunoglobulin (mIg) molecules and associated Igα/Igβ (CD79a/CD79b) heterodimers (α/β). The mIg subunits bind antigen, resulting in receptor aggregation, while the α/β subunits transduce signals to the cell interior. BCR aggregation rapidly activates 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 PLCγ2, 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, the IL-21 receptor, 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 here 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, FcγRIIB1, PIR-B, and internalization of the BCR. *In vivo*, B cells are often activated by antigen-presenting cells that capture antigens and display them on their cell surface. Activation of B cells by such membrane-associated antigens requires BCR-induced cytoskeletal reorganization. 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.

Select Reviews:

Dal Porto, J.M., Gauld, S.B., Merrell, K.T., et al. (2004) *Mol. Immunol.* 41, 599–613. • Goodnow, C.C., Vinuesa, C.G., Randall, K.L., et al. (2010) *Nat. Immunol.* 11, 681–688. • Harwood, N.E. and Batista, F.D. (2010) *Annu. Rev. Immunol.* 28, 185–210. • Harwood, N.E. and Batista, F.D. (2008) *Immunity* 28, 609–619. • Kurosaki, T., Shinohara, H., and Baba, Y. (2010) *Annu. Rev. Immunol.* 28, 21–55. • Szydłowski, M., Jabłońska, E., and Juszczyński, P. (2014) *Int. Rev. Immunol.* 33, 146–157.

 • We would like to thank Prof. Michael R. Gold, University of British Columbia, Vancouver, British Columbia, Canada for reviewing this diagram.

T Cell Receptor Signaling



Tumor cells employ multiple defense strategies to evade detection by the immune system. One common strategy, upregulation of immune checkpoint proteins and ligands, takes advantage of a natural immune mechanism for self-tolerance and prevention of collateral tissue damage. Immune checkpoint proteins, such as PD-1, CTLA-4, and many others, are located on T cells and engage with their corresponding ligand on tumor cells or dendritic cells, sending inhibitory signals that repress T cell activation or response. One of the first discovered checkpoint proteins, CTLA-4, plays a role at the stage of T cell priming by binding to the CD28 ligands CD80 or CD86 to prevent co-stimulatory signals necessary for T cell activation. In contrast, the PD-1/PD-L1 checkpoint acts later in the process, inhibiting anti-tumor immune responses by effector T cells such as $CD4^+$ T helper 1 (Th1) cells and $CD8^+$ cytotoxic T lymphocytes (CTLs), leading to decreases in IFNγ production and cytolytic activity. Upregulation of PD-L1 expression on the tumor cell surface is mediated by IFNγR signaling to Stat1, as well as oncogenic signaling through several receptor tyrosine kinases (EGFR, ALK, ROS, HER2, and others) to activate the MAPK, Akt, and Stat3 pathways.

