Sangdun Choi
Editor

Encyclopedia of Signaling Molecules

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With 1893 Figures and 247 Tables

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Editor
Sangdun Choi
Department of Molecular Science and Technology
Ajou University
Suwon, Korea

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MyD-1

► Sirpa

Myd118

► GADD45

MyD88

► MyD88 (Myeloid Differentiation Primary Response Gene 88)

MyD88 (Myeloid Differentiation Primary Response Gene 88)

Shaherin Basith[1,2], Balachandran Manavalan[1,3] and Sangdun Choi[1]
[1]Department of Molecular Science and Technology, Ajou University, Suwon, Korea
[2]National Leading Research Laboratory (NLRL) of Molecular Modeling and Drug Design, College of Pharmacy and Graduate School of Pharmaceutical Sciences, Ewha Womans University, Seoul, Korea
[3]Center for In Silico Protein Science, School of Computational Sciences, Korea Institute for Advanced Study, Seoul, Korea

Synonyms

MyD88; Myd88; Myeloid differentiation primary response gene 88

Historical Background

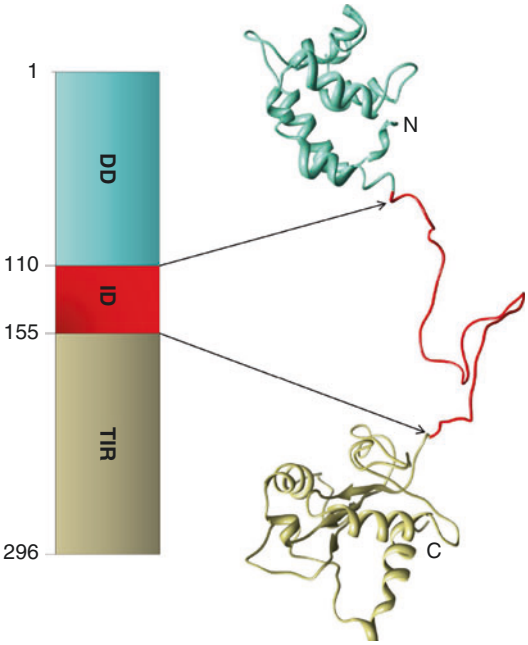
Myeloid differentiation primary response gene 88 (MyD88) was originally discovered and cloned by Liebermann and Hoffman in 1990 as one of the 12 different mRNA transcripts that were induced in M1 myeloblastic leukemia cells upon activation with lung-conditioned medium or recombinant interleukin (IL)-6 (Lord et al. 1990). The "MyD" portion of the name stands for myeloid differentiation, while "88" refers to the gene number in the list of induced genes (Lord et al. 1990). At the time of its discovery, the MyD88 sequence showed no homology with other sequences available in the databases and contained no recognizable protein motifs. In 1994, the C-terminal portion of MyD88 was found to be similar to a conserved stretch of approximately 200 amino acids in the intracellular regions of the *Drosophila* Toll receptor and the mammalian interleukin-1 receptor (IL-1R) (Hultmark 1994), and was thus referred to as the TLR (Toll-like receptor)- and IL-1R-related (TIR) domain. The N-terminal portion of MyD88 encodes the death domain (DD) (Feinstein et al. 1995) that was originally identified in apoptosis-promoting proteins. By 1997, the function of MyD88 had been determined. Specifically, MyD88 was first shown to be involved in type 1 interleukin-1 receptor (IL-1R1) signaling and subsequently in all TLRs (Hultmark 1994) signaling except for TLR3 responses and ▶ TLR4-mediated late responses. The MyD88 adaptor protein links members of the TLR and IL-1R superfamily to the downstream activation of nuclear factor-κB (▶ NF-κB) and mitogen-activated protein kinases (MAPKs). Although originally identified as a myeloid-differentiation marker, MyD88 is known to play an essential role in the innate immune response of insects and mammals. The generation of MyD88-deficient mice as well as the identification of MyD88-related proteins and regulators of MyD88 signaling have revealed new and important insights into the functions of MyD88 (Janssens and Beyaert 2002).

MyD88 Localization and Structure

MyD88 is a 296 amino acid cytoplasmic adaptor protein that relays signals from IL-1, IL-18, IFNγ, IL-33, and most TLRs. MyD88 transcript is detected in most tissues including the heart, brain, spleen, lung, liver, muscle, kidney, and testis, as well as in the T, B, and myeloid cell lines. MyD88 is localized in distinct condensed particles that is scattered throughout the cytoplasm, reportedly in organelles yet to be identified (Nishiya et al. 2007).

MyD88 has a clear-cut modular structure composed of three main domains that are encoded by five exons (Hardiman et al. 1997). The first exon encodes the N-terminal DD, which mediates downstream interactions with the IRAK family of kinases. Exon 2 encodes the short linker ID, while the last three exons encode the C-terminal TIR domain, which mediates the interaction of MyD88 with other TIR domain receptors. The N-terminal DD is related to a motif that was originally defined as the region of similarity between the cytoplasmic tails of the FAS/Apol/CD95 and TNF (tumor necrosis factor) receptors that is

