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REVIEW

A comprehensive map of the toll-like receptor signaling network

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Recognition of pathogen-associated molecular signatures is critically important in proper activation of the immune system. The toll-like receptor (TLR) signaling network is responsible for innate immune response. In mammalians, there are 11 TLRs that recognize a variety of ligands from pathogens to trigger immunological responses. In this paper, we present a comprehensive map of TLRs and interleukin 1 receptor signaling networks based on papers published so far. The map illustrates the possible existence of a main network subsystem that has a bow-tie structure in which myeloid differentiation primary response gene 88 (MyD88) is a nonredundant core element, two collateral subsystems with small GTPase and phosphatidylinositol signaling, and MyD88-independent pathway. There is extensive crosstalk between the main bow-tie network and subsystems, as well as feedback and feedforward controls. One obvious feature of this network is the fragility against removal of the nonredundant core element, which is MyD88, and involvement of collateral subsystems for generating different reactions and gene expressions for different stimuli.

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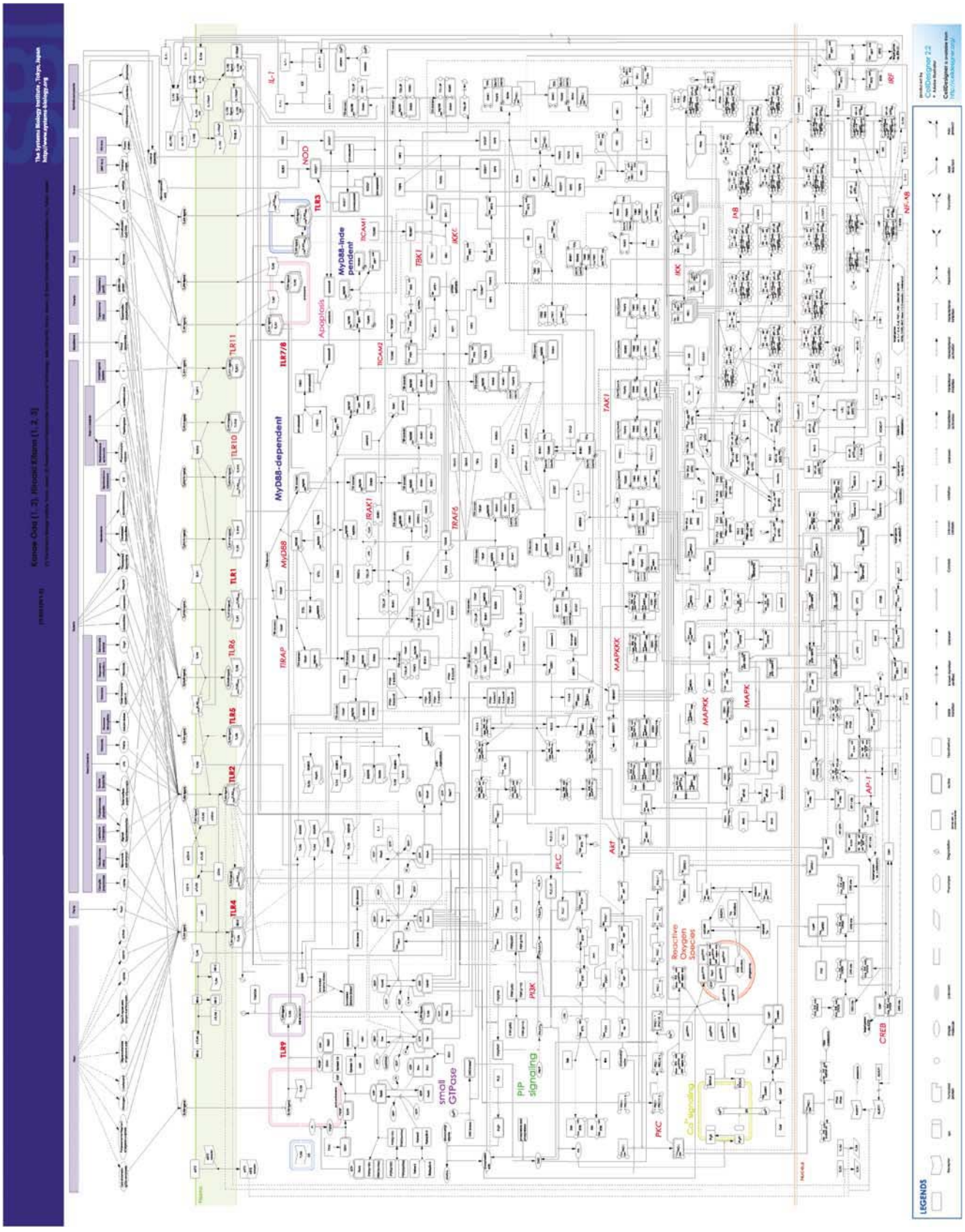
Introduction

The toll-like receptor (TLR) signaling pathway is the front-line subsystem against invasive microorganisms for both innate and adaptive immunity (Iwasaki and Medzhitov, 2004). To sense innumerable and various pathogenic threats, TLRs have evolved to recognize pathogen-associated molecular patterns (PAMPs), which represent molecular features on the surface of pathogens. The TLR gene family and their pathways have been evolutionarily well conserved in both invertebrates and vertebrates (Hoffmann and Reichhart, 2002; Roach *et al*, 2005). One of the fundamental questions is how pathogenic stimuli in the form of PAMPs induce various responses that ultimately protect the host. Each TLR binds to a variety of PAMPs that work as molecular markers of potential pathogens that the host shall be defended against. For example, TLR4 was found to be a receptor for lipolysaccharide (LPS) and essential to generate responses to Gram-negative bacteria in which LPS is a part of the outer membrane (Poltorak *et al*, 1998), TLR9 responds to DNA-containing unmethylated CpG motifs (Hemmi *et al*, 2000), TLR3 is activated by double-stranded RNA (Alexopoulou *et al*, 2001), and bacteria flagellin activates TLR5 (Hayashi *et al*, 2001). There are extensive reviews on ligand receptor relationships for further reference (Akira and Takeda, 2004; Beutler, 2004; Iwasaki and Medzhitov, 2004). TLRs and interleukin 1 receptors (IL-1Rs) have a conserved region of amino acids, which is known as the toll/IL-1R (TIR) domain (Slack *et al*, 2000). Signaling of the TLR/IL-1R superfamily is mediated through myeloid differentiation primary response gene 88 (MyD88), IL-1R-associated kinases (IRAKs), transforming growth factor beta-activated kinase 1 (TAK1), TAK1-binding protein 1 (TAB1), TAB2, tumor necrosis factor (TNF) receptor-associated factor 6 (TRAF6), etc. (Akira and Takeda, 2004). It should be mentioned that TLR1, TLR2, TLR6, TLR4, and TLR5 are located on the plasma membrane, whereas TLR3, TLR7, and TLR9 are not located on the cell surface (Akira and Takeda, 2004). While ligands for each TLR and interactions downstream of receptors are now being identified at a dramatic pace, doubt is now being cast on the global logic behind all TLR pathways. It was argued that the TLR pathway forms an hour-glass structure (Beutler, 2004), but the precise shape of the global TLR signaling network and its functional implications has not been elucidated. Since TLRs activate innate immunity and influence the nature of adaptive immunity (Hoebe *et al*, 2004), understanding the logic behind TLR signaling is the most important topic in immunology.

Therefore, we present a map of TLR and IL-1R signaling networks (Figure 1). We manually assembled molecular interactions based on published papers and constructed a TLR map that incorporates the possible pathways in mammalians using a modeling support software, CellDesigner ver.2.2 (http://celldesigner.org/) (Funahashi and Kitano, 2003). The map comprises 652 species and 444 reactions. The species shown on the TLR map can be categorized as follows: 340 proteins, 170 oligomers, 79 simple molecules, 18 genes, eight RNA, three ions, 18 degraded products, and 16 phenotypes. The breakdown of reactions is as follows: 242 state transitions, 106 associations, 25 dissociations, 33 transports, 24 unknown transitions, and 14 omitted transitions. Out of 444 reactions, there are 397 interactions: 270 catalyses, 75 unknown catalyses, 20 inhibitions, nine unknown inhibitions, and 23 transcriptional activations. All the 411 references used for constructing the map are listed in the 'References for TLR Pathway Map' and the CellDesigner software allows the user to access references that are used as grounds of individual reaction using PubMed ID. It should be



noted that the map is a best effort based on existing papers and was created manually. The criteria for inclusion into the map are similar to those for the previous epidermal growth factor receptor (EGFR) signaling map (Oda *et al*, 2005), and we did our best to reconstruct a reliable map. However, errors and missing interactions are inevitable, and we must assume that there are interactions that have yet to be identified. Obviously, the map will be continuously updated and possible errors will be corrected. This correction and updating process has to be a continuous process involving the community of TLR signaling experts.

One of the issues in constructing maps of molecular interactions is the reliability of the map. But what does map accuracy mean, what are the justifications for including specific interactions but excluding others, and how should conflicting and uncertain reports be dealt with? There are at least two major sources of inaccuracies: inaccuracy within each paper of reference, and inaccuracy of interpretation of papers. The former problem is inherent in many pathway databases based on manual curation, and only way to mitigate the problem is to set a certain standard on which papers to be used for map construction. As in the case of the EGFR signaling map, we have included interactions that have been experimentally verified in multiple reports. We may include interactions that are reported in a single paper if there are no conflicting reports. But almost all experiments in them were performed under the distinct conditions at each laboratory. Hence, it is inevitable that drawing the pathway is like the mosaic woodwork that is gathering the 'possible' interactions. The selection of the information on the pathway map must be entrusted to the users according to their purposes, and which interpretation to be widely agreed may rest on the community-wide discusions. For some readers, some interactions may be viewed as premature hypotheses, whereas the same interactions may be considered more plausible by others. The certaintity rating may be used to illustrate how much each interaction is hypothetical or the level of confidence, but such a rating itself may be subjective without a sophisticated evaluation method. Thus, at present the map could be skeptically viewed as merely representing 'The View of the World' of the authors, rather like the 'New Yorkers' View of the World' map sold to tourists. Nevertheless, we consider our map to be useful because it does represent one comprehensive view of the network, the map is based on published articles, and publication of such a map can initiate a community-wide interactive process for creating a more accurate and information-rich map. We are currently working on a scheme to accept community-wide feedback on the map, so that the map can be iteratively improved in both coverage and quality.

In order to make the map a practical and accessible resource, it has to be provided in a standard format. Thus, the map complies with Systems Biology Markup Language (SBML) for machine readable representation (Hucka *et al*, 2003), and adopts a specific graphical notation system called the process

Figure 1 A comprehensive molecular interaction map of TLR signaling network. The SBML and PDF files of the map are available from the Supplementary information. The map can be best viewed in the PDF format. All of the species, proteins, and reactions included in the map are listed in the SBML file when opened by CellDesigner (http://celldesigner.org/). Abbreviations: A20, tumor necrosis factor-inducible protein A20; Akt, v-akt murine thymoma viral oncogene homolog; ASK, apoptosis signal-regulating kinase; ATF, activating transcription factor; Bcl, B-cell CLL/lymphoma; beta-TrCP, beta-transducin repeat-containing protein; BTK, Bruton agammaglobulinemia tyrosine kinase; CaM, calmodulin; CaMKI, calcium/calmodulin-dependent protein kinase; CBP, CREB-binding protein; c-Cbl, Casitas B-lineage lymphoma proto-oncogene; CD, cluster of differentiation; Cdc42, cell division cycle 42 (GTP-binding protein, 25 kDa); CK, casein kinase; c-Myc, v-myc myelocytomatosis viral oncogene homolog; CRE, cAMP response element; CREB, cAMP response element-binding protein; CsgA, major curlin subunit precursor, *Salmonella enterica*; c-Src, v-src sarcoma (Schmidt–Ruppin A-2) viral oncogene homolog (avian); C-TAK1, MAP/microtubule affinity-regulating kinase 3; CYLD, cylindromatosis (turban tumor syndrome); DAG, diacylglycerol; dsRNA, double-strand RNA; ECSIT, evolutionarily conserved signaling intermediate in toll pathway; EEA, early endosome antigen; eIF, eukaryotic translation initiation factor; Elk-1, ETS domain protein Elk-1; ERK, extracellular signal-regulated kinase; FADD, Fas-associated via death domain; Fos, v-fos FBJ murine osteosarcoma viral oncogene homolog; gp91phox, glycoprotein of 91 kDa from phagocyte oxidase; GSK, glycogen synthase kinase; HDAC, histone deacetylase, HMG, high-mobility group nucleosome-binding domain; hnRNP, heterogeneous nuclear ribonucleoprotein; HSP, heat-shock protein; Ibtk, inhibitor of Bruton agammaglobulinemia tyrosine kinase; ICE, interleukin 1-B-converting enzyme; IκB, nuclear factor of κ light polypeptide gene enhancer in B-cells inhibitor; IKK, I-κ-B kinase; IL, interleukin; IL-1ra, interleukin 1 receptor antagonist; IL-1RAcP, interleukin 1 receptor accessory protein; IP3, inositol 1,4,5-triphosphate; IP3R, inositol 1,4,5-triphosphate receptor; IRAK, interleukin 1 receptor-associated kinase; IRF, interferon-regulatory factor; ISRE, interferon-a-stimulated response element; JNK, c-Jun N-terminal kinase; Jun, v-jun sarcoma virus 17 oncogene homolog (avian); KSR, kinase suppressor of ras; LBP, lipopolysaccharide-binding protein; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; MAPKAPK, mitogen-activated protein kinase-activated protein kinase; MBP, myelin basic protein; MD-2, lymphocyte antigen 96; MEKK, MAPK/ERK kinase kinase; MKK, mitogen-activated protein kinase kinase; MKP, MAP kinase phosphatase; MMT virus, mouse mammary tumor virus; Mnk, MAP kinase interacting serine/threonine kinase; MSK, mitogen- and stress-activated protein kinase; MyD88, myeloid differentiation primary response gene 88; NF-κB, nuclear factor κB; NIK, nuclear factor κB-inducing kinase; NOD, nucleotide-binding oligomerization domain; NSF, N-ethylmaleimide-sensitive factor; NUR77, nuclear receptor subfamily 4, group A, member 1; p62, phosphotyrosine-independent ligand for the Lck SH2 domain p62; PAK, p21-activated kinase; PDK, 3-phosphoinositide-dependent protein kinase; pellino, pellino (*Drosophila*) homolog; PI(4)P5K, phosphatidylinositol-5-kinase; PI, phosphatidylinositol; Pi, phosphoric ion; PI3,4,5-P3, phosphatidylinositol-3,4,5-triphosphate; PI3,4-P2, phosphatidylinositol-3,4-bisphosphate; PI3K, phosphatidyl-inositol-3-kinase; PI3-P, phosphatidylinositol-3-phosphate; PI4,5-P2, phosphatidylinositol-4,5-bisphosphate; PI4-P, phosphatidylinositol-4-phosphate; PKA, protein kinase A; PKC, protein kinase C; PKR, eukaryotic translation initiation factor 2-α kinase; PLC, phospholipase C; PLD, phospholipase D; PP, protein phosphatase; Rab, RAS-associated protein; Rabaptin, RAB GTPase-binding effector protein; Rabex, RAB guanine nucleotide exchange factor; Rac, ras-related C3 botulinum toxin substrate; Raf, v-raf-1 murine leukemia viral oncogene homolog; Ras, rat sarcoma viral oncogene homolog; Rho, ras homolog gene family; RhoGDI, GDP dissociation inhibitor; Rin, Ras interaction; RIP, receptor-interacting serine–threonine kinase; RKIP, Raf kinase inhibitor protein; RS virus, respiratory syncytial virus; Sab, SH3-domain-binding protein 5 (BTK-associated); SERCA, sarcoplasmic/endoplasmic reticulum calcium ATPase; SIGIRR, single immunoglobulin and toll-interleukin 1 receptor (TIR) domain; SOCS, suppressor of cytokine signaling; ssRNA, single-strand RNA; ST2L, interleukin 1 receptor-like 1; STF, soluble tuberculosis factor; TAB, transforming growth factor beta-activated kinase-binding protein; TAK, transforming growth factor beta-activated kinase; TBK, TRAF family member-associated nuclear factor κB activator-binding kinase; TICAM, toll-like receptor adaptor molecule; TIFA, TRAF-interacting protein with a forkhead-associated domain; TIR, toll-interleukin 1 receptor; TIRAP, toll-interleukin 1 receptor domain-containing adaptor protein; TLR, toll-like receptor; TOLLIP, toll-interacting protein; TPL, tumor progression locus; TRAF, tumor necrosis factor receptor-associated factor; TRAILR, tumor necrosis factor-related apoptosis-inducing ligand receptor; TRIAD3A, ubiquitin-conjugating enzyme 7-interacting protein 1, isoform A; TRIP, thyroid hormone receptor interactor; Trx, thioredoxin; Ubc, ubiquitin-conjugating enzyme; Uev, ubiquitin-conjugating enzyme E2 variant; Vav1, vav 1 oncogene.

diagram, which intends to provide a standard for representing molecular interactions in an unambiguous way (Kitano *et al*, 2005). The main symbols used to represent molecules and interactions in this map are the same as those of the EGFR map (Oda *et al*, 2005), which is based on the process diagram of Systems Biology Graphical Notation (SBGN: http://www.sbgn.org/) (Kitano *et al*, 2005). The compounds, except proteins, genes, RNAs, and ions, such as lipids and carbohydrates, although they are complicated, are all shown as 'simple molecule' for the sake of convenience. Because the TLR system has numerous combinations of protein complex, we adopted another local rule in the TLR Pathway Map to enhance the readability of the map. A protein with '*' at the end of its name means that it binds to other molecules and often makes a conformational change. The circle-headed 'catalysis' arrow towards a state transition of a protein with '*' means binding with it. Readers may notice that there are substantial numbers of molecular components appearing in both the EGFR map and TLR map. In future, CellDesigner will provide a powerful means to merge several large-scale maps so that an integrated map, possibly genome-wide in scale, can be created and used by researchers to navigate through the network.

Architectural features of the TLR map

It is important to construct a comprehensive map of molecular interactions in order to understand the possible logic behind the network. Even without kinetic parameters to run a dynamic simulation, the map provides information that can be used to analyze architectural features of the network. In order to analyze the global network architecture, a simpler diagram that focuses on the flow of information and causal relationships is needed. Figure 2 is a reduced version of Figure 1 in which only flows of activations and inhibitions are shown for the sake of readability. In Figure 2, filled arrows indicate activation and bar-headed arrows indicate inhibition.