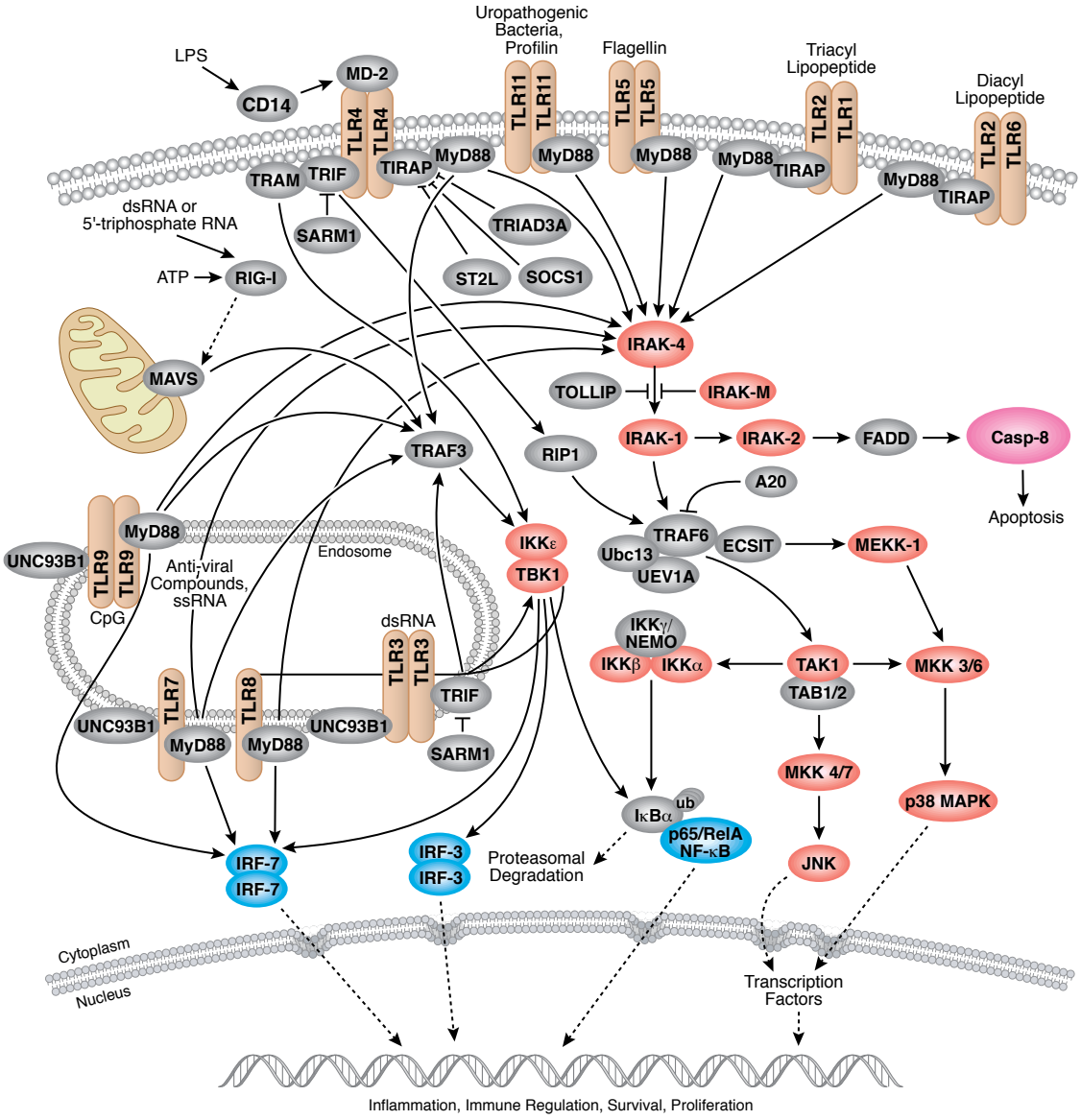
Cells in the tumor microenvironment can also influence tumor progression. $FoxP3^+/CD4^+$ T regulatory cells (T_{Regs}) and myeloid-derived suppressor cells (MSCs) secrete immunosuppressive cytokines IL-10 and TGF-β to inhibit the activity of Th1 cells and CTLs. Natural killer (NK) cells release cytotoxic granules against the tumor cell and secrete IFNγ, which stimulates surrounding pro-inflammatory M1 macrophages. Pro-tumorigenic M2 macrophages suppress anti-tumor immune responses via production of IL-10 and TGF-β and promote metastasis through release of MMPs. MMPs and TGF-β are also released by surrounding mast cells.

Select Reviews:

Burbach, B.J., Medeiros, R.B., Mueller, K.L., and Shimizu, Y. (2007) *Immunol. Rev.* 218, 65–81. • Chen, L. and Flies, D.B. (2013) *Nat. Rev. Immunol.* 13, 227–242. • Cheng, J., Montecalvo, A., and Kane, L.P. (2011) *Immunol. Res.* 50, 113–117. • Cronin, S.J. and Penninger, J.M. (2007) *Immunol. Rev.* 220, 151–168. • Fracchia, K.M., Pai, C.Y., and Walsh, C.M. (2013) *Front Immunol.* 4, 324. • Marsland, B.J. and Kopf, M. (2008) *Trends Immunol.* 29, 179–185. • Thome, M. (2008) *Nat. Rev. Immunol.* 8, 495–500.

 • We would like to thank Prof. Sankar Ghosh, Columbia University, New York, NY for reviewing this diagram.

