

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 mammals, 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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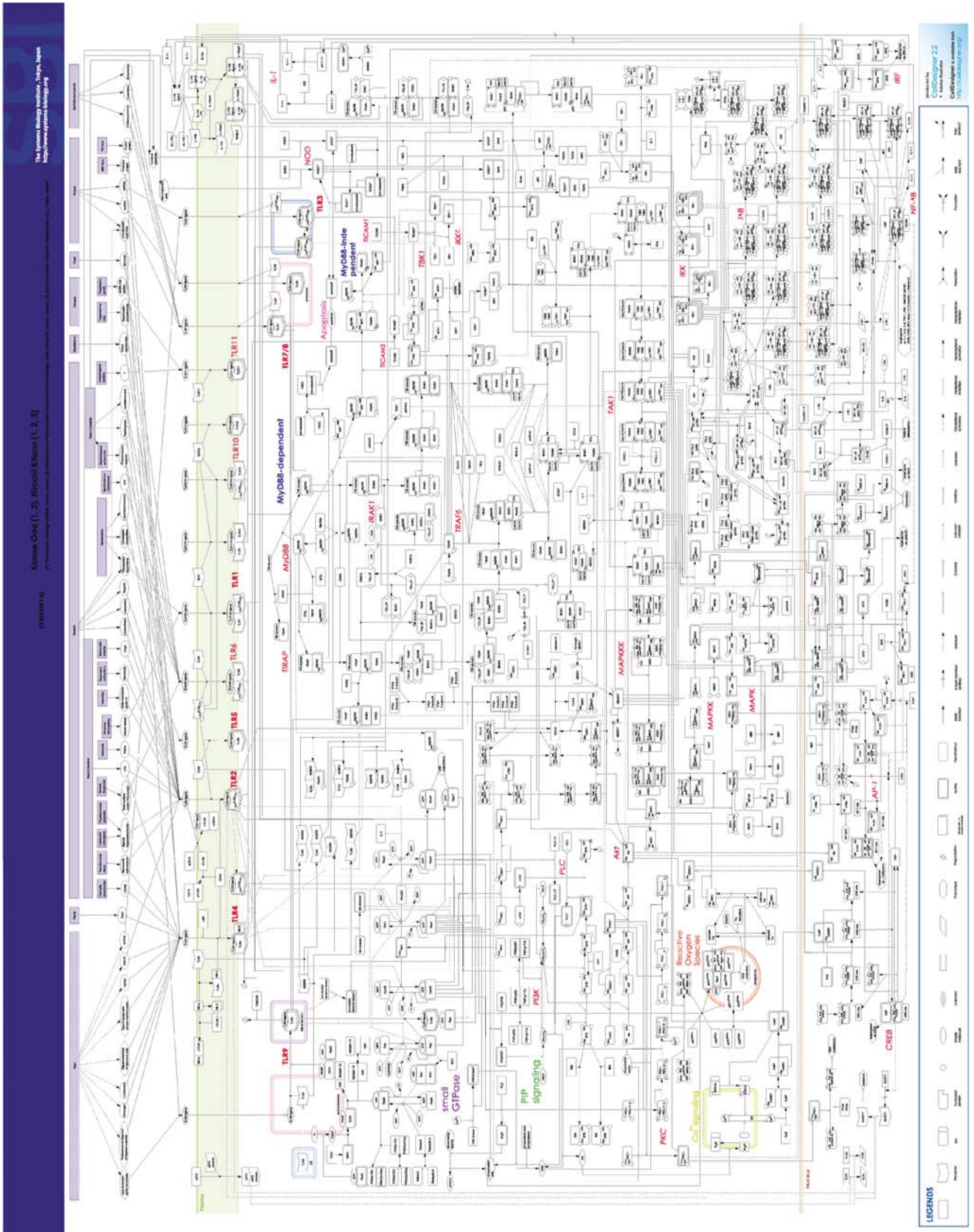
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Introduction

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 lipopolysaccharide (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 mammals 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 discussions. For some readers, some interactions may be viewed as premature hypotheses, whereas the same interactions may be considered more plausible by others. The certainty 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; CaMK1, 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- β -converting enzyme; I κ B, 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- α -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- κ B, nuclear factor κ B; NIK, nuclear factor κ B-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, phosphatidylinositol-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 κ B 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 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- κ B) 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- κ B 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- κ B 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-1 α and IL-1 β to IL-1RI (Nos. 1 and 2, respectively) provides positive 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