It shows that TLR signaling pathways are roughly divided into four possible subsystems. The first is the main system with MyD88–IRAK4–IRAK1–TRAF6 as a bow-tie core process to activate nuclear factor kappa B (NF-κB) and mitogen-activated protein kinase (MAPK) cascade, leading to the induction of many target genes such as cytokines that are essential for the innate immune response and the maturation and proliferation of the cell. Almost all TLRs utilize this core process and so various distinct signals from pathogens are assembled to only a handful of proteins. The second and third systems seem to be subsystems with a small GTPase module and phosphatidylinositol phosphate (PIP) signaling module, respectively. We consider the small GTPase module and PIP signaling module to be distinct modules, rather than merging them into a central MyD88 module. This is because both the small GTPase module and PIP signaling module receive extensive inputs directly from receptors and transmit them to various molecules downstream of MyD88 as well as outside of downstream of MyD88. For example, the small GTPase module receives inputs from IL-1R, TLR9, TLR4, and TLR2, and the PIP signaling module receives inputs from IL-1R, small GTPase module, TLR2, TLR3, and MyD88, whereas components within the MyD88 module such as IRAK4, IRAK1, IRAK2, and TRAF6 are only activated through MyD88 activation. At the same time, small GTPase and PI3 kinase (PI3K) activates NF-κB and MAPK (Arbibe *et al*, 2000; Xu *et al*, 2003; Sarkar *et al*, 2004). Thus, the small GTPase and PIP signaling modules shall be considered as collateral modules, instead of merging into the central MyD88 module. These subsystems are essential for the battle against invaders. Their pathways are merged at several points and cooperate with each other to exclude pathogens by actin reorganization leading to chemotaxis and phagocytosis and the production of reactive oxygen species (ROS) to kill them. The last subsystem is limited to TLR3 and TLR4, which can stimulate another pathway called MyD88-independent pathway through the TLR adaptor molecule (TICAM)1/2 (Yamamoto *et al*, 2003). It remains to be investigated how it signals to MAPK cascade (Chu *et al*, 1999; Goh *et al*, 2000), but it can activate NF-κB on the late phase as well as the interferon-regulatory factor family that induces potential cytokines, type I interferon, and the induction of IL-1 activates autocrinely MyD88-dependent pathways and two subsystems leading to the full activation of the whole system. Thus, this pathway would appear to be a detour.

One of the notable features of the TLR signaling network is the possible existence of a bow-tie structure as the central subsystem of the TLR network in which MyD88 is a nonredundant core. The bow-tie structure has also been observed in the EGFR signaling network (Oda *et al*, 2005), and has been considered to be a characteristic architectural feature of robust systems (Csete and Doyle, 2004; Kitano, 2004). At the same time, the TLR signaling network is different from the EGFR signaling network as it has extensive collateral pathways that may modulate downstream behaviors of the main bow-tie network.

Multiple system controls

As shown in Figure 2, there are multiple system controls in the TLR system. In total, seven positive feedback and seven negative feedback loops are identified (shown in red and blue, respectively). Among positive feedback loops, the four loops (Nos. 1–4 in Table I) are the regulation from the output to the input, and one (No. 5) is in the bow-tie lower wing. Six negative feedback loops are classified as follows: two (Nos. 8 and 9) are in the bow-tie lower wing, two (Nos. 10 and 11) are from the output to the lower wing, one (No. 12) is from the output to the bow-tie core process, and the last one (No. 13) is from the output to the input. The remaining two positive (Nos. 6 and 7) and one negative (No. 14) feedback loops exist in the subsystems involved in the regulation of concentration of the cytosol calcium. There are conflicting feedback loops. For example, feedback from IL-1α and IL-1β to IL-1RI (Nos. 1 and 2, respectively) provides postitive feedbacks, whereas feedback from interleukin 1 receptor antagonist (IL-1ra) to IL-1RI (No. 13) provides a negative feedback. The map predicts balance of activation between IL-1 and IL-1ra affects proinflammatory response of the system. A recent paper reports this is actually a case(Matsuki *et al*, 2006).

In addition to these feedback controls, there is a possible negative feedforward control (shown in purple). MyD88 also

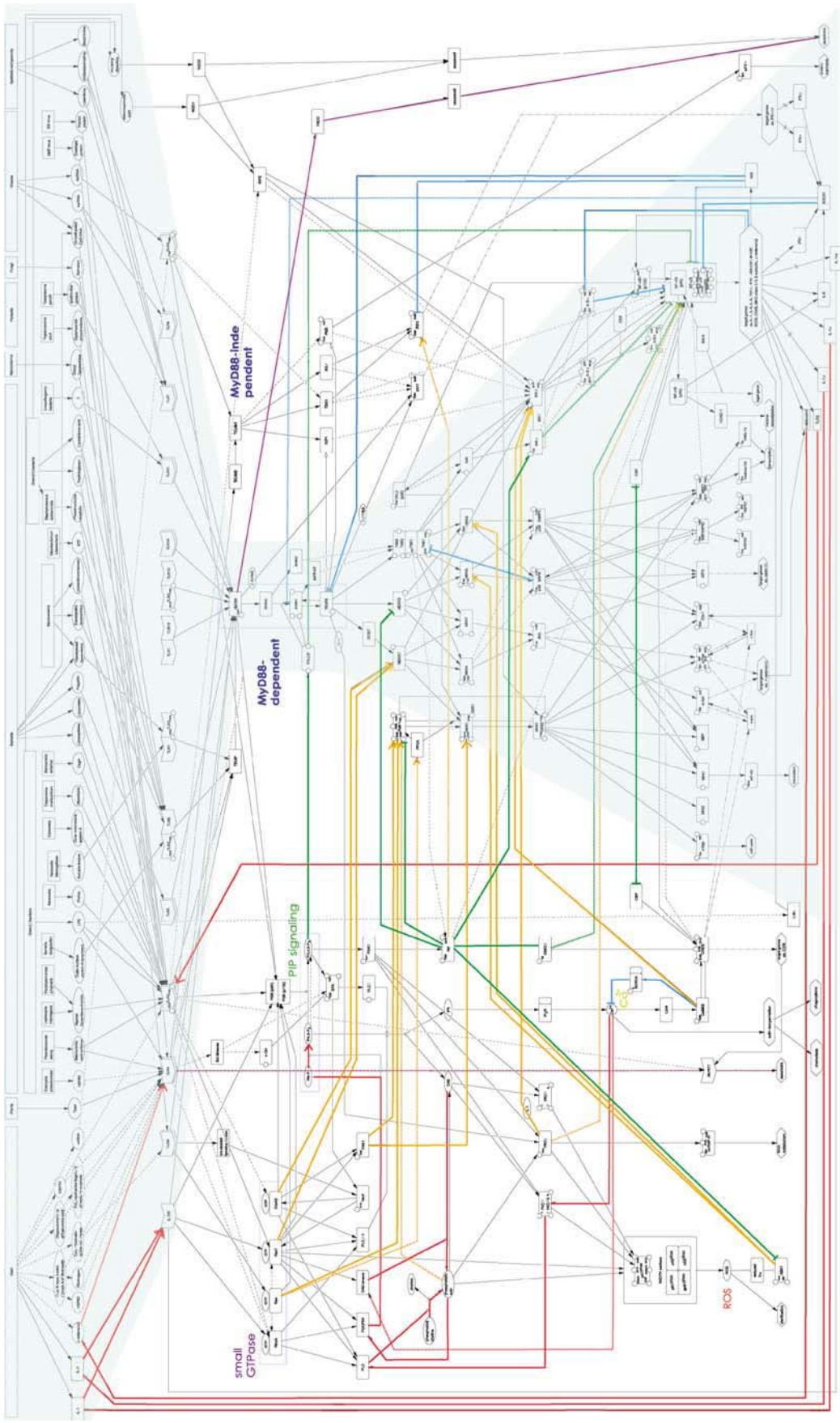


Figure 2 The architecture of the TLR signaling network. A reduced map of TLR signaling network that extracts the flow of activation and inhibition. This diagram is created based on the comprehensive TLR signaling network map as shown in Figure 1. Filled arrows in this figure indicate 'activation', and other arrows such as bar-headed, circle-headed, dashed, and dot-dot-dashed lines are the same as Figure 1. The double line denotes 'binding' in this figure. A molecule shown to connect with both 'activation' and 'inhibition' arrows can act oppositely according to the condition. A line of mutual inhibition that connects two CREB-binding protein (CBP) molecules means the competition for limiting amounts of CBP, which is a transcriptional coactivator that interacts with both NF-κ B p65 and CREB. TLR signaling network consists of the main bow-tie network and three collateral subnetworks that involves small GTPase, PIPs, and MyD88-independent pathways. There are extensive crosstalk regulations between the main bow-tie network and other subsystems, as well as multiple feedback and feedforward controls. Notable interactions are color-coded: red, positive feedback loop; blue, negative feedback loop; purple, inhibitory feedforward path; orange, positive crosstalk from subsystems to the bow-tie network; and green, negative crosstalk from subsystems to the bow-tie network. High resolution file for this figure is available from the Supplementary information.

Table I Feedback and feedforward controls in the TLRs system

	No.	Origin		Destination		Note
Feedback						
Positive	1	IL-1α	Transcriptional target of NF-κB	IL-1RI	Activates NF-κB via the MyD88-dependent pathway	
	2	IL-1β	Transcriptional target of NF-κB	IL-1RI	Activates NF-κB via the MyD88-dependent pathway	
	3	TLR2	Transcriptional target of NF-κB	MyD88, PI3K, small GTPase	Activates NF-κB	
	4	β-Defensin2	Transcriptional target of NF-κB	TLR4	Activates NF-κB via the MyD88-dependent and -independent pathway	Controversial
	5	IKKβ	Activated by NIK	TPL2(p58)	Activates NIK	Through the process yet identified
	6	PLD	Activated by PKC alpha, beta II, and cytosol Ca^{2+}	PI4,5-P2	Material of IP3 which increases cytosol Ca^{2+} via IP3R	
	7	DAG kinase	Activated by cytosol Ca^{2+}	PI4,5-P2	Material of IP3 which increases cytosol Ca^{2+} via IP3R	Through the process yet identified
Negative	8	NF-κB1(p105)	Activated by IKKβ	TPL2(p58)	Activates IKKβ via NIK	
	9	p38αMAPK	Activated by MKK3	TAK1	Activates MKK3	
	10	IκBα	Transcriptional target of NF-κB	NF-κB	Transcriptional factor of A20	
	11	A20	Transcriptional target of NF-κB	NF-κB	Transcriptional factor of A20	
	12	A20	Transcriptional target of NF-κB	TRAF6	Activates NF-κB via the MyD88-dependent pathway	
	13	IL-1ra	Transcriptional target of NF-κB	IL-1RI	Activates NF-κB via the MyD88-dependent pathway	
	14	CaMKII	Activated by cytosol Ca^{2+}	SERCA	Decreases cytosol Ca^{2+}	
Feedforward						
Negative	15	TLR2		NUR77	Causes apoptosis	
	16	TLR4		NUR77	Causes apoptosis	
	17	MyD88		FADD	Causes apoptosis via the activation of caspase-8	
	18	Src kinases	Activates BTK	BTK	Inhibited by Src kinases via c-Cbl	Through the process yet identified

mediates apoptosis via a Fas-associated death domain–caspase-8-dependent pathway, and TLR4 and TLR2 can induce apoptosis through an orphan nuclear receptor Nur77 by a caspase-independent pathway, although its precise mechanism is unclear (Kim *et al*, 2003). Thus, the TLR system induces the activation of the immunity to survive, while it prepares cell death at the same time. At a cell-level view, this mechanism could be considered as a negative feedforward control (Table I).

Regulations between main and subsystems

There are many crosstalk regulations between the main bow-tie pathway and two subsystems. Especially, we identified a lot of crosstalk regulations from a subsystem to the main bow-tie pathway; positive and negative regulations are shown in orange and green, respectively. There are 13 positive and seven negative crosstalk regulations, and interestingly all the crosstalk regulations go towards the bow-tie lower wing. For example, small GTPases and ROS can stimulate MAPK cascade by nine ways, and v-akt murine thymoma viral oncogene homolog (Akt) can inhibit both MAPK cascade and NF-κB activation by means of five distinct mechanisms. Thus, the fact that regulations from other systems concentrate in the bow-tie lower wing is highly suggestive.

Possible undiscovered negative regulations

The bow-tie structure has extensive system controls to govern the system's dynamics. In this paper, we demonstrate that TLR pathway forms a bow-tie structure and the two related subsystems with multiple positive/negative system controls and crosstalk regulations. However, we could identify no negative regulations from the lower wing and/or the outputs to the upper wing and/or inputs in the TLR system while constructing this map. While both 'inhibition' and 'activation' usually exist to regulate the balance, there may be undiscovered negative regulations in this pathway. For example, NF-κB induces both IL-1 and IL-1ra, an inhibitor of IL-1R, so there must be negative regulations from the lower wing and/or outputs against each TLR. Recently, many negative regulators of TLRs such as soluble TLR4 (Iwami *et al*, 2000) have been reported (reviewed by Liew *et al*, 2005) and, although their regulations remains to be investigated, they must be strong candidates. It is important to understand the TLR system in depth to research the negative regulations that seem to be lacking in a system-level view.

Naturally, there is a huge cytokine/chemokine network in the downstream region of the TLR system and it is regulated from the network both positively and negatively. For example, suppressor of cytokine signaling 1, which is the downstream element of cytokine signaling such as interferon and IL-6, has been found to inhibit both NF-κB (p65) and IRAK1 activation. (Kinjyo *et al*, 2002; Nakagawa *et al*, 2002; Ryo *et al*, 2003) We are planning to construct and analyze the complicated cytokine/chemokine networks and their interactions in the future.

Mechanisms for differential responses for different stimuli

Since MyD88 is the single core element in the bow-tie structure, any inputs that converge into this network are only able to change the activation level of MyD88. This subsystem alone cannot make different responses regardless of different stimuli.

One of the major questions in signal-transduction research is how a specific signal-transduction network generates different responses for each set of combinatorial stimuli. Recently, an extensive study has been made to demonstrate some signaling pathway function as classifier of stimuli (Janes *et al*, 2005). What is the logic behind such processes? Previously, we have created a comprehensive map of the EGFR signaling network in which the core of the bow-tie structure consists of PIPs, small GTPase, nonreceptor tyrosine kinase (non-RTK), and possibly signal transducer and activator of transcription 1/2. There are three or four possible elements in the core of the bow-tie architecture. A similar structure may be found in the G-protein-coupled receptor (GPCR) signaling network where calcium, cyclic AMP, and inositol phosphate are likely candidates for core elements of the bow-tie structure. In these networks, we can assume the existence of hyperspace, a mathematical term referring to *N*-dimensional space, created by activation levels of a small number of core elements, where each subregion within the hyperspace may correspond to different responses (Figure 3A). Therefore, various inputs may be clustered in the hyperspace, which may be called 'classifier hyperspace', and relayed to outputs. In other words, how the signaling network responds to a specific set of stimuli depends on the activation levels and temporal dynamics of molecules in this theoretical hyperspace. However, in the TLR signaling network, there is only one element in the core of the bow-tie network that precludes the capability to generate differential outputs alone. Differential outputs are attained by modulation of subnetworks that are MyD88-independent pathways, by the small GTPase subnetwork, and by the PIPs subnetwork. The MyD88-dependent pathway may only function to trigger the activation of the downstream signaling system (Figure 3B). In this case, differences of responses for each stimuli are greatly influenced by the activity of the classifier hyperspace composed of TICAM1 for the MyD88-independent pathway, small GTPases including cell division cycle 42 (Cdc42), ras-related C3 botulinum toxin substrate 1 (Rac1), rat sarcoma viral oncogene homolog (Ras), ras homolog gene family A (RhoA), and PIPs. The essential idea behind the classifier hyperspace is that it implies that a certain abstract representation exists in the signal-transduction process, similar to a learning layer of certain types of neural networks. In other words, a signal-transduction network is an evolved network that can classify various stimuli into a limited number of categories where each category triggers a specific sequence of responses. This classification depends on the activity level and temporal dynamics, often called attractor dynamics (Strogatz, 1994), of the components involved. Figure 3 indicates a simple view in which the activity levels of each component appear to be used for classification, but classification can generally be made by attractor dynamics where each attractor can be interpreted as a symbol corresponding to our subjectively

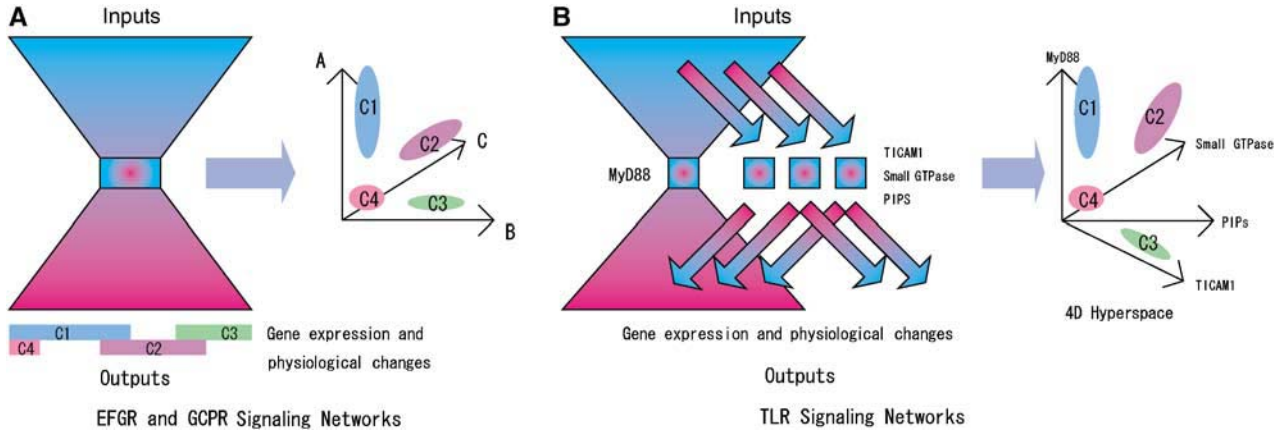


Figure 3 The core of bow-tie networks may have 'classifier hyperspace' where reactions to various inputs can be classified within subregions within the hyperspace that consists of activation levels of core elements of the bow-tie structure. (**A**) EGFR signaling and GPCR signaling network has a small numbers of core elements such as small GTPases, PIPs, and non-RTKs for EGFR signaling, and calcium, cAMP, and inositol phosphate for GPCR signaling. For example, a group of stimuli may all activate core elements in the way that can be classified into region C1, for example, and these stimuli triggers transcription of genes and physiological responses as denoted as C1. (**B**) TLR signaling network has a salient feature where possible bow-tie core is composed of a single element, MyD88, thus there is no classifier hyperspace created within the bow-tie network. Differences of responses against various stimuli are modulated by the activation of elements in collateral pathways, such as small GTPases, PIPs, and TICAM1 involved in MyD88-independent pathway, and MyD88 pathway essentially calibrates the whole network. Thus, for TLR signaling network, the classifier hyperspace has four dimensions.

labeled interpretation of cellular responses (Hao, 1991). If this insight is correct, it suggests the existence of a common principle on how the signal-transduction network generates various responses to a broad range of stimuli in a consistent manner. This is an important hypothesis that needs to be experimentally verified.