Toll-like Receptor Signaling



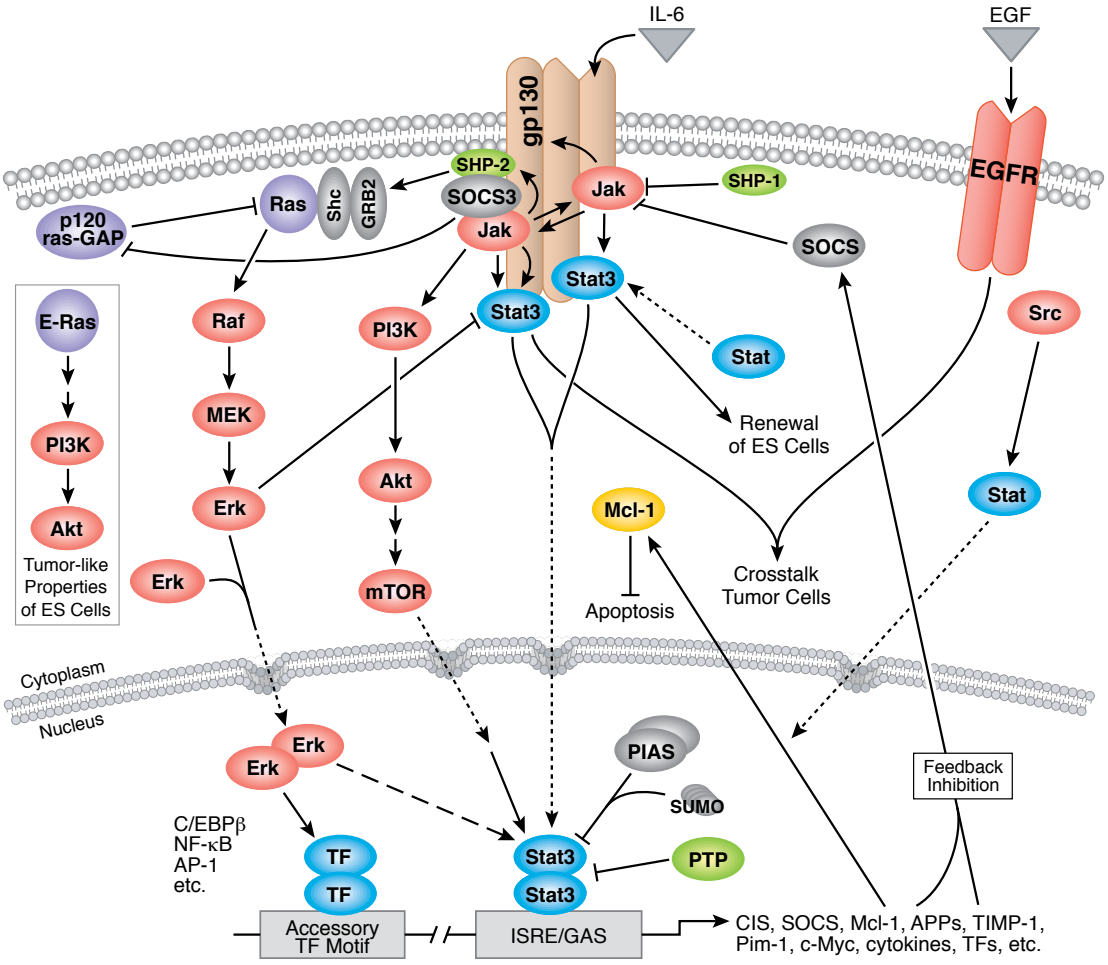
Toll-like receptors (TLRs) recognize distinct pathogen-associated molecular patterns and play a critical role in innate immune responses. They participate in the first line of defense against invading pathogens and play a significant role in inflammation, immune cell regulation, survival, and proliferation. To date, 11 members of the TLR family have been identified, of which TLR1, TLR2, TLR4, TLR5, TLR6, and TLR11 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 is activated by phosphorylation and associates with TRAF6, thereby activating the IKK complex and leading to activation of MAP kinases (JNK, p38 MAPK) and NF-κB. 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. Activation of MyD88-independent pathways occurs via TRIF and TRAF3, leading to recruitment of IKKε/TBK1, phosphorylation 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. TRAF3 plays a critical role in the regulation of both MyD88-dependent and TRIF-dependent signaling via TRAF3 degradation, which activates MyD88-dependent signaling and suppresses TRIF-dependent signaling (and vice versa).