required for cytotoxic signaling by the so-called death receptors (Tartaglia et al. 1993). Conversely, the MyD88 C-terminal TIR domain is homologous with the cytoplasmic signaling regions of the *Drosophila* Toll receptor and the IL-1 receptor complex. To date, the entire structure of MyD88 has not been solved. However, the crystal structure of the MyD88 DD in complex with DDs of IRAK4 (interleukin-1 receptor associated kinase 4)-IRAK2 (PDB ID: 3MOP) was solved in vitro in the absence of MyD88 TIR domain and of TLRs (Lin et al. 2010). Recently another group has proposed a hexamer helical model showing MyD88 TIR interactions (Vyncke et al. 2016). They modeled the interaction surface of MyD88 TIR domain with full-length MyD88 or with homologous domain of TLR4 and Mal (MyD88-adaptor like protein)/TIRAP (TIR domain containing adaptor protein) using site-directed mutagenesis and in vivo biochemical techniques. This study identified the presence of four important binding sites (BS I-IV) in the MyD88 TIR domain, thus providing a clear picture of the TIR domain dimerization complementing the previously proposed Myddosome complex. The NMR solution structures of the TIR domain of MyD88 (PDB ID: 2Z5V and 2JS7) were solved by two independent research groups (Ohnishi et al. 2009). The entire structure of MyD88 is depicted in Fig. 1.



MyD88 (Myeloid Differentiation Primary Response Gene 88), Fig. 1 Representation of protein domains found in the MyD88 adaptor protein. (**a**) Schematic representation of MyD88 protein domains. MyD88 contains a Toll/interleukin-1 receptor (TIR) domain, an intermediary domain (ID), and a death domain (DD). The N-terminal (N) DD is shown in *aquamarine color*, ID is shown in *red color*, and the C-terminal (C) TIR domain is represented by *khaki color*. (**b**) *Ribbon* representation of the entire structure of MyD88, where the N-terminal DD represents the crystal structure solved by Lin et al. (Lin et al. 2010) and the C-terminal TIR domain represents the NMR solution structure solved by Ohnishi et al. (Ohnishi et al. 2009). The ID domain shown is the modeled structure generated using the MOE program (Molecular Operating Environment: http://www.chemcomp.com/software.htm)

The importance of the MyD88 DD is that it interacts with IRAKs, including IRAK1, IRAK2, IRAK4, and IRAK-M (IL-1R-associated kinase M), which are characterized by an N-terminal DD and a carboxy-terminal Ser/Thr kinase or kinase-like domain. The ensuing pathway eventually activates transcription factors NF-κB, activator protein (AP)-1, and interferon regulatory factors (IRFs) to elicit antipathogen responses and inflammation (Akira et al. 2006). The crystal structure of the DD of MyD88 consists of six helices (H1–H6) with a short H3 and an extraordinarily long H6 from residue 99 to the end of the construct at residue 117, which includes part of the ID (residues 110–154). For the loop regions, MyD88 has the longest H1–H2 loop, shortest H3–H4 loop, and longest H4–H5 loop (Lin et al. 2010). The MyD88 DD structure explains the disruptive phenotypes of mutations ΔE52 and L93P in children suffering from life-threatening pyogenic bacterial infections (von Bernuth et al. 2008). Structure-based mutagenesis studies identified critical residues of MyD88 DD (V43, A44, E52, Y58, I61, and R62). In particular, E52 and Y58 were found to be involved in IRAK4 recruitment and NF-κB signaling (Loiarro et al. 2009).

Following the MyD88 DD is an ID. Alternative splicing of MyD88 results in a variant that lacks the ID – MyD88 short (MyD88s), which is only expressed in the spleen and brain. When

overexpressed in HEK293 cells, MyD88s is able to bind IRAK, but it does not activate NF-κB because it cannot induce IRAK phosphorylation. Hence, it has been suggested that MyD88 ID plays a potent role in the differential activation of distinct (NF-κB versus JNK-dependent) transcriptional programs (Janssens et al. 2003). Another group designed a peptide from the ID (INT peptide) and showed that it inhibited MyD88-dependent TLR receptors and IL-1R. INT peptide binding to IRAK4 highlights the importance of ID in MyD88 signaling as well as interaction with IRAK4 (Avbelj et al. 2011).