Conclusion

A comprehensive TLR signaling network that provides an overall network architecture of molecular interaction was created based on papers published so far. Although this map is far from complete in covering all interactions of the TLR signaling network, it represents a comprehensive body of knowledge available today. The map reveals the existence of a possible bow-tie network accompanied with collateral sub-networks that involve MyD88-independent pathways, small GTPase, and PIPs. The central bow-tie network relies on MyD88, which is a nonredundant core element of the network. This makes the whole system susceptible to the removal of MyD88 as seen in the phenotype of MyD88−/−-deficient mouse (Akira, 2000). This is a weakness of the system. Comparison with other signaling networks such as the EGFR signaling network and GPCR signaling network illustrates several characteristic features of the TLR signaling network as well as common features, which we proposed as a 'classifier hyperspace'. This is interesting because similar operational principles on how to generate different responses to various input stimuli have emerged from investigating the structure of networks alone. Further elaboration of the concept and experimental verification of this hypothesis will be important in signal-transduction research in the future. While extensive feedback loops exist, we have noticed that only a few negative feedback loops have been reported so far. We consider that there may be a number of undiscovered negative feedback loops in this signaling network. We hope this map will contribute to system-wide studies of TLR signaling as well as immunology in general. However, the map is not complete and a number of undiscovered interactions are predicted; the map will be updated in collaboration with experts in the field.

Supplementary information

Supplementary Information is available at the *Molecular Systems Biology* website (www.nature.com/msb).

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References

Akira S (2000) Toll-like receptors: lessons from knockout mice. *Biochem Soc Trans* **28:** 551–556

Akira S, Takeda K (2004) Toll-like receptor signalling. *Nat Rev Immunol* **4:** 499–511

Alexopoulou L, Holt AC, Medzhitov R, Flavell RA (2001) Recognition of double-stranded RNA and activation of NF-kappaB by Toll-like receptor 3. *Nature* **413:** 732–738

Arbibe L, Mira JP, Teusch N, Kline L, Guha M, Mackman N, Godowski PJ, Ulevitch RJ, Knaus UG (2000) Toll-like receptor 2-mediated

NF-kappa B activation requires a Rac1-dependent pathway. *Nat Immunol* **1:** 533–540

Beutler B (2004) Inferences, questions and possibilities in Toll-like receptor signalling. *Nature* **430:** 257–263

Chu WM, Ostertag D, Li ZW, Chang L, Chen Y, Hu Y, Williams B, Perrault J, Karin M (1999) JNK2 and IKKbeta are required for activating the innate response to viral infection. *Immunity* **11:** 721–731

Csete M, Doyle J (2004) Bow ties, metabolism and disease. *Trends Biotechnol* **22:** 446–450

Funahashi A, Kitano H (2003) CellDesigner: a process diagram editor for gene-regulatory and biochemical networks. *Biosilico* **1:** 159–162

Goh KC, deVeer MJ, Williams BR (2000) The protein kinase PKR is required for p38 MAPK activation and the innate immune response to bacterial endotoxin. *EMBO J* **19:** 4292–4297

Hao B (1991) Symbolic dynamics and characterization of complexity. *Physica D* **51:** 161–176

Hayashi F, Smith KD, Ozinsky A, Hawn TR, Yi EC, Goodlett DR, Eng JK, Akira S, Underhill DM, Aderem A (2001) The innate immune response to bacterial flagellin is mediated by Toll-like receptor 5. *Nature* **410:** 1099–1103

Hemmi H, Takeuchi O, Kawai T, Kaisho T, Sato S, Sanjo H, Matsumoto M, Hoshino K, Wagner H, Takeda K, Akira S (2000) A Toll-like receptor recognizes bacterial DNA. *Nature* **408:** 740–745

Hoebe K, Janssen E, Beutler B (2004) The interface between innate and adaptive immunity. *Nat Immunol* **5:** 971–974

Hoffmann JA, Reichhart JM (2002) Drosophila innate immunity: an evolutionary perspective. *Nat Immunol* **3:** 121–126

Hucka M, Finney A, Sauro HM, Bolouri H, Doyle JC, Kitano H, Arkin AP, Bornstein BJ, Bray D, Cornish-Bowden A, Cuellar AA, Dronov S, Gilles ED, Ginkel M, Gor V, Goryanin II, Hedley WJ, Hodgman TC, Hofmeyr JH, Hunter PJ, Juty NS, Kasberger JL, Kremling A, Kummer U, Le Novere N, Loew LM, Lucio D, Mendes P, Minch E, Mjolsness ED, Nakayama Y, Nelson MR, Nielsen PF, Sakurada T, Schaff JC, Shapiro BE, Shimizu TS, Spence HD, Stelling J, Takahashi K, Tomita M, Wagner J, Wang J (2003) The Systems Biology Markup Language (SBML): a medium for representation and exchange of biochemical network models. *Bioinformatics* **19:** 524–531

Iwami KI, Matsuguchi T, Masuda A, Kikuchi T, Musikacharoen T, Yoshikai Y (2000) Cutting edge: naturally occurring soluble form of mouse Toll-like receptor 4 inhibits lipopolysaccharide signaling. *J Immunol* **165:** 6682–6686

Iwasaki A, Medzhitov R (2004) Toll-like receptor control of the adaptive immune responses. *Nat Immunol* **5:** 987–995

Janes KA, Albeck JG, Gaudet S, Sorger PK, Lauffenburger DA, Yaffe MB (2005) A systems model of signaling identifies a molecular basis set for cytokine-induced apoptosis. *Science* **310:** 1646–1653

Kim SO, Ono K, Tobias PS, Han J (2003) Orphan nuclear receptor Nur77 is involved in caspase-independent macrophage cell death. *J Exp Med* **197:** 1441–1452

Kinjyo I, Hanada T, Inagaki-Ohara K, Mori H, Aki D, Ohishi M, Yoshida H, Kubo M, Yoshimura A (2002) SOCS1/JAB is a negative regulator of LPS-induced macrophage activation. *Immunity* **17:** 583–591

Kitano H (2004) Biological robustness. *Nat Rev Genet* **5:** 826–837

Kitano H, Funahashi A, Matsuoka Y, Oda K (2005) Using process diagrams for the graphical representation of biological networks. *Nat Biotechnol* **23:** 961–966

Liew FY, Xu D, Brint EK, O'Neill LA (2005) Negative regulation of toll-like receptor-mediated immune responses. *Nat Rev Immunol* **5:** 446–458

Matsuki T, Nakae S, Sudo K, Horai R, Iwakura Y (2006) Abnormal T cell activation caused by the imbalance of the IL-1/IL-1R antagonist system is responsible for the development of experimental autoimmune encephalomyelitis. *Int Immunol* **18:** 399–407

Nakagawa R, Naka T, Tsutsui H, Fujimoto M, Kimura A, Abe T, Seki E, Sato S, Takeuchi O, Takeda K, Akira S, Yamanishi K, Kawase I, Nakanishi K, Kishimoto T (2002) SOCS-1 participates in negative regulation of LPS responses. *Immunity* **17:** 677–687

Oda K, Matsuoka Y, Funahashi A, Kitano H (2005) A comprehensive pathway map of epidermal growth factor receptor signaling. *Mol Syst Biol* **1:** E1–E17

Poltorak A, He X, Smirnova I, Liu MY, Van Huffel C, Du X, Birdwell D, Alejos E, Silva M, Galanos C, Freudenberg M, Ricciardi-Castagnoli P, Layton B, Beutler B (1998) Defective LPS signaling in C3H/HeJ and C57BL/10ScCr mice: mutations in Tlr4 gene. *Science* **282:** 2085–2088

Roach JC, Glusman G, Rowen L, Kaur A, Purcell MK, Smith KD, Hood LE, Aderem A (2005) The evolution of vertebrate Toll-like receptors. *Proc Natl Acad Sci USA* **102:** 9577–9582

Ryo A, Suizu F, Yoshida Y, Perrem K, Liou YC, Wulf G, Rottapel R, Yamaoka S, Lu KP (2003) Regulation of NF-kappaB signaling by Pin1-dependent prolyl isomerization and ubiquitin-mediated proteolysis of p65/RelA. *Mol Cell* **12:** 1413–1426

Sarkar SN, Peters KL, Elco CP, Sakamoto S, Pal S, Sen GC (2004) Novel roles of TLR3 tyrosine phosphorylation and PI3 kinase in double-stranded RNA signaling. *Nat Struct Mol Biol* **11:** 1060–1067

Slack JL, Schooley K, Bonnert TP, Mitcham JL, Qwarnstrom EE, Sims JE, Dower SK (2000) Identification of two major sites in the type I interleukin-1 receptor cytoplasmic region responsible for coupling to pro-inflammatory signaling pathways. *J Biol Chem* **275:** 4670–4678

Strogatz S (1994) *Nonlinear Dynamics and Chaos: With Applications in Physics, Biology, Chemistry, and Engineering*. New York: Perseus Books

Xu H, An H, Yu Y, Zhang M, Qi R, Cao X (2003) Ras participates in CpG oligodeoxynucleotide signaling through association with toll-like receptor 9 and promotion of interleukin-1 receptor-associated kinase/tumor necrosis factor receptor-associated factor 6 complex formation in macrophages. *J Biol Chem* **278:** 36334–36340

Yamamoto M, Sato S, Hemmi H, Hoshino K, Kaisho T, Sanjo H, Takeuchi O, Sugiyama M, Okabe M, Takeda K, Akira S (2003) Role of adaptor TRIF in the MyD88-independent toll-like receptor signaling pathway. *Science* **301:** 640–643

References for TLR Pathway Map

Abo A, Pick E, Hall A, Totty N, Teahan CG, Segal AW (1991) Activation of the NADPH oxidase involves the small GTP-binding protein p21rac1. *Nature* **353:** 668–670

Adachi M, Fukuda M, Nishida E (1999) Two co-existing mechanisms for nuclear import of MAP kinase: passive diffusion of a monomer and active transport of a dimer. *EMBO J* **18:** 5347–5358

Adams JM, Houston H, Allen J, Lints T, Harvey R (1992) The hematopoietically expressed vav proto-oncogene shares homology with the dbl GDP-GTP exchange factor, the bcr gene and a yeast gene (CDC24) involved in cytoskeletal organization. *Oncogene* **7:** 611–618

Ahn NG, Seger R, Bratlien RL, Diltz CD, Tonks NK, Krebs EG (1991) Multiple components in an epidermal growth factor-stimulated protein kinase cascade. *In vitro* activation of a myelin basic protein/microtubule-associated protein 2 kinase. *J Biol Chem* **266:** 4220–4227

Akira S (2003) Toll-like receptor signaling. *J Biol Chem* **278:** 38105–38108

Alexopoulou L, Holt AC, Medzhitov R, Flavell RA (2001) Recognition of double-stranded RNA and activation of NF-kappaB by Toll-like receptor 3. *Nature* **413:** 732–738

Aliprantis AO, Yang RB, Mark MR, Suggett S, Devaux B, Radolf JD, Klimpel GR, Godowski P, Zychlinsky A (1999) Cell activation and apoptosis by bacterial lipoproteins through toll-like receptor-2. *Science* **285:** 736–739

Aliprantis AO, Yang RB, Weiss DS, Godowski P, Zychlinsky A (2000) The apoptotic signaling pathway activated by Toll-like receptor-2. *EMBO J* **19:** 3325–3336

Anders HJ, Banas B, Schlondorff D (2004) Signaling danger: toll-like receptors and their potential roles in kidney disease. *J Am Soc Nephrol* **15:** 854–867

Anderson KE, Coadwell J, Stephens LR, Hawkins PT (1998) Translocation of PDK-1 to the plasma membrane is important in allowing PDK-1 to activate protein kinase B. *Curr Biol* **8:** 684–691

Anrather J, Csizmadia V, Soares MP, Winkler H (1999) Regulation of NF-kappaB RelA phosphorylation and transcriptional activity by p21(ras) and protein kinase Czeta in primary endothelial cells. *J Biol Chem* **274:** 13594–13603

Arbibe L, Mira JP, Teusch N, Kline L, Guha M, Mackman N, Godowski PJ, Ulevitch RJ, Knaus UG (2000) Toll-like receptor 2-mediated NF-kappa B activation requires a Rac1-dependent pathway. *Nat Immunol* **1:** 533–540

Arenzana-Seisdedos F, Turpin P, Rodriguez M, Thomas D, Hay RT, Virelizier JL, Dargemont C (1997) Nuclear localization of I kappa B alpha promotes active transport of NF-kappa B from the nucleus to the cytoplasm. *J Cell Sci* **110** (Part 3)**:** 369–378

Asea A, Rehli M, Kabingu E, Boch JA, Bare O, Auron PE, Stevenson MA, Calderwood SK (2002) Novel signal transduction pathway utilized by extracellular HSP70: role of toll-like receptor (TLR) 2 and TLR4. *J Biol Chem* **277:** 15028–15034

Backer JM (2000) Phosphoinositide 3-kinases and the regulation of vesicular trafficking. *Mol Cell Biol Res Commun* **3:** 193–204

Balendran A, Hare GR, Kieloch A, Williams MR, Alessi DR (2000) Further evidence that 3-phosphoinositide-dependent protein kinase-1 (PDK1) is required for the stability and phosphorylation of protein kinase C (PKC) isoforms. *FEBS Lett* **484:** 217–223

Bannerman DD, Erwert RD, Winn RK, Harlan JM (2002) TIRAP mediates endotoxin-induced NF-kappaB activation and apoptosis in endothelial cells. *Biochem Biophys Res Commun* **295:** 157–162

Bard F, Patel U, Levy JB, Jurdic P, Horne WC, Baron R (2002) Molecular complexes that contain both c-Cbl and c-Src associate with Golgi membranes. *Eur J Cell Biol* **81:** 26–35

Baud V, Liu ZG, Bennett B, Suzuki N, Xia Y, Karin M (1999) Signaling by proinflammatory cytokines: oligomerization of TRAF2 and TRAF6 is sufficient for JNK and IKK activation and target gene induction via an amino-terminal effector domain. *Genes Dev* **13:** 1297–1308

Baumann B, Weber CK, Troppmair J, Whiteside S, Israel A, Rapp UR, Wirth T (2000) Raf induces NF-kappaB by membrane shuttle kinase MEKK1, a signaling pathway critical for transformation. *Proc Natl Acad Sci USA* **97:** 4615–4620

Bavelloni A, Santi S, Sirri A, Riccio M, Faenza I, Zini N, Cecchi S, Ferri A, Auron P, Maraldi NM, Marmiroli S (1999) Phosphatidylinositol 3-kinase translocation to the nucleus is induced by interleukin 1 and prevented by mutation of interleukin 1 receptor in human osteosarcoma Saos-2 cells. *J Cell Sci* **112** (Part 5)**:** 631–640

Beaty CD, Franklin TL, Uehara Y, Wilson CB (1994) Lipopolysaccharide-induced cytokine production in human monocytes: role of tyrosine phosphorylation in transmembrane signal transduction. *Eur J Immunol* **24:** 1278–1284

Belham C, Wu S, Avruch J (1999) Intracellular signalling: PDK1—a kinase at the hub of things. *Curr Biol* **9:** R93–96

Ben-Levy R, Hooper S, Wilson R, Paterson HF, Marshall CJ (1998) Nuclear export of the stress-activated protein kinase p38 mediated by its substrate MAPKAP kinase-2. *Curr Biol* **8:** 1049–1057

Beutler B (2004) Inferences, questions and possibilities in Toll-like receptor signalling. *Nature* **430:** 257–263

Biragyn A, Ruffini PA, Leifer CA, Klyushnenkova E, Shakhov A, Chertov O, Shirakawa AK, Farber JM, Segal DM, Oppenheim JJ, Kwak LW (2002) Toll-like receptor 4-dependent activation of dendritic cells by beta-defensin 2. *Science* **298:** 1025–1029

Bird TA, Schooley K, Dower SK, Hagen H, Virca GD (1997) Activation of nuclear transcription factor NF-kappaB by interleukin-1 is accompanied by casein kinase II-mediated phosphorylation of the p65 subunit. *J Biol Chem* **272:** 32606–32612

Bishop AL, Hall A (2000) Rho GTPases and their effector proteins. *Biochem J* **348** (Part 2)**:** 241–255

Bokoch GM, Vlahos CJ, Wang Y, Knaus UG, Traynor-Kaplan AE (1996) Rac GTPase interacts specifically with phosphatidylinositol 3-kinase. *Biochem J* **315** (Part 3)**:** 775–779

Bol GF, Jurrmann N, Brigelius-Flohe R (2005) Cellular trafficking of the IL-1RI-associated kinase-1 requires intact kinase activity. *Biochem Biophys Res Commun* **332:** 279–287

Bonnard M, Mirtsos C, Suzuki S, Graham K, Huang J, Ng M, Itie A, Wakeham A, Shahinian A, Henzel WJ, Elia AJ, Shillinglaw W, Mak TW, Cao Z, Yeh WC (2000) Deficiency of T2K leads to apoptotic liver degeneration and impaired NF-kappaB-dependent gene transcription. *EMBO J* **19:** 4976–4985

Bonnet MC, Weil R, Dam E, Hovanessian AG, Meurs EF (2000) PKR stimulates NF-kappaB irrespective of its kinase function by interacting with the IkappaB kinase complex. *Mol Cell Biol* **20:** 4532–4542

Boone DL, Turer EE, Lee EG, Ahmad RC, Wheeler MT, Tsui C, Hurley P, Chien M, Chai S, Hitotsumatsu O, McNally E, Pickart C, Ma A (2004) The ubiquitin-modifying enzyme A20 is required for termination of Toll-like receptor responses. *Nat Immunol* **5:** 1052–1060

Borgatti P, Martelli AM, Bellacosa A, Casto R, Massari L, Capitani S, Neri LM (2000) Translocation of Akt/PKB to the nucleus of osteoblast-like MC3T3-E1 cells exposed to proliferative growth factors. *FEBS Lett* **477:** 27–32

Bornancin F, Parker PJ (1996) Phosphorylation of threonine 638 critically controls the dephosphorylation and inactivation of protein kinase Calpha. *Curr Biol* **6:** 1114–1123

Bornancin F, Parker PJ (1997) Phosphorylation of protein kinase C-alpha on serine 657 controls the accumulation of active enzyme and contributes to its phosphatase-resistant state. *J Biol Chem* **272:** 3544–3549

Boulet I, Ralph S, Stanley E, Lock P, Dunn AR, Green SP, Phillips WA (1992) Lipopolysaccharide- and interferon-gamma-induced expression of hck and lyn tyrosine kinases in murine bone marrow-derived macrophages. *Oncogene* **7:** 703–710

Bowman EP, Uhlinger DJ, Lambeth JD (1993) Neutrophil phospholipase D is activated by a membrane-associated Rho family small molecular weight GTP-binding protein. *J Biol Chem* **268:** 21509–21512