Select Reviews:

Barton, G.M. and Kagan, J.C. (2009) *Nat. Rev. Immunol.* 9, 535–542. • Blasius, A.L. and Beutler, B. (2010) *Immunity* 32, 305–315. • Kawai, T., and Akira, S. (2010) *Nat. Immunol.* 11, 373–384. • Lester, S.N. and Li, K. (2014) *J. Mol. Biol.* 426, 1246–1264. • Li, X., Jiang, S., and Tapping, R.I. (2010) *Cytokine* 49, 1–9. • McGettrick, A.F. and O'Neill, L.A. (2010) *Curr. Opin. Immunol.* 22, 20–27. • Miggin, S.M. and O'Neill, L.A. (2006) *J. Leukoc. Biol.* 80, 220–226. • Pasare, C. and Medzhitov, R. (2005) *Adv. Exp. Med. Biol.* 560, 11–18. • Reuven, E.M., Fink, A., and Shai, Y. (2014) *Biochim. Biophys. Acta.* 1838, 1586–1593.

 • We would like to thank Dr. Pranoti Mandrekar, University of Massachusetts Medical School, Worcester, MA, for reviewing this diagram.

Jak/Stat Signaling: IL-6 Receptor Family



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 coregulate 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.

Phosphorylated Stats dimerize and translocate into the nucleus to regulate target gene transcription. Members of the suppressor of cytokine signaling (SOCS) 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. Researchers have found Stat3 and Stat5 to be constitutively activated by tyrosine kinases other than Jaks in several solid tumors.

The Jak/Stat pathway mediates the effects of cytokines, like erythropoietin, thrombopoietin, and G-CSF, which are protein drugs for the treatment of anemia, thrombocytopenia, and neutropenia, respectively. The pathway also mediates signaling by interferons, which are used as antiviral and antiproliferative agents. Researchers have found that dysregulated cytokine signaling contributes to cancer. Aberrant IL-6 signaling contributes to the pathogenesis of autoimmune diseases, inflammation, and cancers such as prostate cancer and multiple myeloma. Jak inhibitors currently are being tested in models of multiple myeloma. Stat3 can act as an oncogene and is constitutively active in many tumors. Crosstalk between cytokine signaling and EGFR family members is seen in some cancer cells. Research has shown that in glioblastoma cells overexpressing EGFR, resistance to EGFR kinase inhibitors is induced by Jak2 binding to EGFR via the FERM domain of the former (Sci. Signal. (2013) 6, ra55).