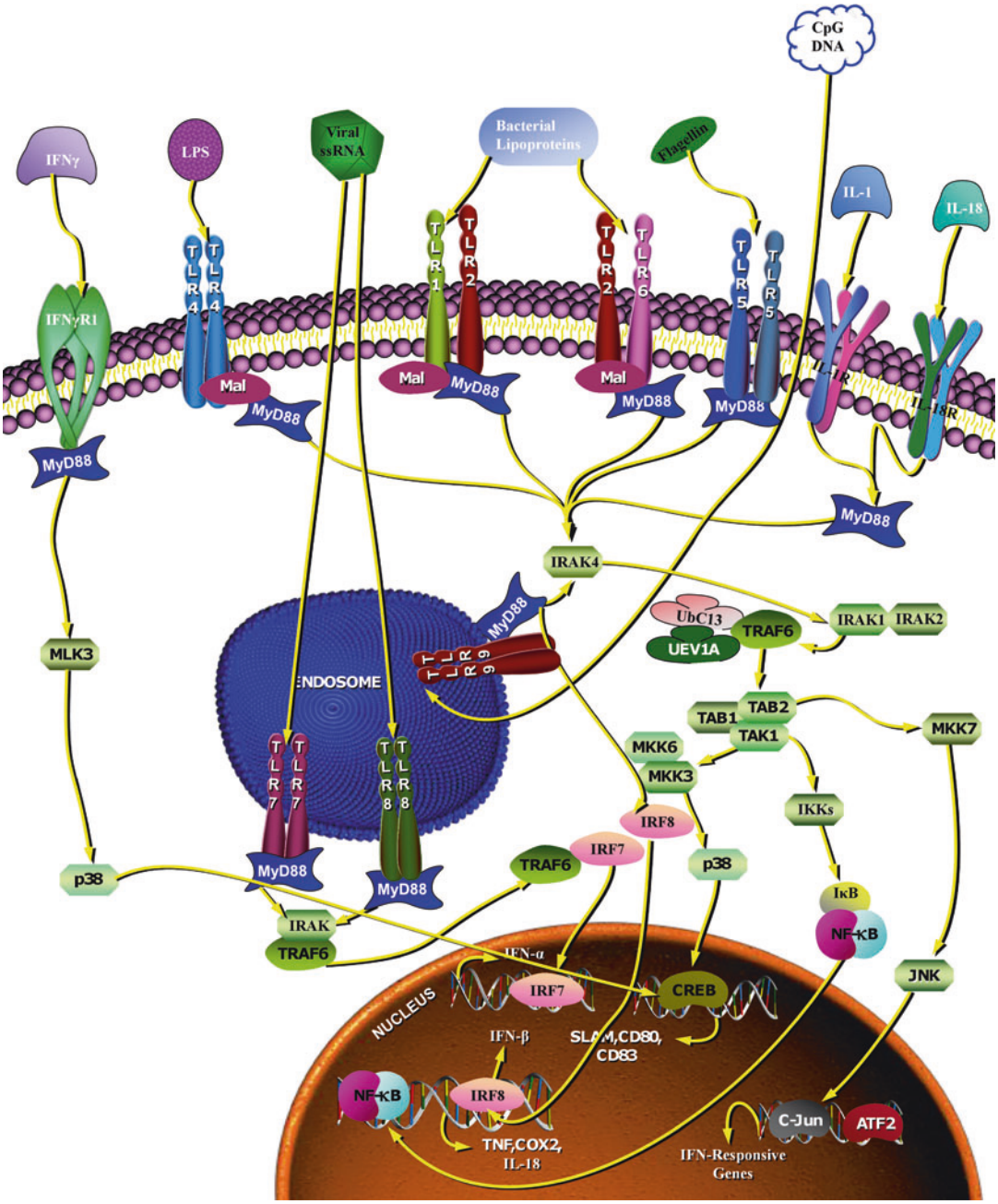
The C-terminal portion of MyD88 contains a TIR domain that mediates homo- and heterotypic protein interactions during signal transduction. The NMR solution structure of the MyD88 TIR domain (residues 157–296) identified by Ohnishi et al. comprised a central five-stranded parallel β-sheet (βA-βE) surrounded by four α-helices (αA-αC and αE) (Ohnishi et al. 2009). Rossi et al. also released the solution structure of the TIR domain of human MyD88 in the Protein Data Bank (PDB). The overall folding was identical to that reported by Ohnishi, despite minor differences. At high concentrations in NMR experiments, MyD88-TIR was found to reside in a monomeric state suggesting that the isolated TIR domain hardly forms oligomeric complexes in vitro. However, recent study proposed that the formation of in vitro MyD88 TIR complex could be possible by S244D or L252P mutations and by extending the TIR domain with C-terminal residues of the ID (Vyncke et al. 2016). The DD including the ID of MyD88 existed in a dimeric state. Therefore, the reported MyD88 dimerization was likely mediated by DD + ID and not by the TIR domain. TIR domains in TLRs, IL receptors, and the adaptors MyD88 and Mal contain three conserved boxes (boxes 1, 2, and 3), which are required for signaling (Li et al. 2005). A mutagenesis study conducted by Jiang et al. in conjunction with previous docking studies revealed that the BB loop and Poc site (I179N) in the TIR domain are critical for responses to most TLR ligands and for all other MyD88-dependent TIR signaling events (Jiang et al. 2006).

Universal Role of MyD88 in Signaling

A great deal has been learnt about the role of MyD88 in signaling pathways. In terms of signaling, the situation regarding MyD88 has become more complex. MyD88 is considered to be a critical component in the signaling cascades mediated by most TLRs, IL-1R, IL-18R, IFNγ, and IL-33 (Muzio et al. 1997; Wesche et al. 1997; Burns et al. 1998; Medzhitov et al. 1998; Kakkar and Lee 2008) (Fig. 2).

MyD88 adaptor protein links members of the TLR and IL-1R superfamily to the downstream activation of NF-κB and MAPKs. The extracellular domains of the TLRs and IL-1Rs are divergent; however, their intracellular domains share a high degree of similarity and activate similar signaling cascades upon stimulation. It is generally accepted that MyD88 is recruited to all members of the TLR/IL-1R family. The signaling in IL-1R and TLRs is initiated by the direct recruitment of MyD88 to the activated receptor complex. However, in the case of TLR2 and 4 signaling, a bridging adaptor, Mal, is required for MyD88 recruitment. Members of the IRAK family are recruited immediately downstream of MyD88. IRAK4 appears to be the MyD88-proximal kinase, which in turn recruits IRAK1. IRAK2 can also be found in the MyD88 complex (although this has only been shown when IRAK2 is overexpressed). A key downstream target for IRAK1 is believed to be TNF-receptor-associated factor 6 (▶ TRAF6) which, through the recruitment of transforming-growth-factor-β-activated kinase 1 (TAK1) and TAK1-binding protein 2 (TAB2), and the ubiquitylating factors, ubiquitin-conjugating enzyme E2 variant 1 isoform A (UEV1A) and ubiquitin-conjugating enzyme 13 (UBC13), ultimately engages with the upstream kinases for p38 and JNK and with the inhibitor of NF-κB kinase (IKK) complex, leading to NF-κB activation.