Brint EK, Xu D, Liu H, Dunne A, McKenzie AN, O'Neill LA, Liew FY (2004) ST2 is an inhibitor of interleukin 1 receptor and Toll-like receptor 4 signaling and maintains endotoxin tolerance. *Nat Immunol* **5:** 373–379

Bulut Y, Faure E, Thomas L, Equils O, Arditi M (2001) Cooperation of Toll-like receptor 2 and 6 for cellular activation by soluble tuberculosis factor and Borrelia burgdorferi outer surface protein A lipoprotein: role of Toll-interacting protein and IL-1 receptor signaling molecules in Toll-like receptor 2 signaling. *J Immunol* **167:** 987–994

Bulut Y, Faure E, Thomas L, Karahashi H, Michelsen KS, Equils O, Morrison SG, Morrison RP, Arditi M (2002) Chlamydial heat shock protein 60 activates macrophages and endothelial cells through Toll-like receptor 4 and MD2 in a MyD88-dependent pathway. *J Immunol* **168:** 1435–1440

Burns K, Clatworthy J, Martin L, Martinon F, Plumpton C, Maschera B, Lewis A, Ray K, Tschopp J, Volpe F (2000) Tollip, a new component of the IL-1RI pathway, links IRAK to the IL-1 receptor. *Nat Cell Biol* **2:** 346–351

Burns K, Janssens S, Brissoni B, Olivos N, Beyaert R, Tschopp J (2003) Inhibition of interleukin 1 receptor/Toll-like receptor signaling through the alternatively spliced, short form of MyD88 is due to its failure to recruit IRAK-4. *J Exp Med* **197:** 263–268

Butler MP, Hanly JA, Moynagh PN (2005) Pellino3 is a novel upstream regulator of p38 MAPK and activates CREB in a p38-dependent manner. *J Biol Chem* **280:** 27759–27768

Callaghan J, Simonsen A, Gaullier JM, Toh BH, Stenmark H (1999) The endosome fusion regulator early-endosomal autoantigen 1 (EEA1) is a dimer. *Biochem J* **338** (Part 2)**:** 539–543

Cantrell D (1998) Lymphocyte signalling: a coordinating role for Vav? *Curr Biol* **8:** R535–R538

Cardone MH, Salvesen GS, Widmann C, Johnson G, Frisch SM (1997) The regulation of anoikis: MEKK-1 activation requires cleavage by caspases. *Cell* **90:** 315–323

Carruth LM, Demczuk S, Mizel SB (1991) Involvement of a calpain-like protease in the processing of the murine interleukin 1 alpha precursor. *J Biol Chem* **266:** 12162–12167

Casamayor A, Morrice NA, Alessi DR (1999) Phosphorylation of Ser-241 is essential for the activity of 3-phosphoinositide-dependent protein kinase-1: identification of five sites of phosphorylation *in vivo*. *Biochem J* **342** (Part 2)**:** 287–292

Cataldi A, Centurione L, Di Pietro R, Rapino M, Bosco D, Grifone G, Garaci F, Rana R (2003) Protein kinase C zeta nuclear translocation mediates the occurrence of radioresistance in friend erythroleukemia cells. *J Cell Biochem* **88:** 144–151

Cerretti DP, Kozlosky CJ, Mosley B, Nelson N, Van Ness K, Greenstreet TA, March CJ, Kronheim SR, Druck T, Cannizzaro LA, Huebner K, Black RA (1992) Molecular cloning of the interleukin-1 beta converting enzyme. *Science* **256:** 97–100

Chamaillard M, Hashimoto M, Horie Y, Masumoto J, Qiu S, Saab L, Ogura Y, Kawasaki A, Fukase K, Kusumoto S, Valvano MA, Foster SJ, Mak TW, Nunez G, Inohara N (2003) An essential role for NOD1 in host recognition of bacterial peptidoglycan containing diaminopimelic acid. *Nat Immunol* **4:** 702–707

Channavajhala PL, Wu L, Cuozzo JW, Hall JP, Liu W, Lin LL, Zhang Y (2003) Identification of a novel human kinase supporter of Ras (hKSR-2) that functions as a negative regulator of Cot (Tpl2) signaling. *J Biol Chem* **278:** 47089–47097

Chen L, Fischle W, Verdin E, Greene WC (2001) Duration of nuclear NF-kappaB action regulated by reversible acetylation. *Science* **293:** 1653–1657

Chen LF, Greene WC (2004) Shaping the nuclear action of NF-kappaB. *Nat Rev Mol Cell Biol* **5:** 392–401

Chen LF, Mu Y, Greene WC (2002a) Acetylation of RelA at discrete sites regulates distinct nuclear functions of NF-kappaB. *EMBO J* **21:** 6539–6548

Chen LY, Zuraw BL, Liu FT, Huang S, Pan ZK (2002b) IL-1 receptor-associated kinase and low molecular weight GTPase RhoA signal molecules are required for bacterial lipopolysaccharide-induced cytokine gene transcription. *J Immunol* **169:** 3934–3939

Chen RH, Sarnecki C, Blenis J (1992) Nuclear localization and regulation of erk- and rsk-encoded protein kinases. *Mol Cell Biol* **12:** 915–927

Cheung PC, Campbell DG, Nebreda AR, Cohen P (2003) Feedback control of the protein kinase TAK1 by SAPK2a/p38alpha. *EMBO J* **22:** 5793–5805

Cheung PC, Nebreda AR, Cohen P (2004) TAB3, a new binding partner of the protein kinase TAK1. *Biochem J* **378:** 27–34

Cho J, Melnick M, Solidakis GP, Tsichlis PN (2005) Tpl2 (tumor progression locus 2) phosphorylation at Thr290 is induced by lipopolysaccharide via an Ikappa-B kinase-beta-dependent pathway and is required for Tpl2 activation by external signals. *J Biol Chem* **280:** 20442–20448

Cho J, Tsichlis PN (2005) Phosphorylation at Thr-290 regulates Tpl2 binding to NF-kappaB1/p105 and Tpl2 activation and degradation by lipopolysaccharide. *Proc Natl Acad Sci USA* **102:** 2350–2355

Choi KB, Wong F, Harlan JM, Chaudhary PM, Hood L, Karsan A (1998) Lipopolysaccharide mediates endothelial apoptosis by a FADD-dependent pathway. *J Biol Chem* **273:** 20185–20188

Chrivia JC, Kwok RP, Lamb N, Hagiwara M, Montminy MR, Goodman RH (1993) Phosphorylated CREB binds specifically to the nuclear protein CBP. *Nature* **365:** 855–859

Chu ZL, McKinsey TA, Liu L, Qi X, Ballard DW (1996) Basal phosphorylation of the PEST domain in the I(kappa)B(beta) regulates its functional interaction with the c-rel proto-oncogene product. *Mol Cell Biol* **16:** 5974–5984

Chuang TH, Ulevitch RJ (2004) Triad3A, an E3 ubiquitin–protein ligase regulating Toll-like receptors. *Nat Immunol* **5:** 495–502

Coelho PS, Klein A, Talvani A, Coutinho SF, Takeuchi O, Akira S, Silva JS, Canizzaro H, Gazzinelli RT, Teixeira MM (2002) Glycosylphosphatidylinositol-anchored mucin-like glycoproteins isolated from *Trypanosoma cruzi trypomastigotes* induce *in vivo* leukocyte recruitment dependent on MCP-1 production by IFN-gamma-primed-macrophages. *J Leukocyte Biol* **71:** 837–844

Cohen S, Achbert-Weiner H, Ciechanover A (2004) Dual effects of IkappaB kinase beta-mediated phosphorylation on p105 Fate: SCF(beta-TrCP)-dependent degradation and SCF(beta-TrCP)-independent processing. *Mol Cell Biol* **24:** 475–486

Cohen S, Orian A, Ciechanover A (2001) Processing of p105 is inhibited by docking of p50 active subunits to the ankyrin repeat domain, and inhibition is alleviated by signaling via the carboxyl-terminal phosphorylation/ubiquitin-ligase binding domain. *J Biol Chem* **276:** 26769–26776

Colbran RJ, Schworer CM, Hashimoto Y, Fong YL, Rich DP, Smith MK, Soderling TR (1989) Calcium/calmodulin-dependent protein kinase II. *Biochem J* **258:** 313–325

Colicelli J (2004) Human RAS superfamily proteins and related GTPases. *Sci STKE* **2004:** RE13

Coronella-Wood J, Terrand J, Sun H, Chen QM (2004) c-Fos phosphorylation induced by H2O2 prevents proteasomal degradation of c-Fos in cardiomyocytes. *J Biol Chem* **279:** 33567–33574

Cory GO, Lovering RC, Hinshelwood S, MacCarthy-Morrogh L, Levinsky RJ, Kinnon C (1995) The protein product of the c-cbl protooncogene is phosphorylated after B cell receptor stimulation and binds the SH3 domain of Bruton's tyrosine kinase. *J Exp Med* **182:** 611–615

Cox JA (1988) Interactive properties of calmodulin. *Biochem J* **249:** 621–629

Crespo P, Schuebel KE, Ostrom AA, Gutkind JS, Bustelo XR (1997) Phosphotyrosine-dependent activation of Rac-1 GDP/GTP exchange by the vav proto-oncogene product. *Nature* **385:** 169–172

Crews CM, Alessandrini A, Erikson RL (1992) The primary structure of MEK, a protein kinase that phosphorylates the ERK gene product. *Science* **258:** 478–480

Cuenda A, Alonso G, Morrice N, Jones M, Meier R, Cohen P, Nebreda AR (1996) Purification and cDNA cloning of SAPKK3, the major activator of RK/p38 in stress- and cytokine-stimulated monocytes and epithelial cells. *EMBO J* **15:** 4156–4164

Dalton S, Treisman R (1992) Characterization of SAP-1, a protein recruited by serum response factor to the c-fos serum response element. *Cell* **68:** 597–612

Dang PM, Fontayne A, Hakim J, El Benna J, Perianin A (2001) Protein kinase C zeta phosphorylates a subset of selective sites of the NADPH oxidase component p47phox and participates in formyl peptide-mediated neutrophil respiratory burst. *J Immunol* **166:** 1206–1213

Davis M, Hatzubai A, Andersen JS, Ben-Shushan E, Fisher GZ, Yaron A, Bauskin A, Mercurio F, Mann M, Ben-Neriah Y (2002) Pseudosubstrate regulation of the SCF(beta-TrCP) ubiquitin ligase by hnRNP-U. *Genes Dev* **16:** 439–451

Deacon K, Blank JL (1999) MEK kinase 3 directly activates MKK6 and MKK7, specific activators of the p38 and c-Jun NH2-terminal kinases. *J Biol Chem* **274:** 16604–16610

Deak JC, Cross JV, Lewis M, Qian Y, Parrott LA, Distelhorst CW, Templeton DJ (1998a) Fas-induced proteolytic activation and intracellular redistribution of the stress-signaling kinase MEKK1. *Proc Natl Acad Sci USA* **95:** 5595–5600

Deak M, Clifton AD, Lucocq LM, Alessi DR (1998b) Mitogen- and stress-activated protein kinase-1 (MSK1) is directly activated by MAPK and SAPK2/p38, and may mediate activation of CREB. *EMBO J* **17:** 4426–4441

Delhase M, Hayakawa M, Chen Y, Karin M (1999) Positive and negative regulation of IkappaB kinase activity through IKKbeta subunit phosphorylation. *Science* **284:** 309–313

Deng L, Wang C, Spencer E, Yang L, Braun A, You J, Slaughter C, Pickart C, Chen ZJ (2000) Activation of the IkappaB kinase complex by TRAF6 requires a dimeric ubiquitin-conjugating enzyme complex and a unique polyubiquitin chain. *Cell* **103:** 351–361

Derijard B, Hibi M, Wu IH, Barrett T, Su B, Deng T, Karin M, Davis RJ (1994) JNK1: a protein kinase stimulated by UV light and Ha-Ras

that binds and phosphorylates the c-Jun activation domain. *Cell* **76:** 1025–1037

Dhillon AS, Kolch W (2002) Untying the regulation of the Raf-1 kinase. *Arch Biochem Biophys* **404:** 3–9

Diaz-Meco MT, Berra E, Municio MM, Sanz L, Lozano J, Dominguez I, Diaz-Golpe V, Lain de Lera MT, Alcamí J, Payá CV, Arenzana-Seisdedos F, Virelizier JL, Moscat J (1993) A dominant negative protein kinase C zeta subspecies blocks NF-kappa B activation. *Mol Cell Biol* **13:** 4770–4775

DiDonato J, Mercurio F, Rosette C, Wu-Li J, Suyang H, Ghosh S, Karin M (1996) Mapping of the inducible IkappaB phosphorylation sites that signal its ubiquitination and degradation. *Mol Cell Biol* **16:** 1295–1304

Diebold SS, Kaisho T, Hemmi H, Akira S, Reis e Sousa C (2004) Innate antiviral responses by means of TLR7-mediated recognition of single-stranded RNA. *Science* **303:** 1529–1531

Diehl GE, Yue HH, Hsieh K, Kuang AA, Ho M, Morici LA, Lenz LL, Cado D, Riley LW, Winoto A (2004) TRAIL-R as a negative regulator of innate immune cell responses. *Immunity* **21:** 877–889

Diekmann D, Abo A, Johnston C, Segal AW, Hall A (1994) Interaction of Rac with p67phox and regulation of phagocytic NADPH oxidase activity. *Science* **265:** 531–533

Dumitru CD, Ceci JD, Tsatsanis C, Kontoyiannis D, Stamatakis K, Lin JH, Patriotis C, Jenkins NA, Copeland NG, Kollias G, Tsichlis PN (2000) TNF-alpha induction by LPS is regulated posttranscriptionally via a Tpl2/ERK-dependent pathway. *Cell* **103:** 1071–1083

Dunne A, Ejdeback M, Ludidi PL, O'Neill LA, Gay NJ (2003) Structural complementarity of Toll/interleukin-1 receptor domains in Toll-like receptors and the adaptors Mal and MyD88. *J Biol Chem* **278:** 41443–41451

Edwards AS, Newton AC (1997) Phosphorylation at conserved carboxyl-terminal hydrophobic motif regulates the catalytic and regulatory domains of protein kinase C. *J Biol Chem* **272:** 18382–18390

El Benna J, Faust RP, Johnson JL, Babior BM (1996) Phosphorylation of the respiratory burst oxidase subunit p47phox as determined by two-dimensional phosphopeptide mapping. Phosphorylation by protein kinase C, protein kinase A, and a mitogen-activated protein kinase. *J Biol Chem* **271:** 6374–6378

El-Benna J, Dang PM, Gougerot-Pocidalo MA, Elbim C (2005) Phagocyte NADPH oxidase: a multicomponent enzyme essential for host defenses. *Arch Immunol Ther Exp (Warsz)* **53:** 199–206

Fagerlund R, Kinnunen L, Kohler M, Julkunen I, Melen K (2005) NF-kappaB is transported into the nucleus by importin alpha3 and importin alpha4. *J Biol Chem* **280:** 15942–15951

Fan CM, Maniatis T (1991) Generation of p50 subunit of NF-kappa B by processing of p105 through an ATP-dependent pathway. *Nature* **354:** 395–398

Farnell MB, He H, Genovese K, Kogut MH (2003) Pharmacological analysis of signal transduction pathways required for oxidative burst in chicken heterophils stimulated by a Toll-like receptor 2 agonist. *Int Immunopharmacol* **3:** 1677–1684

Fass DM, Butler JE, Goodman RH (2003) Deacetylase activity is required for cAMP activation of a subset of CREB target genes. *J Biol Chem* **278:** 43014–43019

Faust LR, el Benna J, Babior BM, Chanock SJ (1995) The phosphorylation targets of p47phox, a subunit of the respiratory burst oxidase. Functions of the individual target serines as evaluated by site-directed mutagenesis. *J Clin Invest* **96:** 1499–1505

Feng Y, Longmore GD (2005) The LIM protein Ajuba influences interleukin-1-induced NF-kappaB activation by affecting the assembly and activity of the protein kinase Czeta/p62/TRAF6 signaling complex. *Mol Cell Biol* **25:** 4010–4022

Fitzgerald KA, McWhirter SM, Faia KL, Rowe DC, Latz E, Golenbock DT, Coyle AJ, Liao SM, Maniatis T (2003a) IKKepsilon and TBK1 are essential components of the IRF3 signaling pathway. *Nat Immunol* **4:** 491–496

Fitzgerald KA, Palsson-McDermott EM, Bowie AG, Jefferies CA, Mansell AS, Brady G, Brint E, Dunne A, Gray P, Harte MT, McMurray D, Smith DE, Sims JE, Bird TA, O'Neill LA (2001) Mal (MyD88-adapter-like) is required for Toll-like receptor-4 signal transduction. *Nature* **413:** 78–83

Fitzgerald KA, Rowe DC, Barnes BJ, Caffrey DR, Visintin A, Latz E, Monks B, Pitha PM, Golenbock DT (2003b) LPS-TLR4 signaling to IRF-3/7 and NF-kappaB involves the toll adapters TRAM and TRIF. *J Exp Med* **198:** 1043–1055

Fitzgerald KA, Rowe DC, Golenbock DT (2004) Endotoxin recognition and signal transduction by the TLR4/MD2-complex. *Microbes Infect* **6:** 1361–1367

Fontayne A, Dang PM, Gougerot-Pocidalo MA, El-Benna J (2002) Phosphorylation of p47phox sites by PKC alpha, beta II, delta, and zeta: effect on binding to p22phox and on NADPH oxidase activation. *Biochemistry* **41:** 7743–7750

Frost JA, Steen H, Shapiro P, Lewis T, Ahn N, Shaw PE, Cobb MH (1997) Cross-cascade activation of ERKs and ternary complex factors by Rho family proteins. *EMBO J* **16:** 6426–6438

Fuchs SY, Chen A, Xiong Y, Pan ZQ, Ronai Z (1999) HOS, a human homolog of Slimb, forms an SCF complex with Skp1 and Cullin1 and targets the phosphorylation-dependent degradation of IkappaB and beta-catenin. *Oncogene* **18:** 2039–2046

Fujioka S, Niu J, Schmidt C, Sclabas GM, Peng B, Uwagawa T, Li Z, Evans DB, Abbruzzese JL, Chiao PJ (2004) NF-kappaB and AP-1 connection: mechanism of NF-kappaB-dependent regulation of AP-1 activity. *Mol Cell Biol* **24:** 7806–7819

Fukao T, Koyasu S (2003) PI3K and negative regulation of TLR signaling. *Trends Immunol* **24:** 358–363

Fukunaga R, Hunter T (1997) MNK1, a new MAP kinase-activated protein kinase, isolated by a novel expression screening method for identifying protein kinase substrates. *EMBO J* **16:** 1921–1933

Funakoshi-Tago M, Tago K, Andoh K, Sonoda Y, Tominaga S, Kasahara T (2005) Functional role of c-Src in IL-1-induced NF-kappa B activation: c-Src is a component of the IKK complex. *J Biochem (Tokyo)* **137:** 189–197