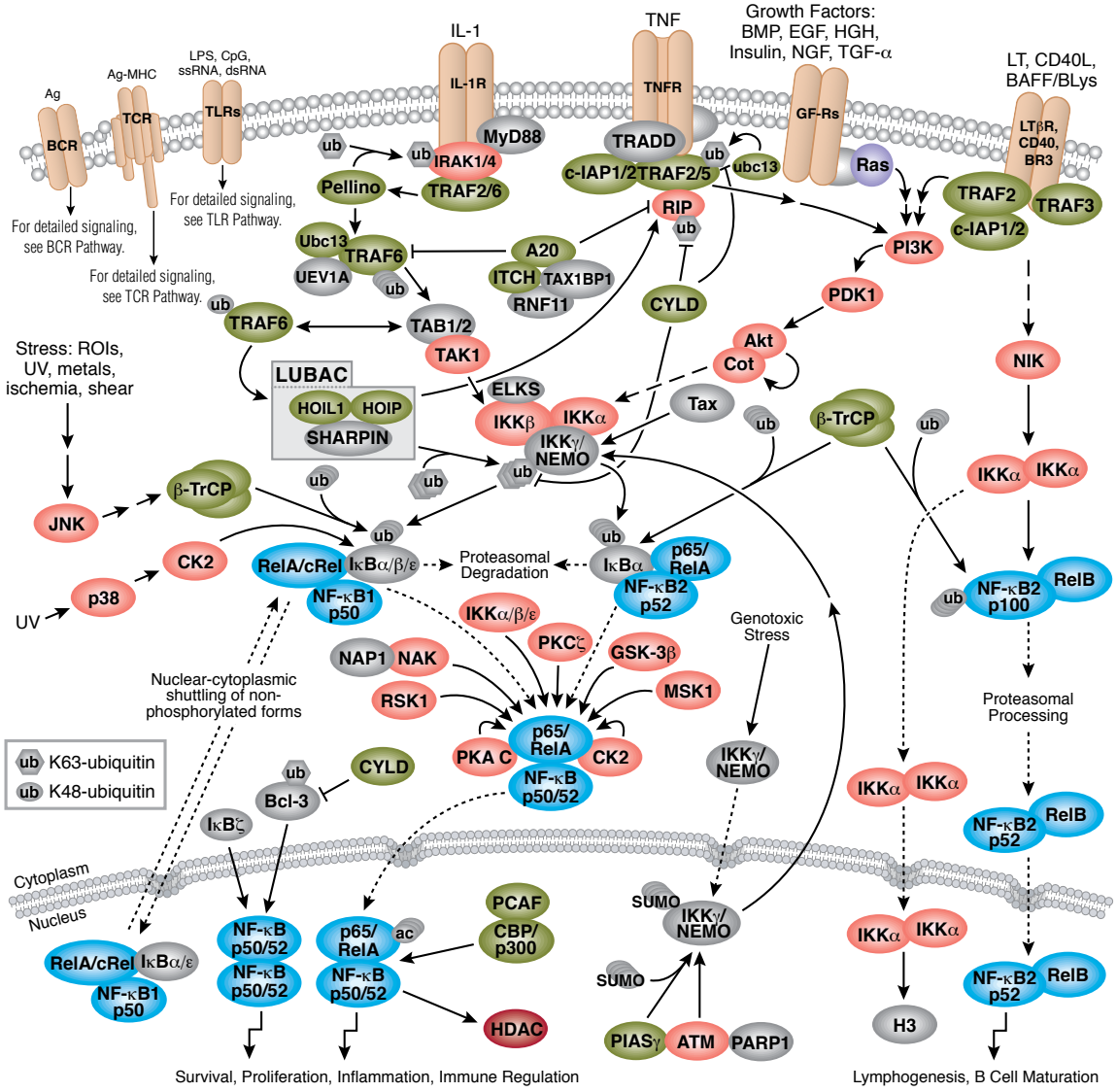
Activating Jak mutations are major molecular events in human hematological malignancies. Researchers have found a unique somatic mutation in the Jak2 pseudokinase domain (V617F) that commonly occurs in polycythemia vera, essential thrombocythemia, and idiopathic myelofibrosis. This mutation results in the pathologic activation Jak2, associated with receptors for erythropoietin, thrombopoietin, and G-CSF, which control erythroid, megakaryocytic, and granulocytic proliferation and differentiation. Researchers have also shown that somatic acquired gain-of-function mutations of Jak1 are found in adult T cell acute lymphoblastic leukemia. Somatic activating mutations in Jak1, Jak2, and Jak3 have also been identified in pediatric acute lymphoblastic leukemia (ALL). Furthermore, Jak2 mutations have been detected around pseudokinase domain R683 (R683G or DIREED) in Down syndrome childhood B-ALL and pediatric B-ALL.

Select Reviews:

Beekman, R. and Touw, I.P. (2010) *Blood* 115, 5131–5136. • Neurath, M.F. and Finotto, S. (2011) *Cytokine Growth Factor Rev.* 22, 83–89. • Sansone, P. and Bromberg, J. (2012) *J. Clin. Oncol.* 30, 1005–1014. • Vainchenker, W. and Constantinescu, S.N. (2013) *Oncogene* 32, 2601–2613. • Yu, H., Pardoll, D., and Jove, R. (2009) *Nat. Rev. Cancer* 9, 798–809.

 • We would like to thank Prof. Stefan Constantinescu, Ludwig Institute for Cancer Research, Brussels, Belgium for reviewing this diagram.