In addition to the MyD88 pathway, which results in NF-κB translocation, there is a cell-specific pathway that is required for the induction of type I IFNs by TLR7, 8, and 9. MyD88 has also been shown to be essential for the activation of



MyD88 (Myeloid Differentiation Primary Response Gene 88), Fig. 2 Overview of MyD88-dependent signaling pathways. The MyD88-dependent signaling pathway is utilized by all TLRs (with the exception of TLR3 and certain signals of TLR4), IL-1R, IL-18R, and IL-33. As the name suggests, the adaptor molecule, MyD88 is the key mediator of this pathway, and its main role is the activation of NF-κB (a hallmark of MyD88 signaling). MyD88 possesses its own C-terminal TIR domain, which drives the heterodimerization of the adaptor with the activated receptor. The N-terminal DD of MyD88 then recruits the IRAK1 and IRAK4 kinases. IRAK4 phosphorylates and activates IRAK1, which in turn initiates autophosphorylation and recruits TRAF6. TRAF6 together with IRAK dissociates from the activated receptor and binds to the preformed complex of TAK1/TAB1/TAB2. TAK1 is a MAP3K involved in the activation of IκB kinase (IKK). Activation of IKK appears to require atypical poly-ubiquitination. The TRAF6/TAK1/TAB1/TAB2 complex

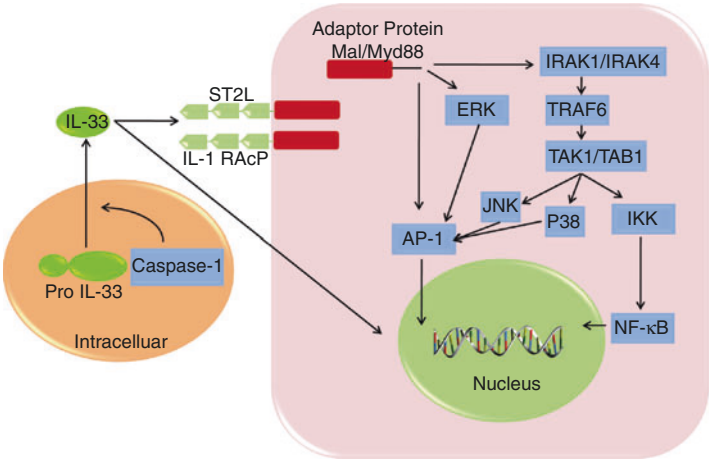
IRF7 by these TLRs, which leads to IFNα production (Honda et al. 2005). Furthermore, a complex comprising MyD88, IRAK1, IRAK4, TRAF6, and IRF7 has been detected, with IRF7 being phosphorylated by IRAK1. This phosphorylation appears to be a key signaling event of IRAK1 in TLR7, 8, and 9 signaling, as the IRF7 response is totally abolished in IRAK1-deficient cells, whereas NF-κB activation is only partially impaired (Uematsu et al. 2005). In the case of ▶ TLR9, IRF7 activation seems to require a stable interaction between MyD88 and the TIR domain of TLR9, which occurs on the cytosolic side of endosomes (Honda et al. 2005). These studies have expanded our understanding on the role of MyD88 in signaling during the host defense response.

MyD88 also interacts with ▶ IRF5 and IRF1 and is required for the activation of these IRFs. IRF5 was found to be crucial for the induction of proinflammatory cytokines and type I IFNs by all TLRs tested (Takaoka et al. 2005). The association of MyD88 with IRF1 appears to be required for the translocation of IRF1 to the nucleus in myeloid DCs, and IRF1 is required for the induction of several TLR-dependent genes in these cells. IFNγ is required to induce IRF1, which might be the basis for the priming effect of IFNγ on TLR action. Another intriguing link to the IFNγ system is the reported association between MyD88 and IFNγ receptor 1 (IFNγR1) (Sun and Ding 2006). MyD88 recruits mixed-lineage kinase 3 (MLK3) downstream of IFNγR1, which in turn activates p38. Therefore, an alternative signaling pathway for MyD88 that does not involve TIR-domain-containing receptors has been revealed.

Involvement of MyD88 in IL-33 signaling has been proposed (Fig. 3). IL-33 appears to bind a receptor complex composed of ST2L (transmembrane bound form of ST2) and IL-1RAcP (IL-1 receptor accessory protein). In general, upon activation of a Toll-like receptor/IL-1-receptor superfamily member, the transmembrane receptor's TIR domain dimerizes with the TIR domain of cytosolic adaptor molecules. The adaptor proteins, MyD88 and the associated protein IRAKs, activate downstream MAPKs through TRAF6 signaling, which in turn activates AP-1 through c-Jun N-terminal kinases (JNKs). TRAF6 also activates the inhibitor of NF-κB kinase (IKK) complex, leading to the downstream liberation of active NF-κB from the complex. IL-33 signaling appears to share many of these properties, and events downstream of IL-33 stimulation may include phosphorylation of extracellular signal-regulated kinase (ERK) 1/2, p38 MAPK, JNKs, and activation of NF-κB (Kakkar and Lee 2008).