Ge B, Gram H, Di Padova F, Huang B, New L, Ulevitch RJ, Luo Y, Han J (2002) MAPKK-independent activation of p38alpha mediated by TAB1-dependent autophosphorylation of p38alpha. *Science* **295:** 1291–1294

Gerritsen ME, Williams AJ, Neish AS, Moore S, Shi Y, Collins T (1997) CREB-binding protein/p300 are transcriptional coactivators of p65. *Proc Natl Acad Sci USA* **94:** 2927–2932

Ghosh S, Karin M (2002) Missing pieces in the NF-kappaB puzzle. *Cell* **109** (Suppl)**:** S81–S96

Ghosh S, Strum JC, Sciorra VA, Daniel L, Bell RM (1996) Raf-1 kinase possesses distinct binding domains for phosphatidylserine and phosphatidic acid. Phosphatidic acid regulates the translocation of Raf-1 in 12-*O*-tetradecanoylphorbol-13-acetate-stimulated Madin–Darby canine kidney cells. *J Biol Chem* **271:** 8472–8480

Giese KP, Fedorov NB, Filipkowski RK, Silva AJ (1998) Autophosphorylation at Thr286 of the alpha calcium-calmodulin kinase II in LTP and learning. *Science* **279:** 870–873

Gil J, Garcia MA, Gomez-Puertas P, Guerra S, Rullas J, Nakano H, Alcami J, Esteban M (2004) TRAF family proteins link PKR with NF-kappa B activation. *Mol Cell Biol* **24:** 4502–4512

Girardin SE, Boneca IG, Carneiro LA, Antignac A, Jehanno M, Viala J, Tedin K, Taha MK, Labigne A, Zahringer U, Coyle AJ, DiStefano PS, Bertin J, Sansonetti PJ, Philpott DJ (2003a) Nod1 detects a unique muropeptide from Gram-negative bacterial peptidoglycan. *Science* **300:** 1584–1587

Girardin SE, Boneca IG, Viala J, Chamaillard M, Labigne A, Thomas G, Philpott DJ, Sansonetti PJ (2003b) Nod2 is a general sensor of peptidoglycan through muramyl dipeptide (MDP) detection. *J Biol Chem* **278:** 8869–8872

Girardin SE, Tournebize R, Mavris M, Page AL, Li X, Stark GR, Bertin J, DiStefano PS, Yaniv M, Sansonetti PJ, Philpott DJ (2001) CARD4/Nod1 mediates NF-kappaB and JNK activation by invasive Shigella flexneri. *EMBO Rep* **2:** 736–742

Gon Y, Asai Y, Hashimoto S, Mizumura K, Jibiki I, Machino T, Ra C, Horie T (2004) A20 inhibits toll-like receptor 2- and 4-mediated interleukin-8 synthesis in airway epithelial cells. *Am J Respir Cell Mol Biol* **31:** 330–336

Gonzalez FA, Seth A, Raden DL, Bowman DS, Fay FS, Davis RJ (1993) Serum-induced translocation of mitogen-activated protein kinase to the cell surface ruffling membrane and the nucleus. *J Cell Biol* **122:** 1089–1101

Gonzalez GA, Montminy MR (1989) Cyclic AMP stimulates somatostatin gene transcription by phosphorylation of CREB at serine 133. *Cell* **59:** 675–680

Gratton JP, Morales-Ruiz M, Kureishi Y, Fulton D, Walsh K, Sessa WC (2001) Akt down-regulation of p38 signaling provides a novel mechanism of vascular endothelial growth factor-mediated cytoprotection in endothelial cells. *J Biol Chem* **276:** 30359–30365

Grimes CA, Jope RS (2001) CREB DNA binding activity is inhibited by glycogen synthase kinase-3 beta and facilitated by lithium. *J Neurochem* **78:** 1219–1232

Guan H, Hou S, Ricciardi RP (2005) DNA binding of repressor nuclear factor-kappaB p50/p50 depends on phosphorylation of Ser337 by the protein kinase A catalytic subunit. *J Biol Chem* **280:** 9957–9962

Guinamard R, Fougereau M, Seckinger P (1997) The SH3 domain of Bruton's tyrosine kinase interacts with Vav, Sam68 and EWS. *Scand J Immunol* **45:** 587–595

Gupta S, Seth A, Davis RJ (1993) Transactivation of gene expression by Myc is inhibited by mutation at the phosphorylation sites Thr-58 and Ser-62. *Proc Natl Acad Sci USA* **90:** 3216–3220

Hajjar AM, O'Mahony DS, Ozinsky A, Underhill DM, Aderem A, Klebanoff SJ, Wilson CB (2001) Cutting edge: functional interactions between toll-like receptor (TLR) 2 and TLR1 or TLR6 in response to phenol-soluble modulin. *J Immunol* **166:** 15–19

Han L, Colicelli J (1995) A human protein selected for interference with Ras function interacts directly with Ras and competes with Raf1. *Mol Cell Biol* **15:** 1318–1323

Hardy MP, O'Neill LA (2004) The murine IRAK2 gene encodes four alternatively spliced isoforms, two of which are inhibitory. *J Biol Chem* **279:** 27699–27708

Harhaj EW, Maggirwar SB, Sun SC (1996) Inhibition of p105 processing by NF-kappaB proteins in transiently transfected cells. *Oncogene* **12:** 2385–2392

Hasan U, Chaffois C, Gaillard C, Saulnier V, Merck E, Tancredi S, Guiet C, Briere F, Vlach J, Lebecque S, Trinchieri G, Bates EE (2005) Human TLR10 is a functional receptor, expressed by B cells and plasmacytoid dendritic cells, which activates gene transcription through MyD88. *J Immunol* **174:** 2942–2950

Hatakeyama S, Kitagawa M, Nakayama K, Shirane M, Matsumoto M, Hattori K, Higashi H, Nakano H, Okumura K, Onoe K, Good RA (1999) Ubiquitin-dependent degradation of IkappaBalpha is mediated by a ubiquitin ligase Skp1/Cul 1/F-box protein FWD1. *Proc Natl Acad Sci USA* **96:** 3859–3863

Hayakawa J, Depatie C, Ohmichi M, Mercola D (2003) The activation of c-Jun NH2-terminal kinase (JNK) by DNA-damaging agents serves to promote drug resistance via activating transcription factor 2 (ATF2)-dependent enhanced DNA repair. *J Biol Chem* **278:** 20582–20592

Hayashi F, Smith KD, Ozinsky A, Hawn TR, Yi EC, Goodlett DR, Eng JK, Akira S, Underhill DM, Aderem A (2001) The innate immune response to bacterial flagellin is mediated by Toll-like receptor 5. *Nature* **410:** 1099–1103

Hayden MS, Ghosh S (2004) Signaling to NF-kappaB. *Genes Dev* **18:** 2195–2224

Heil F, Ahmad-Nejad P, Hemmi H, Hochrein H, Ampenberger F, Gellert T, Dietrich H, Lipford G, Takeda K, Akira S, Wagner H, Bauer S (2003) The Toll-like receptor 7 (TLR7)-specific stimulus loxoribine uncovers a strong relationship within the TLR7, 8 and 9 subfamily. *Eur J Immunol* **33:** 2987–2997

Heil F, Hemmi H, Hochrein H, Ampenberger F, Kirschning C, Akira S, Lipford G, Wagner H, Bauer S (2004) Species-specific recognition of single-stranded RNA via toll-like receptor 7 and 8. *Science* **303:** 1526–1529

Heissmeyer V, Krappmann D, Hatada EN, Scheidereit C (2001) Shared pathways of IkappaB kinase-induced SCF(betaTrCP)-mediated ubiquitination and degradation for the NF-kappaB precursor p105 and IkappaBalpha. *Mol Cell Biol* **21:** 1024–1035

Heissmeyer V, Krappmann D, Wulczyn FG, Scheidereit C (1999) NF-kappaB p105 is a target of IkappaB kinases and controls signal induction of Bcl-3–p50 complexes. *EMBO J* **18:** 4766–4778

Hemmi H, Kaisho T, Takeuchi O, Sato S, Sanjo H, Hoshino K, Horiuchi T, Tomizawa H, Takeda K, Akira S (2002) Small anti-viral compounds activate immune cells via the TLR7 MyD88-dependent signaling pathway. *Nat Immunol* **3:** 196–200

Hemmi H, Takeuchi O, Kawai T, Kaisho T, Sato S, Sanjo H, Matsumoto M, Hoshino K, Wagner H, Takeda K, Akira S (2000) A Toll-like receptor recognizes bacterial DNA. *Nature* **408:** 740–745

Heyninck K, De Valck D, Vanden Berghe W, Van Criekinge W, Contreras R, Fiers W, Haegeman G, Beyaert R (1999) The zinc finger protein A20 inhibits TNF-induced NF-kappaB-dependent gene expression by interfering with an RIP- or TRAF2-mediated transactivation signal and directly binds to a novel NF-kappaB-inhibiting protein ABIN. *J Cell Biol* **145:** 1471–1482

Heyninck K, Kreike MM, Beyaert R (2003) Structure-function analysis of the A20-binding inhibitor of NF-kappa B activation, ABIN-1. *FEBS Lett* **536:** 135–140

Hibi M, Lin A, Smeal T, Minden A, Karin M (1993) Identification of an oncoprotein- and UV-responsive protein kinase that binds and potentiates the c-Jun activation domain. *Genes Dev* **7:** 2135–2148

Hipskind RA, Rao VN, Mueller CG, Reddy ES, Nordheim A (1991) Ets-related protein Elk-1 is homologous to the c-fos regulatory factor p62TCF. *Nature* **354:** 531–534

Hirschfeld M, Weis JJ, Toshchakov V, Salkowski CA, Cody MJ, Ward DC, Qureshi N, Michalek SM, Vogel SN (2001) Signaling by toll-like receptor 2 and 4 agonists results in differential gene expression in murine macrophages. *Infect Immun* **69:** 1477–1482

Hoebe K, Du X, Georgel P, Janssen E, Tabeta K, Kim SO, Goode J, Lin P, Mann N, Mudd S, Crozat K, Sovath S, Han J, Beutler B (2003) Identification of Lps2 as a key transducer of MyD88-independent TIR signalling. *Nature* **424:** 743–748

Hoeflich KP, Luo J, Rubie EA, Tsao MS, Jin O, Woodgett JR (2000) Requirement for glycogen synthase kinase-3beta in cell survival and NF-kappaB activation. *Nature* **406:** 86–90

Horng T, Barton GM, Flavell RA, Medzhitov R (2002) The adaptor molecule TIRAP provides signalling specificity for Toll-like receptors. *Nature* **420:** 329–333

Huang J, Gao X, Li S, Cao Z (1997) Recruitment of IRAK to the interleukin 1 receptor complex requires interleukin 1 receptor accessory protein. *Proc Natl Acad Sci USA* **94:** 12829–12832

Huang Q, Yang J, Lin Y, Walker C, Cheng J, Liu ZG, Su B (2004) Differential regulation of interleukin 1 receptor and Toll-like receptor signaling by MEKK3. *Nat Immunol* **5:** 98–103

Hughes K, Edin S, Antonsson A, Grundstrom T (2001) Calmodulin-dependent kinase II mediates T cell receptor/CD3- and phorbol ester-induced activation of IkappaB kinase. *J Biol Chem* **276:** 36008–36013

Hyakushima N, Mitsuzawa H, Nishitani C, Sano H, Kuronuma K, Konishi M, Himi T, Miyake K, Kuroki Y (2004) Interaction of soluble form of recombinant extracellular TLR4 domain with MD-2 enables lipopolysaccharide binding and attenuates TLR4-mediated signaling. *J Immunol* **173:** 6949–6954

Ichijo H, Nishida E, Irie K, ten Dijke P, Saitoh M, Moriguchi T, Takagi M, Matsumoto K, Miyazono K, Gotoh Y (1997) Induction of apoptosis by ASK1, a mammalian MAPKKK that activates SAPK/JNK and p38 signaling pathways. *Science* **275:** 90–94

Idriss H, Kumar A, Casas-Finet JR, Guo H, Damuni Z, Wilson SH (1994) Regulation of *in vitro* nucleic acid strand annealing activity of heterogeneous nuclear ribonucleoprotein protein A1 by reversible phosphorylation. *Biochemistry* **33:** 11382–11390

Illenberger D, Schwald F, Pimmer D, Binder W, Maier G, Dietrich A, Gierschik P (1998) Stimulation of phospholipase C-beta2 by the Rho GTPases Cdc42Hs and Rac1. *EMBO J* **17:** 6241–6249

Inohara N, Koseki T, del Peso L, Hu Y, Yee C, Chen S, Carrio R, Merino J, Liu D, Ni J, Nunez G (1999) Nod1, an Apaf-1-like activator of caspase-9 and nuclear factor-kappaB. *J Biol Chem* **274:** 14560–14567

Inohara N, Ogura Y, Fontalba A, Gutierrez O, Pons F, Crespo J, Fukase K, Inamura S, Kusumoto S, Hashimoto M, Foster SJ, Moran AP, Fernandez-Luna JL, Nunez G (2003) Host recognition of bacterial muramyl dipeptide mediated through NOD2. Implications for Crohn's disease. *J Biol Chem* **278:** 5509–5512

Irie T, Muta T, Takeshige K (2000) TAK1 mediates an activation signal from toll-like receptor(s) to nuclear factor-kappaB in lipopolysaccharide-stimulated macrophages. *FEBS Lett* **467:** 160–164

Ishida A, Shigeri Y, Taniguchi T, Kameshita I (2003) Protein phosphatases that regulate multifunctional Ca^{2+}/calmodulin-dependent protein kinases: from biochemistry to pharmacology. *Pharmacol Ther* **100:** 291–305

Ishii KJ, Takeshita F, Gursel I, Gursel M, Conover J, Nussenzweig A, Klinman DM (2002) Potential role of phosphatidylinositol 3 kinase, rather than DNA-dependent protein kinase, in CpG DNA-induced immune activation. *J Exp Med* **196:** 269–274

Ishitani T, Takaesu G, Ninomiya-Tsuji J, Shibuya H, Gaynor RB, Matsumoto K (2003) Role of the TAB2-related protein TAB3 in IL-1 and TNF signaling. *EMBO J* **22:** 6277–6288

Islam S, Hassan F, Mu MM, Ito H, Koide N, Mori I, Yoshida T, Yokochi T (2004) Piceatannol prevents lipopolysaccharide (LPS)-induced nitric oxide (NO) production and nuclear factor (NF)-kappaB activation by inhibiting IkappaB kinase (IKK). *Microbiol Immunol* **48:** 729–736

Iwami KI, Matsuguchi T, Masuda A, Kikuchi T, Musikacharoen T, Yoshikai Y (2000) Cutting edge: naturally occurring soluble form of mouse Toll-like receptor 4 inhibits lipopolysaccharide signaling. *J Immunol* **165:** 6682–6686

Jaffer ZM, Chernoff J (2002) p21-activated kinases: three more join the Pak. *Int J Biochem Cell Biol* **34:** 713–717

Jahr TG, Ryan L, Sundan A, Lichenstein HS, Skjak-Braek G, Espevik T (1997) Induction of tumor necrosis factor production from monocytes stimulated with mannuronic acid polymers and involvement of lipopolysaccharide-binding protein, CD14, and bactericidal/permeability-increasing factor. *Infect Immun* **65:** 89–94

Janssens S, Burns K, Tschopp J, Beyaert R (2002) Regulation of interleukin-1- and lipopolysaccharide-induced NF-kappaB activation by alternative splicing of MyD88. *Curr Biol* **12:** 467–471

Jeannin P, Renno T, Goetsch L, Miconnet I, Aubry JP, Delneste Y, Herbault N, Baussant T, Magistrelli G, Soulas C, Romero P, Cerottini JC, Bonnefoy JY (2000) OmpA targets dendritic cells, induces their maturation and delivers antigen into the MHC class I presentation pathway. *Nat Immunol* **1:** 502–509

Jefferies CA, O'Neill LA (2004) Bruton's tyrosine kinase (Btk)-the critical tyrosine kinase in LPS signalling? *Immunol Lett* **92:** 15–22

Jiang Z, Johnson HJ, Nie H, Qin J, Bird TA, Li X (2003) Pellino 1 is required for interleukin-1 (IL-1)-mediated signaling through its interaction with the IL-1 receptor-associated kinase 4 (IRAK4)-IRAK-tumor necrosis factor receptor-associated factor 6 (TRAF6) complex. *J Biol Chem* **278:** 10952–10956

Jiang Z, Ninomiya-Tsuji J, Qian Y, Matsumoto K, Li X (2002) Interleukin-1 (IL-1) receptor-associated kinase-dependent IL-1-induced signaling complexes phosphorylate TAK1 and TAB2 at the plasma membrane and activate TAK1 in the cytosol. *Mol Cell Biol* **22:** 7158–7167

Johnson GB, Brunn GJ, Kodaira Y, Platt JL (2002) Receptor-mediated monitoring of tissue well-being via detection of soluble heparan sulfate by Toll-like receptor 4. *J Immunol* **168:** 5233–5239

Jurk M, Heil F, Vollmer J, Schetter C, Krieg AM, Wagner H, Lipford G, Bauer S (2002) Human TLR7 or TLR8 independently confer responsiveness to the antiviral compound R-848. *Nat Immunol* **3:** 499

Kanayama A, Seth RB, Sun L, Ea CK, Hong M, Shaito A, Chiu YH, Deng L, Chen ZJ (2004) TAB2 and TAB3 activate the NF-kappaB pathway through binding to polyubiquitin chains. *Mol Cell* **15:** 535–548

Kanoh H, Sakane F, Imai S, Wada I (1993) Diacylglycerol kinase and phosphatidic acid phosphatase—enzymes metabolizing lipid second messengers. *Cell Signal* **5:** 495–503

Karandikar M, Xu S, Cobb MH (2000) MEKK1 binds raf-1 and the ERK2 cascade components. *J Biol Chem* **275:** 40120–40127

Kariko K, Ni H, Capodici J, Lamphier M, Weissman D (2004) mRNA is an endogenous ligand for Toll-like receptor 3. *J Biol Chem* **279:** 12542–12550

Karin M, Liu Z, Zandi E (1997) AP-1 function and regulation. *Curr Opin Cell Biol* **9:** 240–246

Kassenbrock CK, Hunter S, Garl P, Johnson GL, Anderson SM (2002) Inhibition of Src family kinases blocks epidermal growth factor (EGF)-induced activation of Akt, phosphorylation of c-Cbl, and ubiquitination of the EGF receptor. *J Biol Chem* **277:** 24967–24975

Kavita U, Mizel SB (1995) Differential sensitivity of interleukin-1 alpha and -beta precursor proteins to cleavage by calpain, a calcium-dependent protease. *J Biol Chem* **270:** 27758–27765