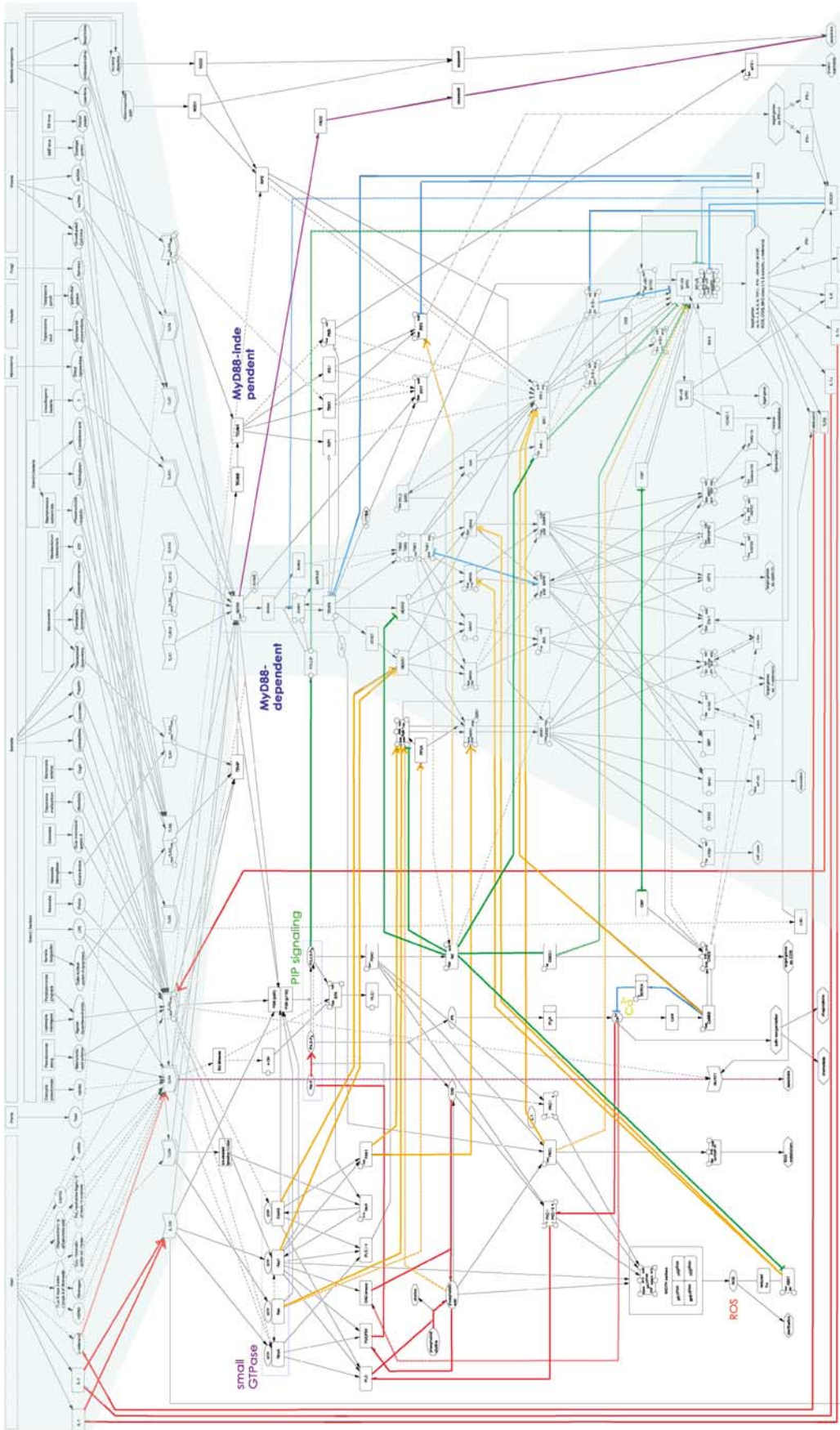


Figure 2 The architecture of the TLR signaling network. A reduced map of TLR signaling network that extracts the flow of activation and inhibition. This diagram is created based on the comprehensive TLR signaling network map as shown in Figure 1. Filled arrows in this figure indicate 'activation', and other arrows such as bar-headed, dashed, and 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 crossstalk 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 crossstalk from subsystems to the bow-tie network; and green, negative crossstalk from subsystems to the bow-tie network. High resolution file for this figure is available in the Supplementary information.