An additional TLR-independent function of MyD88 was reported in CD95 (also known as FAS) signaling. CD95 signaling enhances IL-1R1 signaling by redirecting FADD (FAS-associated death domain) from a complex with MyD88 to the death domain of CD95, thereby allowing IL-1R1 to signal through MyD88 (Ma et al. 2004).

MyD88 (Myeloid Differentiation Primary Response Gene 88), Fig. 2 (continued) associates with the heterodimeric ubiquitin-conjugating-enzyme UBC13/UEV1-A. This results in modification of TRAF6 with the lysin63-linked polyubiquitin chain, which leads to IKK activation, IκB phosphorylation, ubiquitination, and degradation. NF-κB released from IκB translocates to the nucleus and switches on the transcription of a large number of proinflammatory genes. TAK1 is also responsible for the activation of p38 and JNKs. MyD88 also couples to IRF5 and IRF1. In the case of TLR2 and 4 signaling, a bridging adaptor, Mal, is required for MyD88 recruitment. In the case of TLR7, 8, and 9, the MyD88-IRAK4 pathway also leads through TRAF6 to the activation of IRF7. Finally, IFNγR1 can also engage with MyD88, leading to the activation of p38 through MLK3. *MyD88* Myeloid differentiation primary response gene 88, *IL-1R* Interleukin-1 receptor, *NF-κB* nuclear factor-κB, *IRAK4* IL-1R-associated kinase 4, *TRAF6* tumor-necrosis-factor-receptor-associated factor 6, *TAK1* transforming-growth-factor-β-activated kinase, *TAB1* TAK1 binding protein, *MAP3K* mitogen-activated-protein 3 kinase, *UEV1A* ubiquitin-conjugating enzyme E2 variant 1 isoform A, *UBC13* ubiquitin-conjugating enzyme 13, *IFNγR1* interferon-γ-receptor 1, *MLK3* mixed-lineage kinase 3



MyD88 (Myeloid Differentiation Primary Response Gene 88), Fig. 3 A model for IL-33/ST2 signaling. MyD88-dependent pathway of Toll-like receptor signaling involves TIR dimerization between the receptor and the Mal. Recruitment of MyD88 and downstream activation of TRAF6 via IRAK proteins results in TRAF6-mediated activation of the IKK complex and liberation of NF-κB from the complex. Free NF-κB is then able to bind DNA and act as a gene transcription regulator. IL-33 signaling appears to share many of these properties, and events downstream of IL-33 stimulation may include phosphorylation of ERK 1/2, p38 MAPK, and JNKs and activation of NF-κB. IL-33 binds to its receptor complex, which is composed of ST2L and IL-1RAcP. Subsequent sequestering of the adaptor proteins, MyD88 and Mal, results in modulation of IRAK-mediated TRAF6 activation and subsequent MAPK and IKK/NF-κB activation. The nature of this modulation of NF-κB activity by IL-33 is complex. *MyD88* Myeloid differentiation primary response gene 88, *IL-33* Interleukin-33 receptor, *NF-κB* nuclear factor-κB, *IKK* inhibitor of NF-κB kinase, *IRAK* IL-1R-associated kinase, *TRAF6* tumor-necrosis-factor-receptor-associated factor 6, *MAPK* mitogen-activated-protein kinase, *IL-1RAcP* Interleukin-1 receptor accessory protein

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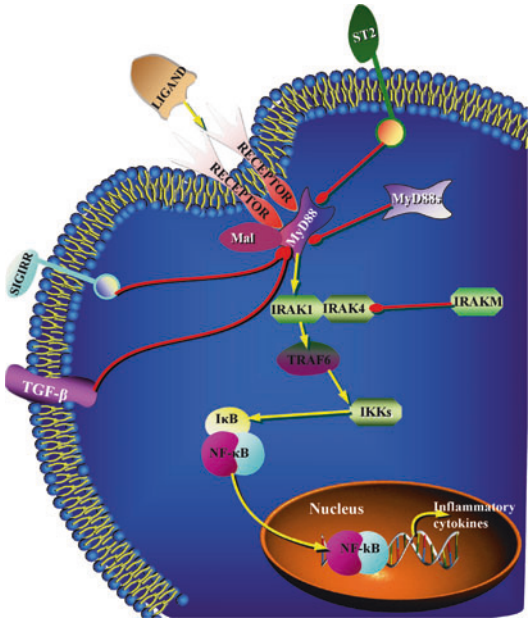
Antagonists of MyD88 Signaling

Although positive regulation of NF-κB, AP1, and IRFs via MyD88-dependent signaling has been extensively studied, recent studies have begun to unravel how these pathways are negatively regulated. Few molecules that have been shown to negatively regulate MyD88-dependent signaling include MyD88s, transforming growth factor-β (TGF-β), IRAK-M, SIGIRR (single immunoglobulin IL-1-receptor-related molecule), and ST2L (Fig. 4).