Kawai T, Sato S, Ishii KJ, Coban C, Hemmi H, Yamamoto M, Terai K, Matsuda M, Inoue J, Uematsu S, Takeuchi O, Akira S (2004) Interferon-alpha induction through Toll-like receptors involves a direct interaction of IRF7 with MyD88 and TRAF6. *Nat Immunol* **5:** 1061–1068

Kawasaki H, Kawashima S (1996) Regulation of the calpain-calpastatin system by membranes [review]. *Mol Membr Biol* **13:** 217–224

Kawasaki K, Akashi S, Shimazu R, Yoshida T, Miyake K, Nishijima M (2000) Mouse toll-like receptor 4.MD-2 complex mediates lipopolysaccharide-mimetic signal transduction by Taxol. *J Biol Chem* **275:** 2251–2254

Keranen LM, Dutil EM, Newton AC (1995) Protein kinase C is regulated *in vivo* by three functionally distinct phosphorylations. *Curr Biol* **5:** 1394–1403

Khosravi-Far R, Solski PA, Clark GJ, Kinch MS, Der CJ (1995) Activation of Rac1, RhoA, and mitogen-activated protein kinases is required for Ras transformation. *Mol Cell Biol* **15:** 6443–6453

Kiernan R, Bres V, Ng RW, Coudart MP, El Messaoudi S, Sardet C, Jin DY, Emiliani S, Benkirane M (2003) Post-activation turn-off of NF-kappa B-dependent transcription is regulated by acetylation of p65. *J Biol Chem* **278:** 2758–2766

Kim AH, Khursigara G, Sun X, Franke TF, Chao MV (2001) Akt phosphorylates and negatively regulates apoptosis signal-regulating kinase 1. *Mol Cell Biol* **21:** 893–901

Kim JS, Diebold BA, Kim JI, Kim J, Lee JY, Park JB (2004) Rho is involved in superoxide formation during phagocytosis of opsonized zymosans. *J Biol Chem* **279:** 21589–21597

Kim SO, Ono K, Tobias PS, Han J (2003) Orphan nuclear receptor Nur77 is involved in caspase-independent macrophage cell death. *J Exp Med* **197:** 1441–1452

Kobayashi K, Hernandez LD, Galan JE, Janeway CA, Jr, Medzhitov R, Flavell RA (2002) IRAK-M is a negative regulator of Toll-like receptor signaling. *Cell* **110:** 191–202

Kobayashi Y, Yamamoto K, Saido T, Kawasaki H, Oppenheim JJ, Matsushima K (1990) Identification of calcium-activated neutral protease as a processing enzyme of human interleukin 1 alpha. *Proc Natl Acad Sci USA* **87:** 5548–5552

Kollewe C, Mackensen AC, Neumann D, Knop J, Cao P, Li S, Wesche H, Martin MU (2004) Sequential autophosphorylation steps in the interleukin-1 receptor-associated kinase-1 regulate its availability as an adapter in interleukin-1 signaling. *J Biol Chem* **279:** 5227–5236

Kopp E, Medzhitov R, Carothers J, Xiao C, Douglas I, Janeway CA, Ghosh S (1999) ECSIT is an evolutionarily conserved intermediate in the Toll/IL-1 signal transduction pathway. *Genes Dev* **13:** 2059–2071

Kostura MJ, Tocci MJ, Limjuco G, Chin J, Cameron P, Hillman AG, Chartrain NA, Schmidt JA (1989) Identification of a monocyte specific pre-interleukin 1 beta convertase activity. *Proc Natl Acad Sci USA* **86:** 5227–5231

Kroll M, Margottin F, Kohl A, Renard P, Durand H, Concordet JP, Bachelerie F, Arenzana-Seisdedos F, Benarous R (1999) Inducible degradation of IkappaBalpha by the proteasome requires interaction with the F-box protein h-betaTrCP. *J Biol Chem* **274:** 7941–7945

Kuida K, Lippke JA, Ku G, Harding MW, Livingston DJ, Su MS, Flavell RA (1995) Altered cytokine export and apoptosis in mice deficient in interleukin-1 beta converting enzyme. *Science* **267:** 2000–2003

Kumar S, McDonnell PC, Gum RJ, Hand AT, Lee JC, Young PR (1997) Novel homologues of CSBP/p38 MAP kinase: activation, substrate specificity and sensitivity to inhibition by pyridinyl imidazoles. *Biochem Biophys Res Commun* **235:** 533–538

Kurosaki T, Kurosaki M (1997) Transphosphorylation of Bruton's tyrosine kinase on tyrosine 551 is critical for B cell antigen receptor function. *J Biol Chem* **272:** 15595–15598

Kurt-Jones EA, Popova L, Kwinn L, Haynes LM, Jones LP, Tripp RA, Walsh EE, Freeman MW, Golenbock DT, Anderson LJ, Finberg RW (2000) Pattern recognition receptors TLR4 and CD14 mediate response to respiratory syncytial virus. *Nat Immunol* **1:** 398–401

Laherty CD, Hu HM, Opipari AW, Wang F, Dixit VM (1992) The Epstein–Barr virus LMP1 gene product induces A20 zinc finger protein expression by activating nuclear factor kappa B. *J Biol Chem* **267:** 24157–24160

Laherty CD, Perkins ND, Dixit VM (1993) Human T cell leukemia virus type I Tax and phorbol 12-myristate 13-acetate induce expression of the A20 zinc finger protein by distinct mechanisms involving nuclear factor kappa B. *J Biol Chem* **268:** 5032–5039

Lallena MJ, Diaz-Meco MT, Bren G, Paya CV, Moscat J (1999) Activation of IkappaB kinase beta by protein kinase C isoforms. *Mol Cell Biol* **19:** 2180–2188

Lang V, Janzen J, Fischer GZ, Soneji Y, Beinke S, Salmeron A, Allen H, Hay RT, Ben-Neriah Y, Ley SC (2003) betaTrCP-mediated proteolysis of NF-kappaB1 p105 requires phosphorylation of p105 serines 927 and 932. *Mol Cell Biol* **23:** 402–413

Latz E, Schoenemeyer A, Visintin A, Fitzgerald KA, Monks BG, Knetter CF, Lien E, Nilsen NJ, Espevik T, Golenbock DT (2004) TLR9 signals after translocating from the ER to CpG DNA in the lysosome. *Nat Immunol* **5:** 190–198

Lauw FN, Caffrey DR, Golenbock DT (2005) Of mice and man: TLR11 (finally) finds profilin. *Trends Immunol* **26:** 509–511

Lawrence T, Bebien M, Liu GY, Nizet V, Karin M (2005) IKKalpha limits macrophage NF-kappaB activation and contributes to the resolution of inflammation. *Nature* **434:** 1138–1143

Le Good JA, Ziegler WH, Parekh DB, Alessi DR, Cohen P, Parker PJ (1998) Protein kinase C isotypes controlled by phosphoinositide 3-kinase through the protein kinase PDK1. *Science* **281:** 2042–2045

Leadbetter EA, Rifkin IR, Hohlbaum AM, Beaudette BC, Shlomchik MJ, Marshak-Rothstein A (2002) Chromatin–IgG complexes activate B cells by dual engagement of IgM and Toll-like receptors. *Nature* **416:** 603–607

LeBouder E, Rey-Nores JE, Rushmere NK, Grigorov M, Lawn SD, Affolter M, Griffin GE, Ferrara P, Schiffrin EJ, Morgan BP, Labeta MO (2003) Soluble forms of Toll-like receptor (TLR)2 capable of modulating TLR2 signaling are present in human plasma and breast milk. *J Immunol* **171:** 6680–6689

Lee CW, Chien CS, Yang CM (2004) Lipoteichoic acid-stimulated p42/p44 MAPK activation via Toll-like receptor 2 in tracheal smooth muscle cells. *Am J Physiol Lung Cell Mol Physiol* **286:** L921–L930

Lee J, Mira-Arbibe L, Ulevitch RJ (2000) TAK1 regulates multiple protein kinase cascades activated by bacterial lipopolysaccharide. *J Leukocyte Biol* **68:** 909–915

Lee JY, Lowell CA, Lemay DG, Youn HS, Rhee SH, Sohn KH, Jang B, Ye J, Chung JH, Hwang DH (2005) The regulation of the expression of inducible nitric oxide synthase by Src-family tyrosine kinases mediated through MyD88-independent signaling pathways of Toll-like receptor 4. *Biochem Pharmacol* **70:** 1231–1240

Lee KK, Murakawa M, Takahashi S, Tsubuki S, Kawashima S, Sakamaki K, Yonehara S (1998) Purification, molecular cloning, and characterization of TRP32, a novel thioredoxin-related mammalian protein of 32 kDa. *J Biol Chem* **273:** 19160–19166

Leitges M, Sanz L, Martin P, Duran A, Braun U, Garcia JF, Camacho F, Diaz-Meco MT, Rennert PD, Moscat J (2001) Targeted disruption of the zetaPKC gene results in the impairment of the NF-kappaB pathway. *Mol Cell* **8:** 771–780

Lenormand P, Sardet C, Pages G, L'Allemain G, Brunet A, Pouyssegur J (1993) Growth factors induce nuclear translocation of MAP kinases (p42mapk and p44mapk) but not of their activator MAP kinase kinase (p45mapkk) in fibroblasts. *J Cell Biol* **122:** 1079–1088

Li L, Bin LH, Li F, Liu Y, Chen D, Zhai Z, Shu HB (2005) TRIP6 is a RIP2-associated common signaling component of multiple NF-kappaB activation pathways. *J Cell Sci* **118:** 555–563

Li S, Strelow A, Fontana EJ, Wesche H (2002) IRAK-4: a novel member of the IRAK family with the properties of an IRAK-kinase. *Proc Natl Acad Sci USA* **99:** 5567–5572

Li T, Hu J, Li L (2004) Characterization of Tollip protein upon lipopolysaccharide challenge. *Mol Immunol* **41:** 85–92

Liew FY, Liu H, Xu D (2005a) A novel negative regulator for IL-1 receptor and Toll-like receptor 4. *Immunol Lett* **96:** 27–31

Liew FY, Xu D, Brint EK, O'Neill LA (2005b) Negative regulation of toll-like receptor-mediated immune responses. *Nat Rev Immunol* **5:** 446–458

Limatola C, Schaap D, Moolenaar WH, van Blitterswijk WJ (1994) Phosphatidic acid activation of protein kinase C-zeta overexpressed in COS cells: comparison with other protein kinase C isotypes and other acidic lipids. *Biochem J* **304** (Part 3)**:** 1001–1008

Lin L, DeMartino GN, Greene WC (1998) Cotranslational biogenesis of NF-kappaB p50 by the 26S proteasome. *Cell* **92:** 819–828

Lin R, Mamane Y, Hiscott J (1999a) Structural and functional analysis of interferon regulatory factor 3: localization of the transactivation and autoinhibitory domains. *Mol Cell Biol* **19:** 2465–2474

Lin X, Cunningham Jr ET, Mu Y, Geleziunas R, Greene WC (1999b) The proto-oncogene Cot kinase participates in CD3/CD28 induction of NF-kappaB acting through the NF-kappaB-inducing kinase and IkappaB kinases. *Immunity* **10:** 271–280

Lippe R, Miaczynska M, Rybin V, Runge A, Zerial M (2001) Functional synergy between Rab5 effector Rabaptin-5 and exchange factor Rabex-5 when physically associated in a complex. *Mol Biol Cell* **12:** 2219–2228

Liscovitch M, Ben-Av P, Danin M, Faiman G, Eldar H, Livneh E (1993) Phospholipase D-mediated hydrolysis of phosphatidylcholine: role in cell signalling. *J Lipid Mediat* **8:** 177–182

Liu W, Quinto I, Chen X, Palmieri C, Rabin RL, Schwartz OM, Nelson DL, Scala G (2001) Direct inhibition of Bruton's tyrosine kinase by IBtk, a Btk-binding protein. *Nat Immunol* **2:** 939–946

Lu Y, Wahl LM (2005) Production of matrix metalloproteinase-9 by activated human monocytes involves a phosphatidylinositol-3 kinase/Akt/IKKalpha/NF-kappaB pathway. *J Leukocyte Biol* **78:** 259–265

Luciano BS, Hsu S, Channavajhala PL, Lin LL, Cuozzo JW (2004) Phosphorylation of threonine 290 in the activation loop of Tpl2/Cot is necessary but not sufficient for kinase activity. *J Biol Chem* **279:** 52117–52123

MacKichan ML, Logeat F, Israel A (1996) Phosphorylation of p105 PEST sequence via a redox-insensitive pathway up-regulates processing of p50 NF-kappaB. *J Biol Chem* **271:** 6084–6091

Malcolm KC, Ross AH, Qiu RG, Symons M, Exton JH (1994) Activation of rat liver phospholipase D by the small GTP-binding protein RhoA. *J Biol Chem* **269:** 25951–25954

Malek S, Chen Y, Huxford T, Ghosh G (2001) IkappaBbeta, but not IkappaBalpha, functions as a classical cytoplasmic inhibitor of NF-kappaB dimers by masking both NF-kappaB nuclear localization sequences in resting cells. *J Biol Chem* **276:** 45225–45235

Marais R, Wynne J, Treisman R (1993) The SRF accessory protein Elk-1 contains a growth factor-regulated transcriptional activation domain. *Cell* **73:** 381–393

Marie I, Durbin JE, Levy DE (1998) Differential viral induction of distinct interferon-alpha genes by positive feedback through interferon regulatory factor-7. *EMBO J* **17:** 6660–6669

Marmiroli S, Bavelloni A, Faenza I, Sirri A, Ognibene A, Cenni V, Tsukada J, Koyama Y, Ruzzene M, Ferri A, Auron PE, Toker A, Maraldi NM (1998) Phosphatidylinositol 3-kinase is recruited to a specific site in the activated IL-1 receptor I. *FEBS Lett* **438:** 49–54

Martin M, Rehani K, Jope RS, Michalek SM (2005) Toll-like receptor-mediated cytokine production is differentially regulated by glycogen synthase kinase 3. *Nat Immunol* **6:** 777–784

Massari P, Henneke P, Ho Y, Latz E, Golenbock DT, Wetzler LM (2002) Cutting edge: immune stimulation by neisserial porins is toll-like receptor 2 and MyD88 dependent. *J Immunol* **168:** 1533–1537

Matsuzawa A, Saegusa K, Noguchi T, Sadamitsu C, Nishitoh H, Nagai S, Koyasu S, Matsumoto K, Takeda K, Ichijo H (2005) ROS-dependent activation of the TRAF6–ASK1–p38 pathway is selectively required for TLR4-mediated innate immunity. *Nat Immunol* **6:** 587–592

McBride HM, Rybin V, Murphy C, Giner A, Teasdale R, Zerial M (1999) Oligomeric complexes link Rab5 effectors with NSF and drive membrane fusion via interactions between EEA1 and syntaxin 13. *Cell* **98:** 377–386

McCoy CE, Campbell DG, Deak M, Bloomberg GB, Arthur JS (2005) MSK1 activity is controlled by multiple phosphorylation sites. *Biochem J* **387:** 507–517

McKay LI, Cidlowski JA (1999) Molecular control of immune/inflammatory responses: interactions between nuclear factor-kappa B and steroid receptor-signaling pathways. *Endocr Rev* **20:** 435–459

McWhirter SM, Fitzgerald KA, Rosains J, Rowe DC, Golenbock DT, Maniatis T (2004) IFN-regulatory factor 3-dependent gene expression is defective in Tbk1-deficient mouse embryonic fibroblasts. *Proc Natl Acad Sci USA* **101:** 233–238

Means TK, Wang S, Lien E, Yoshimura A, Golenbock DT, Fenton MJ (1999) Human toll-like receptors mediate cellular activation by Mycobacterium tuberculosis. *J Immunol* **163:** 3920–3927

Meng F, Lowell CA (1997) Lipopolysaccharide (LPS)-induced macrophage activation and signal transduction in the absence of Src-family kinases Hck, Fgr, and Lyn. *J Exp Med* **185:** 1661–1670

Meng W, Swenson LL, Fitzgibbon MJ, Hayakawa K, Ter Haar E, Behrens AE, Fulghum JR, Lippke JA (2002) Structure of mitogen-activated protein kinase-activated protein (MAPKAP) kinase 2 suggests a bifunctional switch that couples kinase activation with nuclear export. *J Biol Chem* **277:** 37401–37405

Meyer TE, Habener JF (1993) Cyclic adenosine 3′,5′-monophosphate response element binding protein (CREB) and related transcription-activating deoxyribonucleic acid-binding proteins. *Endocr Rev* **14:** 269–290

Meylan E, Burns K, Hofmann K, Blancheteau V, Martinon F, Kelliher M, Tschopp J (2004) RIP1 is an essential mediator of Toll-like receptor 3-induced NF-kappa B activation. *Nat Immunol* **5:** 503–507

Miranda-Vizuete A, Gustafsson JA, Spyrou G (1998) Molecular cloning and expression of a cDNA encoding a human thioredoxin-like protein. *Biochem Biophys Res Commun* **243:** 284–288

Mizukami Y, Yoshioka K, Morimoto S, Yoshida K (1997) A novel mechanism of JNK1 activation. Nuclear translocation and activation of JNK1 during ischemia and reperfusion. *J Biol Chem* **272:** 16657–16662

Mori M, Yoneyama M, Ito T, Takahashi K, Inagaki F, Fujita T (2004) Identification of Ser-386 of interferon regulatory factor 3 as critical target for inducible phosphorylation that determines activation. *J Biol Chem* **279:** 9698–9702

Moritz A, De Graan PN, Gispen WH, Wirtz KW (1992) Phosphatidic acid is a specific activator of phosphatidylinositol-4-phosphate kinase. *J Biol Chem* **267:** 7207–7210

Mosley B, Urdal DL, Prickett KS, Larsen A, Cosman D, Conlon PJ, Gillis S, Dower SK (1987) The interleukin-1 receptor binds the human interleukin-1 alpha precursor but not the interleukin-1 beta precursor. *J Biol Chem* **262:** 2941–2944

Mullen GE, Kennedy MN, Visintin A, Mazzoni A, Leifer CA, Davies DR, Segal DM (2003) The role of disulfide bonds in the assembly and function of MD-2. *Proc Natl Acad Sci USA* **100:** 3919–3924

Muller CW, Harrison SC (1995) The structure of the NF-kappa B p50:DNA-complex: a starting point for analyzing the Rel family. *FEBS Lett* **369:** 113–117

Muller J, Ory S, Copeland T, Piwnica-Worms H, Morrison DK (2001) C-TAK1 regulates Ras signaling by phosphorylating the MAPK scaffold, KSR1. *Mol Cell* **8:** 983–993

Murray JT, Panaretou C, Stenmark H, Miaczynska M, Backer JM (2002) Role of Rab5 in the recruitment of hVps34/p150 to the early endosome. *Traffic* **3:** 416–427

Muta T, Takeshige K (2001) Essential roles of CD14 and lipopolysaccharide-binding protein for activation of toll-like receptor (TLR)2 as well as TLR4 reconstitution of TLR2- and TLR4-activation by distinguishable ligands in LPS preparations. *Eur J Biochem* **268:** 4580–4589