NF-κB Signaling

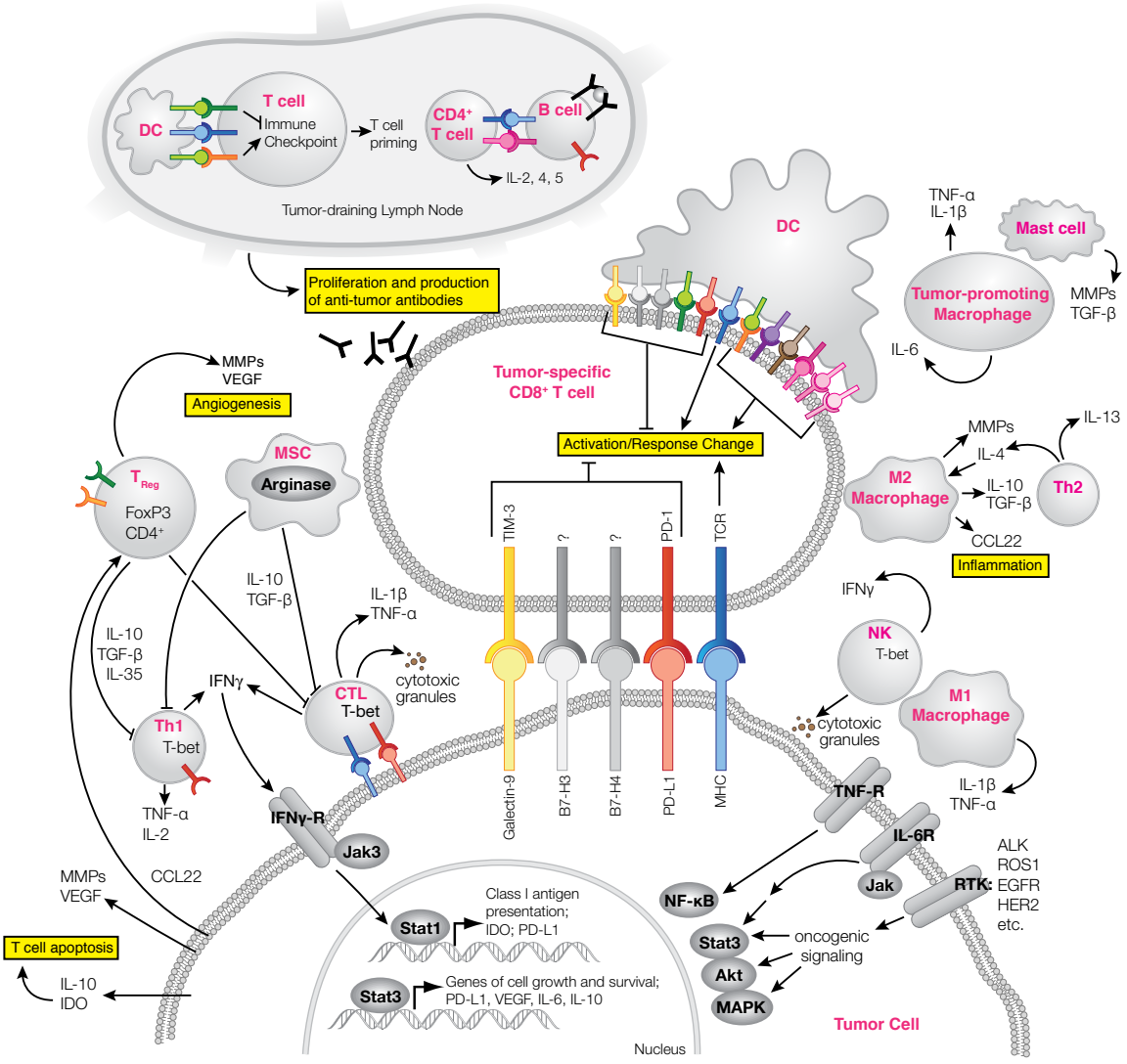


Nuclear factor-κB (NF-κB)/Rel proteins include NF-κB2 p52/p100, NF-κB1 p50/p105, c-Rel, RelA/p65, and RelB. These proteins function as dimeric transcription factors that regulate the expression of genes influencing a broad range of biological processes including innate and adaptive immunity, inflammation, 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 (IKKβ, IKKα, 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 post-translational modifications (phosphorylation, acetylation, glycosylation) and translocate to the nucleus where, either alone or in combination with other transcription factors 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. This creates transcriptionally competent NF-κB 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.

Select Reviews:
Gilmore T.D. (2014) www.nf-kb.org • Hayden M.S. and Ghosh S. (2008) *Cell* 132, 344–362. • Perkins N.D. (2006) *Oncogene* 25, 6717–30. • Sun S-C. (2012) *Immunol Rev.* 246, 125–140. • Chen J. and Chen Z.J. (2013) *Curr. Opin. Immunol.* 25, 4–12.

 • We would like to thank Prof. Thomas D. Gilmore, Boston University, Boston, MA, for reviewing this diagram.