MyD88s, an alternatively spliced variant form of MyD88 that lacks the ID, is induced in monocytes following stimulation with LPS (lipopolysaccharide). Overexpression of MyD88s inhibits IL-1- and LPS-induced NF-κB activation, but not TNF-induced NF-κB activation (Janssens and Beyaert 2002). The mechanism of inhibition has been elucidated and shown to involve altered interactions in the downstream signaling pathway. Overexpression of MyD88s favors formation of MyD88s-MyD88 heterodimers, which are recruited to the receptor in favor of full-length MyD88 homodimers; however, the mechanism responsible for this process is not clear. In the presence of MyD88s-MyD88 heterodimers, IRAK1 was still recruited, presumably through a DD interaction with MyD88s, but was no longer phosphorylated. IRAK4 causes IRAK1 phosphorylation, and the presence of MyD88 is essential for this effect. MyD88s inhibits the ability of IRAK4 to phosphorylate IRAK1 because, unlike full-length MyD88, MyD88s does not interact with IRAK4. Although IRAK4 recruitment primarily requires the DD of MyD88, it also requires the ID for its binding with MyD88; therefore, the kinase is not recruited to the receptor complex (Janssens et al. 2003). This indicates that MyD88s might be involved in a negative-feedback regulatory mechanism to control excessive TLR-mediated signaling. Although MyD88s is inhibitory with respect to NF-κB signaling, overexpression of this adaptor still activates



MyD88 (Myeloid Differentiation Primary Response Gene 88), Fig. 4 Negative regulation of MyD88-dependent signaling. MyD88-dependent signaling pathways are negatively regulated by several molecules that are induced by the stimulation of receptors. IRAK-M inhibits the dissociation of the IRAK1-IRAK4 complex from the receptor. MyD88s blocks the association of IRAK4 with MyD88. TGF-β blocks NF-κB activation and cytokine production in response to TLR2, 4 and 5 ligands by decreasing MyD88 protein. The TIR-domain-containing receptors, SIGIRR and ST2L, have also been shown to negatively regulate MyD88-dependent signaling. *IRAK-M* IL-1R-associated kinase M; *MyD88s* MyD88 short, *TGF-β* transforming growth factor-β, *SIGIRR* single immunoglobulin IL-1-receptor-related molecule, *ST2L* transmembrane bound form of ST2

transcription factor AP1, implying an important role for alternative splicing in the fine-tuning of TLR responses (Janssens et al. 2003).

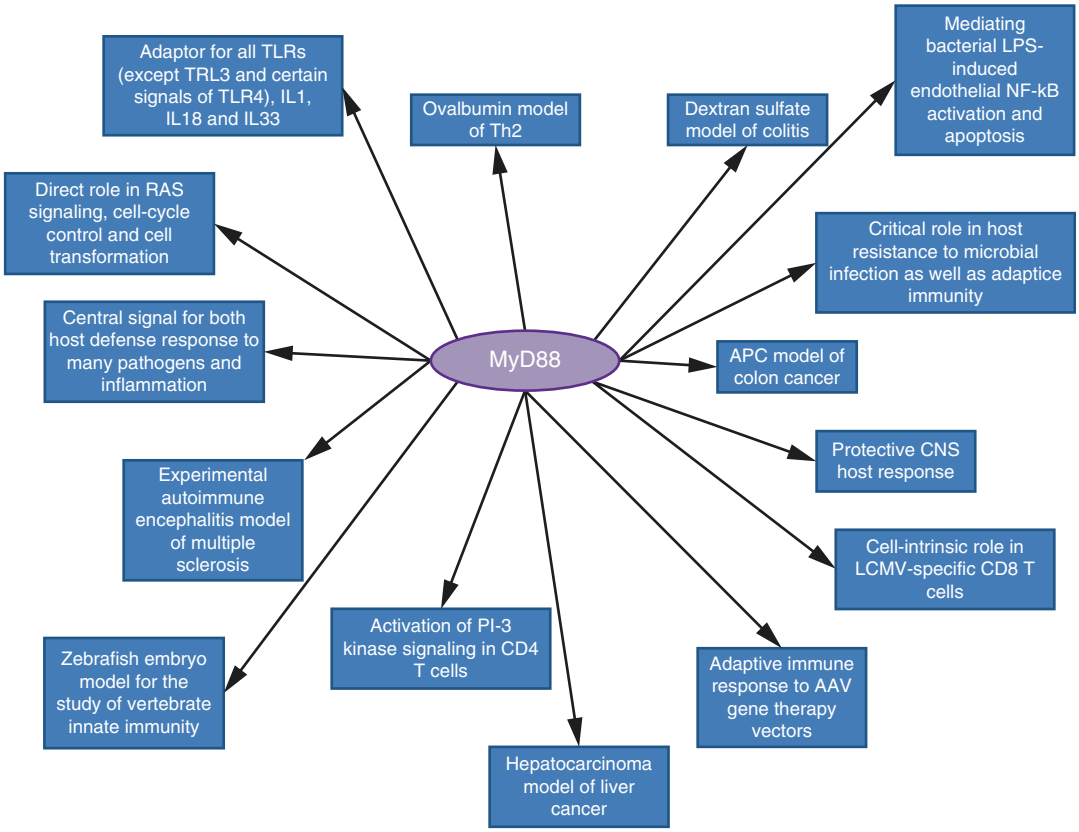
Another molecule that has been shown to negatively regulate MyD88-dependent signaling is TGF-β. Naiki et al. showed that TGF-β blocked NF-κB activation and cytokine production in response to TLR2, 4, and 5 ligands by decreasing MyD88 protein, but not mRNA levels (Naiki et al. 2005). TGF-β was found to cause the ubiquitination of MyD88 and an observed decrease in MyD88 protein levels. Furthermore, a protease inhibitor was found to abolish this effect, suggesting that TGF-β causes the polyubiquitination of MyD88, resulting in its proteasomal degradation.