Muzio M, Stockwell BR, Stennicke HR, Salvesen GS, Dixit VM (1998) An induced proximity model for caspase-8 activation. *J Biol Chem* **273:** 2926–2930

Nakano H, Shindo M, Sakon S, Nishinaka S, Mihara M, Yagita H, Okumura K (1998) Differential regulation of IkappaB kinase alpha and beta by two upstream kinases, NF-kappaB-inducing kinase and mitogen-activated protein kinase/ERK kinase kinase-1. *Proc Natl Acad Sci USA* **95:** 3537–3542

Nakayama K, Hatakeyama S, Maruyama S, Kikuchi A, Onoe K, Good RA, Nakayama KI (2003) Impaired degradation of inhibitory subunit of NF-kappa B (I kappa B) and beta-catenin as a result of targeted disruption of the beta-TrCP1 gene. *Proc Natl Acad Sci USA* **100:** 8752–8757

Napolitani G, Bortoletto N, Racioppi L, Lanzavecchia A, D'Oro U (2003) Activation of src-family tyrosine kinases by LPS regulates cytokine production in dendritic cells by controlling AP-1 formation. *Eur J Immunol* **33:** 2832–2841

Naumann M, Wulczyn FG, Scheidereit C (1993) The NF-kappa B precursor p105 and the proto-oncogene product Bcl-3 are I kappa B molecules and control nuclear translocation of NF-kappa B. *EMBO J* **12:** 213–222

Nisimoto Y, Freeman JL, Motalebi SA, Hirshberg M, Lambeth JD (1997) Rac binding to p67(phox). Structural basis for interactions of the Rac1 effector region and insert region with components of the respiratory burst oxidase. *J Biol Chem* **272:** 18834–18841

Nordberg J, Arner ES (2001) Reactive oxygen species, antioxidants, and the mammalian thioredoxin system. *Free Radic Biol Med* **31:** 1287–1312

Ogura Y, Inohara N, Benito A, Chen FF, Yamaoka S, Nunez G (2001) Nod2, a Nod1/Apaf-1 family member that is restricted to monocytes and activates NF-kappaB. *J Biol Chem* **276:** 4812–4818

Ohashi K, Burkart V, Flohe S, Kolb H (2000) Cutting edge: heat shock protein 60 is a putative endogenous ligand of the toll-like receptor-4 complex. *J Immunol* **164:** 558–561

Ojaniemi M, Glumoff V, Harju K, Liljeroos M, Vuori K, Hallman M (2003) Phosphatidylinositol 3-kinase is involved in Toll-like receptor 4-mediated cytokine expression in mouse macrophages. *Eur J Immunol* **33:** 597–605

Okamura Y, Watari M, Jerud ES, Young DW, Ishizaka ST, Rose J, Chow JC, Strauss III JF (2001) The extra domain A of fibronectin activates Toll-like receptor 4. *J Biol Chem* **276:** 10229–10233

Opitz B, Schroder NW, Spreitzer I, Michelsen KS, Kirschning CJ, Hallatschek W, Zahringer U, Hartung T, Gobel UB, Schumann RR (2001) Toll-like receptor-2 mediates *Treponema* glycolipid and lipoteichoic acid-induced NF-kappaB translocation. *J Biol Chem* **276:** 22041–22047

Orian A, Gonen H, Bercovich B, Fajerman I, Eytan E, Israel A, Mercurio F, Iwai K, Schwartz AL, Ciechanover A (2000) SCF(beta) (−TrCP)

ubiquitin ligase-mediated processing of NF-kappaB p105 requires phosphorylation of its C-terminus by IkappaB kinase. *EMBO J* **19:** 2580–2591

Orlicek SL, Hanke JH, English BK (1999) The src family-selective tyrosine kinase inhibitor PP1 blocks LPS and IFN-gamma-mediated TNF and iNOS production in murine macrophages. *Shock* **12:** 350–354

Ory S, Zhou M, Conrads TP, Veenstra TD, Morrison DK (2003) Protein phosphatase 2A positively regulates Ras signaling by dephosphorylating KSR1 and Raf-1 on critical 14-3-3 binding sites. *Curr Biol* **13:** 1356–1364

Oshiumi H, Matsumoto M, Funami K, Akazawa T, Seya T (2003a) TICAM-1, an adaptor molecule that participates in Toll-like receptor 3-mediated interferon-beta induction. *Nat Immunol* **4:** 161–167

Oshiumi H, Sasai M, Shida K, Fujita T, Matsumoto M, Seya T (2003b) TIR-containing adapter molecule (TICAM)-2, a bridging adapter recruiting to toll-like receptor 4 TICAM-1 that induces interferon-beta. *J Biol Chem* **278:** 49751–49762

Ozes ON, Mayo LD, Gustin JA, Pfeffer SR, Pfeffer LM, Donner DB (1999) NF-kappaB activation by tumour necrosis factor requires the Akt serine-threonine kinase. *Nature* **401:** 82–85

Ozinsky A, Underhill DM, Fontenot JD, Hajjar AM, Smith KD, Wilson CB, Schroeder L, Aderem A (2000) The repertoire for pattern recognition of pathogens by the innate immune system is defined by cooperation between toll-like receptors. *Proc Natl Acad Sci USA* **97:** 13766–13771

Palombella VJ, Rando OJ, Goldberg AL, Maniatis T (1994) The ubiquitin–proteasome pathway is required for processing the NF-kappa B1 precursor protein and the activation of NF-kappa B. *Cell* **78:** 773–785

Pan ZK (2004) Toll-like receptors and TLR-mediated signaling: more questions than answers. *Am J Physiol Lung Cell Mol Physiol* **286:** L918–L920

Pathak SK, Bhattacharyya A, Pathak S, Basak C, Mandal D, Kundu M, Basu J (2004) Toll-like receptor 2 and mitogen- and stress-activated kinase 1 are effectors of *Mycobacterium avium*-induced cyclooxygenase-2 expression in macrophages. *J Biol Chem* **279:** 55127–55136

Patterson RL, Boehning D, Snyder SH (2004) Inositol 1,4,5-trisphosphate receptors as signal integrators. *Annu Rev Biochem* **73:** 437–465

Poltorak A, He X, Smirnova I, Liu MY, Van Huffel C, Du X, Birdwell D, Alejos E, Silva M, Galanos C, Freudenberg M, Ricciardi-Castagnoli P, Layton B, Beutler B (1998) Defective LPS signaling in C3H/HeJ and C57BL/10ScCr mice: mutations in Tlr4 gene. *Science* **282:** 2085–2088

Raingeaud J, Gupta S, Rogers JS, Dickens M, Han J, Ulevitch RJ, Davis RJ (1995) Pro-inflammatory cytokines and environmental stress cause p38 mitogen-activated protein kinase activation by dual phosphorylation on tyrosine and threonine. *J Biol Chem* **270:** 7420–7426

Raingeaud J, Whitmarsh AJ, Barrett T, Derijard B, Davis RJ (1996) MKK3- and MKK6-regulated gene expression is mediated by the p38 mitogen-activated protein kinase signal transduction pathway. *Mol Cell Biol* **16:** 1247–1255

Rao N, Nguyen S, Ngo K, Fung-Leung WP (2005) A novel splice variant of interleukin-1 receptor (IL-1R)-associated kinase 1 plays a negative regulatory role in toll/IL-1R-induced inflammatory signaling. *Mol Cell Biol* **25:** 6521–6532

Rassa JC, Meyers JL, Zhang Y, Kudaravalli R, Ross SR (2002) Murine retroviruses activate B cells via interaction with toll-like receptor 4. *Proc Natl Acad Sci USA* **99:** 2281–2286

Re F, Strominger JL (2002) Monomeric recombinant MD-2 binds toll-like receptor 4 tightly and confers lipopolysaccharide responsiveness. *J Biol Chem* **277:** 23427–23432

Reddy SA, Lin YF, Huang HJ, Samanta AK, Liao WS (2004) The IL-1 receptor accessory protein is essential for PI 3-kinase recruitment and activation. *Biochem Biophys Res Commun* **316:** 1022–1028

Ren XD, Bokoch GM, Traynor-Kaplan A, Jenkins GH, Anderson RA, Schwartz MA (1996) Physical association of the small GTPase Rho with a 68-kDa phosphatidylinositol 4-phosphate 5-kinase in Swiss 3T3 cells. *Mol Biol Cell* **7:** 435–442

Reusch HP, Zimmermann S, Schaefer M, Paul M, Moelling K (2001) Regulation of Raf by Akt controls growth and differentiation in vascular smooth muscle cells. *J Biol Chem* **276:** 33630–33637

Rhee SG, Bae YS (1997) Regulation of phosphoinositide-specific phospholipase C isozymes. *J Biol Chem* **272:** 15045–15048

Romano PR, Garcia-Barrio MT, Zhang X, Wang Q, Taylor DR, Zhang F, Herring C, Mathews MB, Qin J, Hinnebusch AG (1998) Autophosphorylation in the activation loop is required for full kinase activity *in vivo* of human and yeast eukaryotic initiation factor 2alpha kinases PKR and GCN2. *Mol Cell Biol* **18:** 2282–2297

Ruckdeschel K, Mannel O, Schrottner P (2002) Divergence of apoptosis-inducing and preventing signals in bacteria-faced macrophages through myeloid differentiation factor 88 and IL-1 receptor-associated kinase members. *J Immunol* **168:** 4601–4611

Ryo A, Suizu F, Yoshida Y, Perrem K, Liou YC, Wulf G, Rottapel R, Yamaoka S, Lu KP (2003) Regulation of NF-kappaB signaling by Pin1-dependent prolyl isomerization and ubiquitin-mediated proteolysis of p65/RelA. *Mol Cell* **12:** 1413–1426

Saccani S, Marazzi I, Beg AA, Natoli G (2004) Degradation of promoter-bound p65/RelA is essential for the prompt termination of the nuclear factor kappaB response. *J Exp Med* **200:** 107–113

Saitoh M, Nishitoh H, Fujii M, Takeda K, Tobiume K, Sawada Y, Kawabata M, Miyazono K, Ichijo H (1998) Mammalian thioredoxin is a direct inhibitor of apoptosis signal-regulating kinase (ASK) 1. *EMBO J* **17:** 2596–2606

Saitoh T, Yamamoto M, Miyagishi M, Taira K, Nakanishi M, Fujita T, Akira S, Yamamoto N, Yamaoka S (2005) A20 is a negative regulator of IFN regulatory factor 3 signaling. *J Immunol* **174:** 1507–1512

Sakurai H, Miyoshi H, Toriumi W, Sugita T (1999) Functional interactions of transforming growth factor beta-activated kinase 1 with IkappaB kinases to stimulate NF-kappaB activation. *J Biol Chem* **274:** 10641–10648

Salmeron A, Janzen J, Soneji Y, Bump N, Kamens J, Allen H, Ley SC (2001) Direct phosphorylation of NF-kappaB1 p105 by the IkappaB kinase complex on serine 927 is essential for signal-induced p105 proteolysis. *J Biol Chem* **276:** 22215–22222

Sanchez P, De Carcer G, Sandoval IV, Moscat J, Diaz-Meco MT (1998) Localization of atypical protein kinase C isoforms into lysosome-targeted endosomes through interaction with p62. *Mol Cell Biol* **18:** 3069–3080

Sanz L, Diaz-Meco MT, Nakano H, Moscat J (2000) The atypical PKC-interacting protein p62 channels NF-kappaB activation by the IL-1-TRAF6 pathway. *EMBO J* **19:** 1576–1586

Sarkar SN, Peters KL, Elco CP, Sakamoto S, Pal S, Sen GC (2004) Novel roles of TLR3 tyrosine phosphorylation and PI3 kinase in double-stranded RNA signaling. *Nat Struct Mol Biol* **11:** 1060–1067

Sato S, Sugiyama M, Yamamoto M, Watanabe Y, Kawai T, Takeda K, Akira S (2003) Toll/IL-1 receptor domain-containing adaptor inducing IFN-beta (TRIF) associates with TNF receptor-associated factor 6 and TANK-binding kinase 1, and activates two distinct transcription factors, NF-kappa B and IFN-regulatory factor-3, in the Toll-like receptor signaling. *J Immunol* **171:** 4304–4310

Satoh S, Hijikata M, Handa H, Shimotohno K (1999) Caspase-mediated cleavage of eukaryotic translation initiation factor subunit 2alpha. *Biochem J* **342** (Part 1)**:** 65–70

Scheid MP, Woodgett JR (2003) Unravelling the activation mechanisms of protein kinase B/Akt. *FEBS Lett* **546:** 108–112

Scherer DC, Brockman JA, Chen Z, Maniatis T, Ballard DW (1995) Signal-induced degradation of I kappa B alpha requires site-specific ubiquitination. *Proc Natl Acad Sci USA* **92:** 11259–11263

Schwabe RF, Brenner DA (2002) Role of glycogen synthase kinase-3 in TNF-alpha-induced NF-kappaB activation and apoptosis in hepatocytes. *Am J Physiol Gastrointest Liver Physiol* **283:** G204–G211

Schwandner R, Dziarski R, Wesche H, Rothe M, Kirschning CJ (1999) Peptidoglycan- and lipoteichoic acid-induced cell activation is mediated by toll-like receptor 2. *J Biol Chem* **274:** 17406–17409

Seth A, Alvarez E, Gupta S, Davis RJ (1991) A phosphorylation site located in the NH2-terminal domain of c-Myc increases transactivation of gene expression. *J Biol Chem* **266:** 23521–23524

Sharma S, tenOever BR, Grandvaux N, Zhou GP, Lin R, Hiscott J (2003) Triggering the interferon antiviral response through an IKK-related pathway. *Science* **300:** 1148–1151

Sheng M, Thompson MA, Greenberg ME (1991) CREB: a Ca(2+)-regulated transcription factor phosphorylated by calmodulin-dependent kinases. *Science* **252:** 1427–1430

Shibuya H, Yamaguchi K, Shirakabe K, Tonegawa A, Gotoh Y, Ueno N, Irie K, Nishida E, Matsumoto K (1996) TAB1: an activator of the TAK1 MAPKKK in TGF-beta signal transduction. *Science* **272:** 1179–1182

Shimokawa N, Qiu CH, Seki T, Dikic I, Koibuchi N (2004) Phosphorylation of JNK is involved in regulation of H(+)-induced c-Jun expression. *Cell Signal* **16:** 723–729

Shuto T, Xu H, Wang B, Han J, Kai H, Gu XX, Murphy TF, Lim DJ, Li JD (2001) Activation of NF-kappa B by nontypeable Hemophilus influenzae is mediated by toll-like receptor 2-TAK1-dependent NIK-IKK alpha/beta-I kappa B alpha and MKK3/6-p38 MAP kinase signaling pathways in epithelial cells. *Proc Natl Acad Sci USA* **98:** 8774–8779

Singer WD, Brown HA, Jiang X, Sternweis PC (1996) Regulation of phospholipase D by protein kinase C is synergistic with ADP-ribosylation factor and independent of protein kinase activity. *J Biol Chem* **271:** 4504–4510

Singh R, Wang B, Shirvaikar A, Khan S, Kamat S, Schelling JR, Konieczkowski M, Sedor JR (1999) The IL-1 receptor and Rho directly associate to drive cell activation in inflammation. *J Clin Invest* **103:** 1561–1570

Singhirunnusorn P, Suzuki S, Kawasaki N, Saiki I, Sakurai H (2005) Critical roles of threonine 187 phosphorylation in cellular stress-induced rapid and transient activation of transforming growth factor-beta-activated kinase 1 (TAK1) in a signaling complex containing TAK1-binding protein TAB1 and TAB2. *J Biol Chem* **280:** 7359–7368

Smiley ST, King JA, Hancock WW (2001) Fibrinogen stimulates macrophage chemokine secretion through toll-like receptor 4. *J Immunol* **167:** 2887–2894

Smith Jr MF, Mitchell A, Li G, Ding S, Fitzmaurice AM, Ryan K, Crowe S, Goldberg JB (2003) Toll-like receptor (TLR) 2 and TLR5, but not TLR4, are required for Helicobacter pylori-induced NF-kappa B activation and chemokine expression by epithelial cells. *J Biol Chem* **278:** 32552–32560

Sohn HW, Gu H, Pierce SK (2003) Cbl-b negatively regulates B cell antigen receptor signaling in mature B cells through ubiquitination of the tyrosine kinase Syk. *J Exp Med* **197:** 1511–1524

Spencer E, Jiang J, Chen ZJ (1999) Signal-induced ubiquitination of IkappaBalpha by the F-box protein Slimb/beta-TrCP. *Genes Dev* **13:** 284–294

Standaert ML, Bandyopadhyay G, Kanoh Y, Sajan MP, Farese RV (2001) Insulin and PIP3 activate PKC-zeta by mechanisms that are both dependent and independent of phosphorylation of activation loop (T410) and autophosphorylation (T560) sites. *Biochemistry* **40:** 249–255

Stefanova I, Corcoran ML, Horak EM, Wahl LM, Bolen JB, Horak ID (1993) Lipopolysaccharide induces activation of CD14-associated protein tyrosine kinase p53/56lyn. *J Biol Chem* **268:** 20725–20728

Stephens LR, Jackson TR, Hawkins PT (1993) Agonist-stimulated synthesis of phosphatidylinositol(3,4,5)-trisphosphate: a new intracellular signalling system? *Biochim Biophys Acta* **1179:** 27–75

Stokoe D, Engel K, Campbell DG, Cohen P, Gaestel M (1992) Identification of MAPKAP kinase 2 as a major enzyme responsible for the phosphorylation of the small mammalian heat shock proteins. *FEBS Lett* **313:** 307–313

Stovall SH, Yi AK, Meals EA, Talati AJ, Godambe SA, English BK (2004) Role of vav1- and src-related tyrosine kinases in macrophage activation by CpG DNA. *J Biol Chem* **279:** 13809–13816

Stylianou E, Saklatvala J (1998) Interleukin-1. *Int J Biochem Cell Biol* **30:** 1075–1079

Su W, Chardin P, Yamazaki M, Kanaho Y, Du G (2006) RhoA-mediated phospholipase D1 signaling is not required for the formation of stress fibers and focal adhesions. *Cell Signal* **18:** 469–478

Sugiyama T, Fujita M, Koide N, Mori I, Yoshida T, Mori H, Yokochi T (2004) 2-aminopurine inhibits lipopolysaccharide-induced nitric oxide production by preventing IFN-beta production. *Microbiol Immunol* **48:** 957–963

Sun H, Charles CH, Lau LF, Tonks NK (1993) MKP-1 (3CH134), an immediate early gene product, is a dual specificity phosphatase that dephosphorylates MAP kinase *in vivo*. *Cell* **75:** 487–493