Table 1 Feedback and feedforward controls in the TLRs system

	No.	Origin	Destination	Note
<i>Feedback</i> Positive	1	IL-1 α	IL-1RI	Activates NF- κ B via the MyD88-dependent pathway
	2	IL-1 β	IL-1RI	Activates NF- κ B via the MyD88-dependent pathway
	3	TLR2	MyD88, PI3K, small GTPase TLR4	Activates NF- κ B
	4	β -Defensin2	TLR2	Activates NF- κ B via the MyD88-dependent and -independent pathway
	5	IKK β	TPL2 (p58)	Activates NIK Controversial Through the process yet identified
	6	PLD	PI4,5-P2	Material of IP3 which increases cytosol Ca ²⁺ via IP3R
	7	DAG kinase	PI4,5-P2	Material of IP3 which increases cytosol Ca ²⁺ via IP3R Through the process yet identified
Negative	8	NF- κ B1 (p105)	TPL2 (p58)	Activates IKK β via NIK
	9	p38 α MAPK	TAK1	Activates MKK3
	10	I κ B α	NF- κ B	Transcriptional factor of A20
	11	A20	NF- κ B	Transcriptional factor of A20
	12	A20	TRAF6	Activates NF- κ B via the MyD88-dependent pathway
	13	IL-1ra	IL-1RI	Activates NF- κ B via the MyD88-dependent pathway
<i>Feedforward</i> Negative	14	CaMKII	SERCA	Decreases cytosol Ca ²⁺
	15	TLR2	NUR77	Causes apoptosis
	16	TLR4	NUR77	Causes apoptosis
	17	MyD88	FADD	Causes apoptosis via the activation of caspase-8
	18	Src kinases	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- κ B 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- κ B 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- κ B (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

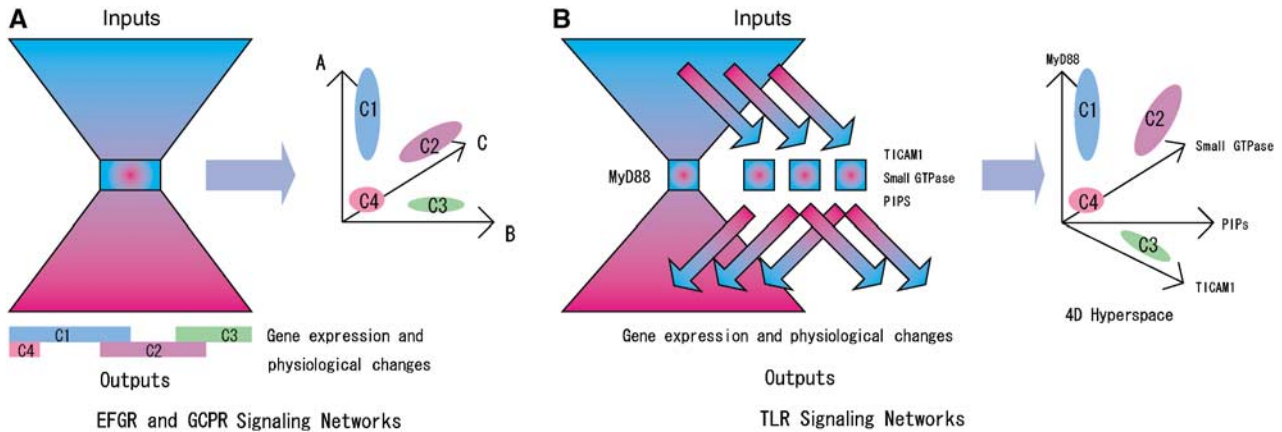


Figure 3 The core of bow-tie networks may have ‘classifier hyperspace’ where reactions to various inputs can be classified within subregions within the hyperspace that consists of activation levels of core elements of the bow-tie structure. **(A)** EGFR signaling and GPCR signaling network has a small 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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The authors declare that there is no financial conflict.

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