Another negative regulator of MyD88 signaling is IRAK-M, which is primarily found in cells of monomyeloic origin such as monocytes and is induced upon TLR stimulation (Wesche et al. 1999). IRAK-M acts to prevent the dissociation of IRAK1 and IRAK4, which results in IRAK1 inability to interact with TRAF6 and therefore unable to induce a signaling cascade. IRAK-M deficient cells exhibited increased cytokine production and bacterial challenge upon TLR/IL-1 stimulation.

Another important negative regulatory mechanism for MyD88-dependent signaling involves the transmembrane proteins, ST2L and SIGIRR (both members of the TIR superfamily). ST2L interacts with MyD88 and Mal and sequesters MyD88-dependent NF-κB activation by TLR2, 4, and 9 signaling pathways (Brint et al. 2004). SIGIRR binds to TLR4 and IRAK and terminates the downstream TLR signaling pathways (Wald et al. 2003). These findings indicate that MyD88 serves as an important point of control for signaling through various receptors.

Multiple Roles of MyD88

Studies conducted in the past few years have firmly established the central role of MyD88 adaptor in inflammation and immunity (Fig. 5). As mentioned above, much of the recent scientific literature has focused on the role of MyD88 with respect to TLR signaling leading to the activation of several signaling cascades including the NF-κB pathway, resulting in the production of pro-inflammatory cytokines/chemokines and upregulation of costimulatory and adhesion molecules involved in both innate and adaptive immune responses. MyD88 is also essential for transducing signals from IL-1R family members, including IL-1R, IL-18R, and several other receptors. Furthermore, Andrew et al. identified the role of MyD88 in the activation of PI-3 kinase signaling in $CD4^+$ T cells, thereby enabling CpG oligodeoxynucleotide-mediated costimulation (Gelman et al. 2006).



MyD88 (Myeloid Differentiation Primary Response Gene 88), Fig. 5 Diverse roles of MyD88. MyD88 is essential for signaling by IL-1, IL-18, IL-33, and all TLRs (except TLR3 and certain TLR4 signals) and is a central signal for many processes involving host defense to infection, inflammation, and cancer. MyD88 is required for inflammation in the ovalbumin model of Th2 responses, the collagen-induced arthritis model of rheumatoid arthritis (RA), the dextran sulfate model of colitis, the APC model of colon cancer, a hepatocarcinoma model, and the experimental autoimmune encephalitis model of multiple sclerosis (MS). MyD88 plays a potent cell-intrinsic role in lymphocytic choriomeningitis virus (LCMV)-specific CD8 T cells, activation of PI-3 kinase signaling in $CD4^+$ T cells, and a direct role in RAS signaling, cell cycle control, and cell transformation, implicating its role in tumorigenesis via proinflammatory mechanisms. MyD88 also plays an important role in innate immune signaling mechanisms during vertebrate embryogenesis in a zebrafish embryo model. TLR9-MyD88 pathway is known to be critical for adaptive immune responses to adeno-associated virus (AAV) gene therapy vectors in mice. Bovine Mal and MyD88 are essential for mediation of bacterial LPS-induced endothelial NF-κB activation and apoptosis. MyD88 also establishes a protective CNS host response during the early stages of brain abscess development, thus exhibiting its central role in the responses of microglia to PAMPs

The overall importance of MyD88 is demonstrated by the results of many studies involving MyD88-deficient mice. Targeted disruption of the MyD88 gene results in loss of TLR, IL-1, IL-33, and IL-18-mediated functions (Adachi et al. 1998). MyD88-deficient mice have been subjected to many models of infection, inflammation, and cancer (Takeuchi et al. 2000b; Naugler et al. 2007; Rakoff-Nahoum and Medzhitov 2007). The studies have shown that MyD88 is essential for the inflammation seen in models of airway hyperreactivity, colitis, APC model of colon cancer and hepatocarcinoma, and skin carcinogenesis (Araki et al. 2005; Piggott et al. 2005; Naugler et al. 2007; Rakoff-Nahoum and Medzhitov 2007; Swann et al. 2008). MyD88 has also been shown to possess antitumorigenic characteristic in the mouse model of pancreatic cancer (Ochi et al. 2012).

MyD88-deficient mice failed to generate pro-inflammatory and Th1 responses when stimulated with TLR ligands (Schnare et al. 2001). Additionally, these mice are highly susceptible to infection by a wide variety of different pathogens, including *Staphylococcus aureus* (Takeuchi et al. 2000a), *Listeria monocytogenes* (Seki et al. 2002), *Toxoplasma gondii* (Scanga et al. 2002), and *Mycobacterium tuberculosis* (Shi et al. 2003). MyD88-deficient mice are also highly susceptible to *Leishmania major* infection associated with a polarized Th2 response (Muraille et al. 2003). An impaired production of proinflammatory cytokines and host resistance to acute infection with *Trypanosoma cruzi* is conspicuous in mice lacking functional MyD88 (Campos et al. 2004). MyD88 has generally been considered to indirectly regulate adaptive immune responses by controlling inflammatory cytokine production and antigen (Ag) presentation in innate immune cells; however, Rahman et al. identified an unappreciated cell-intrinsic role of MyD88 in lymphocytic *choriomeningitis* virus (LCMV)-specific CD8 T cells (Rahman et al. 2008). Their results demonstrated the importance of MyD88-dependent signals for supporting the survival of the cells and sustained accumulation. MyD88-dependent signaling is also required for the control of *ehrlichial* infection via a potent role in immediate activation of the innate immune system and inflammatory cytokine production, as well as in activation of the adaptive immune system at a later stage by providing optimal Th1 immune responses (Koh et al. 2010).