Tumor Immunology



Tumor cells employ multiple defense strategies to evade detection by the immune system. One common strategy, upregulation of immune checkpoint proteins and ligands, takes advantage of a natural immune mechanism for self-tolerance and prevention of collateral tissue damage. Immune checkpoint receptors, such as PD-1, CTLA-4, and many others, are located on T cells and engage with their corresponding ligand on tumor cells and dendritic cells, sending inhibitory signals that repress T cell activation or response. One of the first discovered checkpoint proteins, CTLA-4, plays a role at the stage of T cell priming by binding to the CD28 ligands CD80 or CD86 to prevent co-stimulatory signals necessary for T cell activation. In contrast, the PD-1/PD-L1 checkpoint acts later in the process, inhibiting anti-tumor immune responses by effector T cells such as $CD4^+$ T helper 1 (Th1) cells and $CD8^+$ cytotoxic T lymphocytes (CTLs), leading to decreases in IFNγ production and cytolytic activity. Upregulation of PD-L1 expression on the tumor cell surface is mediated by IFNγR signaling to Stat1, as well as oncogenic signaling through several receptor tyrosine kinases (EGFR, ALK, ROS, HER2, and others) to activate the MAPK, Akt, and Stat3 pathways.

Cells in the tumor microenvironment can also influence tumor progression. $FoxP3^+/CD4^+$ T regulatory cells (Tregs) and myeloid-derived suppressor cells (MDSCs) secrete immunosuppressive cytokines IL-10 and TGF-β to inhibit the activity of Th1 cells and CTLs. Natural killer (NK) cells release cytotoxic granules against the tumor cell and secrete IFNγ, which stimulates surrounding pro-inflammatory M1 macrophages. Pro-tumorigenic M2 macrophages suppress anti-tumor immune responses via production of IL-10 and TGF-β and promote metastasis through release of MMPs. MMPs and TGF-β are also released by surrounding mast cells.

Select Reviews:

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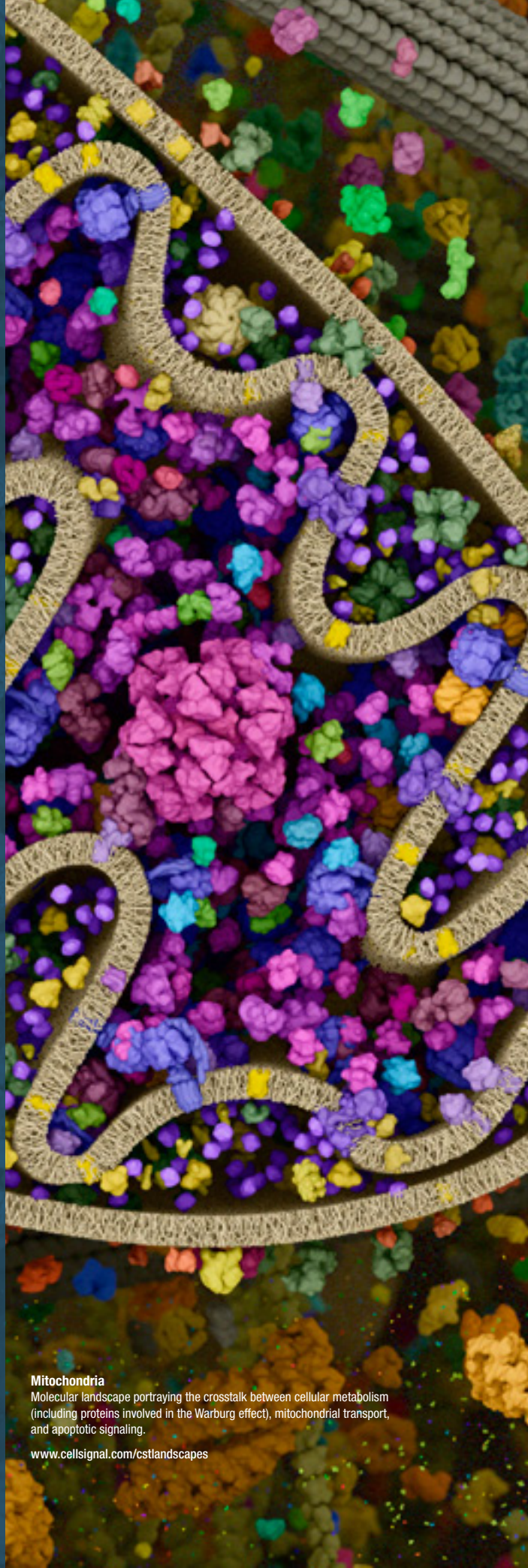

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