Suyang H, Phillips R, Douglas I, Ghosh S (1996) Role of unphosphorylated, newly synthesized I kappa B beta in persistent activation of NF-kappa B. *Mol Cell Biol* **16:** 5444–5449

Suzuki H, Chiba T, Kobayashi M, Takeuchi M, Suzuki T, Ichiyama A, Ikenoue T, Omata M, Furuichi K, Tanaka K (1999) IkappaBalpha ubiquitination is catalyzed by an SCF-like complex containing Skp1, cullin-1, and two F-box/WD40-repeat proteins, betaTrCP1 and betaTrCP2. *Biochem Biophys Res Commun* **256:** 127–132

Sweet MJ, Leung BP, Kang D, Sogaard M, Schulz K, Trajkovic V, Campbell CC, Xu D, Liew FY (2001) A novel pathway regulating lipopolysaccharide-induced shock by ST2/T1 via inhibition of Toll-like receptor 4 expression. *J Immunol* **166:** 6633–6639

Takaesu G, Kishida S, Hiyama A, Yamaguchi K, Shibuya H, Irie K, Ninomiya-Tsuji J, Matsumoto K (2000) TAB2, a novel adaptor protein, mediates activation of TAK1 MAPKKK by linking TAK1 to TRAF6 in the IL-1 signal transduction pathway. *Mol Cell* **5:** 649–658

Takatsuna H, Kato H, Gohda J, Akiyama T, Moriya A, Okamoto Y, Yamagata Y, Otsuka M, Umezawa K, Semba K, Inoue J (2003) Identification of TIFA as an adapter protein that links tumor necrosis factor receptor-associated factor 6 (TRAF6) to interleukin-1 (IL-1) receptor-associated kinase-1 (IRAK-1) in IL-1 receptor signaling. *J Biol Chem* **278:** 12144–12150

Takeda K, Akira S (2005) Toll-like receptors in innate immunity. *Int Immunol* **17:** 1–14

Takeshita F, Gursel I, Ishii KJ, Suzuki K, Gursel M, Klinman DM (2004) Signal transduction pathways mediated by the interaction of CpG DNA with Toll-like receptor 9. *Semin Immunol* **16:** 17–22

Takeuchi O, Hoshino K, Kawai T, Sanjo H, Takada H, Ogawa T, Takeda K, Akira S (1999) Differential roles of TLR2 and TLR4 in recognition of Gram-negative and Gram-positive bacterial cell wall components. *Immunity* **11:** 443–451

Takeuchi O, Kawai T, Muhlradt PF, Morr M, Radolf JD, Zychlinsky A, Takeda K, Akira S (2001) Discrimination of bacterial lipoproteins by Toll-like receptor 6. *Int Immunol* **13:** 933–940

Takeuchi O, Sato S, Horiuchi T, Hoshino K, Takeda K, Dong Z, Modlin RL, Akira S (2002) Cutting edge: role of Toll-like receptor 1 in mediating immune response to microbial lipoproteins. *J Immunol* **169:** 10–14

Tan Y, Rouse J, Zhang A, Cariati S, Cohen P, Comb MJ (1996) FGF and stress regulate CREB and ATF-1 via a pathway involving p38 MAP kinase and MAPKAP kinase-2. *EMBO J* **15:** 4629–4642

Taniguchi T, Ogasawara K, Takaoka A, Tanaka N (2001) IRF family of transcription factors as regulators of host defense. *Annu Rev Immunol* **19:** 623–655

Tegethoff S, Behlke J, Scheidereit C (2003) Tetrameric oligomerization of IkappaB kinase gamma (IKKgamma) is obligatory for IKK complex activity and NF-kappaB activation. *Mol Cell Biol* **23:** 2029–2041

Termeer C, Benedix F, Sleeman J, Fieber C, Voith U, Ahrens T, Miyake K, Freudenberg M, Galanos C, Simon JC (2002) Oligosaccharides of hyaluronan activate dendritic cells via toll-like receptor 4. *J Exp Med* **195:** 99–111

Teusch N, Lombardo E, Eddleston J, Knaus UG (2004) The low molecular weight GTPase RhoA and atypical protein kinase Czeta

are required for TLR2-mediated gene transcription. *J Immunol* **173:** 507–514

Thomson S, Clayton AL, Hazzalin CA, Rose S, Barratt MJ, Mahadevan LC (1999) The nucleosomal response associated with immediate-early gene induction is mediated via alternative MAP kinase cascades: MSK1 as a potential histone H3/HMG-14 kinase. *EMBO J* **18:** 4779–4793

Thornberry NA, Bull HG, Calaycay JR, Chapman KT, Howard AD, Kostura MJ, Miller DK, Molineaux SM, Weidner JR, Aunins J, Elliston KO, Ayala JM, Casano FJ, Chin J, Ding GJF, Egger LA, Gaffney EP, Limjuco G, Palyha OC, Raju SM, Rolando AM, Salley JP, Yamin TT, Lee TD, Shively JE, MacCross M, Mumford RA, Schmidt JA, Tocci MJ (1992) A novel heterodimeric cysteine protease is required for interleukin-1 beta processing in monocytes. *Nature* **356:** 768–774

Tian J, Karin M (1999) Stimulation of Elk1 transcriptional activity by mitogen-activated protein kinases is negatively regulated by protein phosphatase 2B (calcineurin). *J Biol Chem* **274:** 15173–15180

Ting JP, Davis BK (2005) CATERPILLER: a novel gene family important in immunity, cell death, and diseases. *Annu Rev Immunol* **23:** 387–414

Tobiume K, Saitoh M, Ichijo H (2002) Activation of apoptosis signal-regulating kinase 1 by the stress-induced activating phosphorylation of pre-formed oligomer. *J Cell Physiol* **191:** 95–104

Tolias KF, Cantley LC (1999) Pathways for phosphoinositide synthesis. *Chem Phys Lipids* **98:** 69–77

Tolias KF, Cantley LC, Carpenter CL (1995) Rho family GTPases bind to phosphoinositide kinases. *J Biol Chem* **270:** 17656–17659

Tolias KF, Couvillon AD, Cantley LC, Carpenter CL (1998) Characterization of a Rac1- and RhoGDI-associated lipid kinase signaling complex. *Mol Cell Biol* **18:** 762–770

Topham MK, Prescott SM (1999) Mammalian diacylglycerol kinases, a family of lipid kinases with signaling functions. *J Biol Chem* **274:** 11447–11450

Torok AM, Bouton AH, Goldberg JB (2005) *Helicobacter pylori* induces interleukin-8 secretion by Toll-like receptor 2- and Toll-like receptor 5-dependent and -independent pathways. *Infect Immun* **73:** 1523–1531

Toyofuku T, Curotto Kurzydlowski K, Narayanan N, MacLennan DH (1994) Identification of Ser38 as the site in cardiac sarcoplasmic reticulum Ca(2+)-ATPase that is phosphorylated by Ca^{2+}/calmodulin-dependent protein kinase. *J Biol Chem* **269:** 26492–26496

Tran K, Merika M, Thanos D (1997) Distinct functional properties of IkappaB alpha and IkappaB beta. *Mol Cell Biol* **17:** 5386–5399

Tukel C, Raffatellu M, Humphries AD, Wilson RP, Andrews-Polymenis HL, Gull T, Figueiredo JF, Wong MH, Michelsen KS, Akcelik M, Adams LG, Baumler AJ (2005) CsgA is a pathogen-associated molecular pattern of *Salmonella enterica* serotype Typhimurium that is recognized by Toll-like receptor 2. *Mol Microbiol* **58:** 289–304

Ueno Y, Kume N, Miyamoto S, Morimoto M, Kataoka H, Ochi H, Nishi E, Moriwaki H, Minami M, Hashimoto N, Kita T (1999) Lysophosphatidylcholine phosphorylates CREB and activates the jun2TRE site of c-jun promoter in vascular endothelial cells. *FEBS Lett* **457:** 241–245

Underhill DM, Ozinsky A, Hajjar AM, Stevens A, Wilson CB, Bassetti M, Aderem A (1999) The Toll-like receptor 2 is recruited to macrophage phagosomes and discriminates between pathogens. *Nature* **401:** 811–815

Vabulas RM, Ahmad-Nejad P, Ghose S, Kirschning CJ, Issels RD, Wagner H (2002) HSP70 as endogenous stimulus of the Toll/interleukin-1 receptor signal pathway. *J Biol Chem* **277:** 15107–15112

Vanhaesebroeck B, Leevers SJ, Ahmadi K, Timms J, Katso R, Driscoll PC, Woscholski R, Parker PJ, Waterfield MD (2001) Synthesis and function of 3-phosphorylated inositol lipids. *Annu Rev Biochem* **70:** 535–602

Verma IM, Sassone-Corsi P (1987) Proto-oncogene fos: complex but versatile regulation. *Cell* **51:** 513–514

Vermeulen L, De Wilde G, Van Damme P, Vanden Berghe W, Haegeman G (2003) Transcriptional activation of the NF-kappaB p65 subunit by mitogen- and stress-activated protein kinase-1 (MSK1). *EMBO J* **22:** 1313–1324

Vihinen M, Mattsson PT, Smith CI (1997) BTK, the tyrosine kinase affected in X-linked agammaglobulinemia. *Front Biosci* **2:** d27–d42

Visintin A, Latz E, Monks BG, Espevik T, Golenbock DT (2003) Lysines 128 and 132 enable lipopolysaccharide binding to MD-2, leading to Toll-like receptor-4 aggregation and signal transduction. *J Biol Chem* **278:** 48313–48320

Vora P, Youdim A, Thomas LS, Fukata M, Tesfay SY, Lukasek K, Michelsen KS, Wada A, Hirayama T, Arditi M, Abreu MT (2004) Beta-defensin-2 expression is regulated by TLR signaling in intestinal epithelial cells. *J Immunol* **173:** 5398–5405

Wald D, Qin J, Zhao Z, Qian Y, Naramura M, Tian L, Towne J, Sims JE, Stark GR, Li X (2003) SIGIRR, a negative regulator of Toll-like receptor-interleukin 1 receptor signaling. *Nat Immunol* **4:** 920–927

Wang C, Deng L, Hong M, Akkaraju GR, Inoue J, Chen ZJ (2001) TAK1 is a ubiquitin-dependent kinase of MKK and IKK. *Nature* **412:** 346–351

Wang D, Westerheide SD, Hanson JL, Baldwin Jr AS (2000) Tumor necrosis factor alpha-induced phosphorylation of RelA/p65 on Ser529 is controlled by casein kinase II. *J Biol Chem* **275:** 32592–32597

Waskiewicz AJ, Flynn A, Proud CG, Cooper JA (1997) Mitogen-activated protein kinases activate the serine/threonine kinases Mnk1 and Mnk2. *EMBO J* **16:** 1909–1920

Watanabe N, Iwamura T, Shinoda T, Fujita T (1997) Regulation of NFKB1 proteins by the candidate oncoprotein BCL-3: generation of NF-kappaB homodimers from the cytoplasmic pool of p50-p105 and nuclear translocation. *EMBO J* **16:** 3609–3620

Waterfield M, Jin W, Reiley W, Zhang M, Sun SC (2004) IkappaB kinase is an essential component of the Tpl2 signaling pathway. *Mol Cell Biol* **24:** 6040–6048

Werts C, Tapping RI, Mathison JC, Chuang TH, Kravchenko V, Saint Girons I, Haake DA, Godowski PJ, Hayashi F, Ozinsky A, Underhill DM, Kirschning CJ, Wagner H, Aderem A, Tobias PS, Ulevitch RJ (2001) Leptospiral lipopolysaccharide activates cells through a TLR2-dependent mechanism. *Nat Immunol* **2:** 346–352

Wesche H, Gao X, Li X, Kirschning CJ, Stark GR, Cao Z (1999) IRAK-M is a novel member of the Pelle/interleukin-1 receptor-associated kinase (IRAK) family. *J Biol Chem* **274:** 19403–19410

Wesche H, Henzel WJ, Shillinglaw W, Li S, Cao Z (1997) MyD88: an adapter that recruits IRAK to the IL-1 receptor complex. *Immunity* **7:** 837–847

Wick MJ, Ramos FJ, Chen H, Quon MJ, Dong LQ, Liu F (2003) Mouse 3-phosphoinositide-dependent protein kinase-1 undergoes dimerization and trans-phosphorylation in the activation loop. *J Biol Chem* **278:** 42913–42919

Winston JT, Strack P, Beer-Romero P, Chu CY, Elledge SJ, Harper JW (1999) The SCFbeta–TRCP–ubiquitin ligase complex associates specifically with phosphorylated destruction motifs in IkappaBalpha and beta-catenin and stimulates IkappaBalpha ubiquitination *in vitro*. *Genes Dev* **13:** 270–283

Witowsky JA, Johnson GL (2003) Ubiquitylation of MEKK1 inhibits its phosphorylation of MKK1 and MKK4 and activation of the ERK1/2 and JNK pathways. *J Biol Chem* **278:** 1403–1406

Wu C, Ghosh S (1999) Beta-TrCP mediates the signal-induced ubiquitination of IkappaBbeta. *J Biol Chem* **274:** 29591–29594

Wu J, Harrison JK, Dent P, Lynch KR, Weber MJ, Sturgill TW (1993) Identification and characterization of a new mammalian mitogen-activated protein kinase kinase, MKK2. *Mol Cell Biol* **13:** 4539–4548

Wu X, McMurray CT (2001) Calmodulin kinase II attenuation of gene transcription by preventing cAMP response element-binding

protein (CREB) dimerization and binding of the CREB-binding protein. *J Biol Chem* **276:** 1735–1741

Wyllie DH, Kiss-Toth E, Visintin A, Smith SC, Boussouf S, Segal DM, Duff GW, Dower SK (2000) Evidence for an accessory protein function for Toll-like receptor 1 in anti-bacterial responses. *J Immunol* **165:** 7125–7132

Xu H, An H, Yu Y, Zhang M, Qi R, Cao X (2003) Ras participates in CpG oligodeoxynucleotide signaling through association with toll-like receptor 9 and promotion of interleukin-1 receptor-associated kinase/tumor necrosis factor receptor-associated factor 6 complex formation in macrophages. *J Biol Chem* **278:** 36334–36340

Xu S, Robbins D, Frost J, Dang A, Lange-Carter C, Cobb MH (1995) MEKK1 phosphorylates MEK1 and MEK2 but does not cause activation of mitogen-activated protein kinase. *Proc Natl Acad Sci USA* **92:** 6808–6812

Yamamoto M, Sato S, Hemmi H, Hoshino K, Kaisho T, Sanjo H, Takeuchi O, Sugiyama M, Okabe M, Takeda K, Akira S (2003a) Role of adaptor TRIF in the MyD88-independent toll-like receptor signaling pathway. *Science* **301:** 640–643

Yamamoto M, Sato S, Hemmi H, Sanjo H, Uematsu S, Kaisho T, Hoshino K, Takeuchi O, Kobayashi M, Fujita T, Takeda K, Akira S (2002) Essential role for TIRAP in activation of the signalling cascade shared by TLR2 and TLR4. *Nature* **420:** 324–329

Yamamoto M, Sato S, Hemmi H, Uematsu S, Hoshino K, Kaisho T, Takeuchi O, Takeda K, Akira S (2003b) TRAM is specifically involved in the Toll-like receptor 4-mediated MyD88-independent signaling pathway. *Nat Immunol* **4:** 1144–1150

Yamamoto M, Yamazaki S, Uematsu S, Sato S, Hemmi H, Hoshino K, Kaisho T, Kuwata H, Takeuchi O, Takeshige K, Saitoh T, Yamaoka S, Yamamoto N, Yamamoto S, Muta T, Takeda K, Akira S (2004) Regulation of Toll/IL-1-receptor-mediated gene expression by the inducible nuclear protein IkappaBzeta. *Nature* **430:** 218–222

Yang F, Tang E, Guan K, Wang CY (2003) IKK beta plays an essential role in the phosphorylation of RelA/p65 on serine 536 induced by lipopolysaccharide. *J Immunol* **170:** 5630–5635

Yang X, Chang HY, Baltimore D (1998) Autoproteolytic activation of pro-caspases by oligomerization. *Mol Cell* **1:** 319–325

Yaron A, Gonen H, Alkalay I, Hatzubai A, Jung S, Beyth S, Mercurio F, Manning AM, Ciechanover A, Ben-Neriah Y (1997) Inhibition of NF-kappa-B cellular function via specific targeting of the I-kappa-B–ubiquitin ligase. *EMBO J* **16:** 6486–6494

Yaron A, Hatzubai A, Davis M, Lavon I, Amit S, Manning AM, Andersen JS, Mann M, Mercurio F, Ben-Neriah Y (1998) Identification of the receptor component of the IkappaBalpha–ubiquitin ligase. *Nature* **396:** 590–594

Yeung KC, Rose DW, Dhillon AS, Yaros D, Gustafsson M, Chatterjee D, McFerran B, Wyche J, Kolch W, Sedivy JM (2001) Raf kinase inhibitor protein interacts with NF-kappaB-inducing kinase and TAK1 and inhibits NF-kappaB activation. *Mol Cell Biol* **21:** 7207–7217

Zenke FT, King CC, Bohl BP, Bokoch GM (1999) Identification of a central phosphorylation site in p21-activated kinase regulating autoinhibition and kinase activity. *J Biol Chem* **274:** 32565–32573

Zhang D, Zhang G, Hayden MS, Greenblatt MB, Bussey C, Flavell RA, Ghosh S (2004) A toll-like receptor that prevents infection by uropathogenic bacteria. *Science* **303:** 1522–1526

Zhang F, Romano PR, Nagamura-Inoue T, Tian B, Dever TE, Mathews MB, Ozato K, Hinnebusch AG (2001) Binding of double-stranded RNA to protein kinase PKR is required for dimerization and promotes critical autophosphorylation events in the activation loop. *J Biol Chem* **276:** 24946–24958

Zhang G, Ghosh S (2002) Negative regulation of toll-like receptor-mediated signaling by Tollip. *J Biol Chem* **277:** 7059–7065

Zheng Y, Bagrodia S, Cerione RA (1994) Activation of phosphoinositide 3-kinase activity by Cdc42Hs binding to p85. *J Biol Chem* **269:** 18727–18730

Zhong H, May MJ, Jimi E, Ghosh S (2002) The phosphorylation status of nuclear NF-kappa B determines its association with CBP/p300 or HDAC-1. *Mol Cell* **9:** 625–636

Zhong H, SuYang H, Erdjument-Bromage H, Tempst P, Ghosh S (1997) The transcriptional activity of NF-kappaB is regulated by the IkappaB-associated PKAc subunit through a cyclic AMP-independent mechanism. *Cell* **89:** 413–424

Ziegler SF, Wilson CB, Perlmutter RM (1988) Augmented expression of a myeloid-specific protein tyrosine kinase gene (hck) after macrophage activation. *J Exp Med* **168:** 1801–1810

Zimmermann S, Moelling K (1999) Phosphorylation and regulation of Raf by Akt (protein kinase B). *Science* **286:** 1741–1744