MyD88 contributes to regulation of cell proliferation and differentiation in human adipose tissue-derived mesenchymal stem cells (hASCs) (Yu et al. 2008). Astrid et al. demonstrated that the innate immune response of the developing embryo involves MyD88-dependent signaling by utilizing zebrafish embryo as a model for the study of vertebrate innate immunity (van der Sar et al. 2006). The TLR9-MyD88 pathway has also been shown to be critical for adaptive immune responses to adeno-associated virus (AAV) gene therapy vectors in mice (Zhu et al. 2009). Both MAVS and MyD88 are known to be essential for innate immunity, but not cytotoxic T lymphocyte response against respiratory *syncytial* virus (Bhoj et al. 2008), thereby providing an example of a normal and effective adaptive immune response in the absence of innate immunity. Cates et al. demonstrated that bovine Mal and MyD88 are essential for mediation of bacterial LPS-induced endothelial NF-κB activation and apoptosis (Cates et al. 2009). Furthermore, Tammy et al. showed an essential role enacted by MyD88 in establishment of a protective CNS host response during the early stages of brain abscess development (Esen and Kielian 2006), thus exhibiting a central role for MyD88 in the responses of microglia to pathogen-associated molecular patterns (PAMPs).

Isabelle et al. demonstrated that, in addition to its role in inflammation, MyD88 played a crucial direct role in RAS signaling, cell cycle control, and cell transformation, thus demonstrating its potent role in tumorigenesis via proinflammatory mechanisms (Coste et al. 2010). Bettina et al. showed that both MyD88 and TRIF are non-redundant signaling pathways involved in early endotoxin-induced rodent ileus, and that MyD88 is the essential adaptor molecule involved in the transduction of early TLR4-induced ileus and inflammatory signaling (Buchholz et al. 2010). These findings have led to the conclusion that MyD88 plays a critical role in host resistance to microbial infection, inflammation, innate and adaptive immunity, and cancer.

Summary

Numerous reports conducted in the past few years have established MyD88 as a universal and essential signaling adaptor molecule that is critical for an effective immune response against a wide range of microbial pathogens. MyD88 fulfills important functions in both innate and adaptive immunity, inflammation, cancer, and programmed cell death. However, much remains to be learned about the in vivo functions of MyD88 in higher organisms. Future studies should address the prospect of a detailed molecular account of the MyD88 interactions at the DD, ID, and TIR levels with receptors and adaptor proteins. Moreover, the underlying factors involved in MyD88

direct/indirect (via the use of other adaptors) interaction with receptors following ligand stimulation have yet to be elucidated. Joined efforts among researchers will help us to understand the molecular mechanisms by which MyD88 functions in cellular processes. MyD88-related findings have proven to be fruitful in terms of improving our knowledge of the molecular basis for innate immunity, inflammation, and cancer, thus anticipating further discoveries in the coming years.

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MYD88-5

► SARM1 (Sterile Alpha and TIR Motif-Containing Protein 1)
► Toll-Like Receptor Adaptor Protein Family Members

Myd88-Adapter-Like

► Toll-Like Receptor Adaptor Protein Family Members

Myeloid DAP-12-Associating Lectin-1

► CLEC5A

Myeloid Differentiation Primary Response Gene 88

► MyD88 (Myeloid Differentiation Primary Response Gene 88)
► Toll-Like Receptor Adaptor Protein Family Members

Myeloid, Nervy, and DEAF-1

► N-Lysine Methyltransferase SMYD

MYLK (Myosin Light Chain Kinase)

Thomas J. Lukas[1] and Vladimir P. Shirinsky[2]
[1]Department of Pharmacology, Northwestern University, Chicago, IL, USA
[2]Institute of Experimental Cardiology, Russian Cardiology Research and Production Complex, Ministry of Healthcare of Russian Federation, Moscow, Russia

Synonyms

MLCK; MLCK108; MLCK210; MYLK1; Non-muscle myosin light chain kinase; smMLCK; Smooth muscle myosin light chain kinase

Historical Background

The gene for myosin light chain kinase encodes three proteins: MLCK210, MLCK108, and telokin/kinase-related protein (KRP). The first protein discovered was MLCK108 (Mr = 110–140 kDa) as a major cytoplasmic component of smooth muscle and responsible for smooth muscle contractility through the phosphorylation of the regulatory light chain of myosin (Lukas et al. 1998; Kamm and Stull 2001). MLCK210 (Mr = 210–220 kDa) has an amino-terminal extension containing additional protein-binding elements (Fig. 1). It was discovered ~15 years later before the gene for MYLK was characterized from chicken (Birukov et al. 1998) and humans (Shen et al. 2012). Both MLCKs are Ca^{2+}-calmodulin-dependent enzymes. Telokin/KRP is an independently expressed nonkinase gene product containing the C-terminus of MLCK, and functions as a myosin-binding and filament-stabilizing protein (Shirinsky et al. 1993). Telokin/KRP is primarily expressed in smooth