Toll-like Receptor 2 Functions as a Pattern Recognition Receptor for Diverse Bacterial Products*

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Toll-like receptors (TLRs) 2 and 4 are signal transducers for lipopolysaccharide, the major proinflammatory constituent in the outer membrane of Gram-negative bacteria. We observed that membrane lipoproteins/lipo-peptides from Borrelia burgdorferi, Treponema pallidum, and Mycoplasma fermentans activated cells heterologously expressing TLR2 but not those expressing TLR1 or TLR4. These TLR3-expressing cells were also stimulated by living motile B. burgdorferi, suggesting that TLR2 recognition of lipoproteins is relevant to natural Borrelia infection. Importantly, a TLR2 antibody inhibited bacterial lipoprotein/lipopeptide-induced tumor necrosis factor release from human peripheral blood mononuclear cells, and TLR2-null Chinese hamster macrophages were insensitive to lipoprotein/lipopeptide challenge. The data suggest a role for the native protein in cellular activation by these ligands. In addition, TLR2-dependent responses were seen using whole Mycobacterium avium and Staphylococcus aureus, demonstrating that this receptor can function as a signal transducer for a wide spectrum of bacterial products. We conclude that diverse pathogens activate cells through TLR2 and propose that this molecule is a central pattern recognition receptor in host immune responses to microbial invasion.

Microbial invasion of the host is followed by a series of events designed to control and eventually reverse the infection. The immediate response to the invading organism is coordinated by the innate immune system. The cells of this system are responsible for first-line bacterial clearance and modulation of the adaptive immune response through soluble factors or co-stimulatory signals provided by antigen-presenting cells (1). Jane-way and co-workers (2, 3) have hypothesized that the innate immune system can sense invading pathogens by virtue of nonclonal pattern recognition receptors that interact with microbial structures and deliver a danger signal to the host cell.

Toll is a type I transmembrane receptor, first described in Drosophila, that shares homology to components of the interleukin-1 (IL-1) signaling pathway (4). Toll, and the related molecule 18-Wheeler, appear to control important antimicrobial responses against both fungi and bacteria in the fruit fly (5, 6). In evolutionary terms, these proteins are primordial pattern recognition receptors for animals that totally lack acquired immunity. Recently, mammalian homologues of Toll have been cloned and designated Toll-like receptors (TLRs) (7–9). At least 10 such receptors have been identified, but only 2 TLRs have any known function. TLR2 and TLR4 have been implicated in cellular responses to lipopolysaccharide (LPS), the major constituent of the Gram-negative bacterial outer membrane (10–12). However, the mechanism behind TLR-mediated recognition of LPS, the interactions with other receptor molecules, such as CD14 (13, 14), and the details of the subsequent cellular activation pathway still require elucidation.

Lyme disease and syphilis are acute and chronic inflammatory disorders caused by the spirochetal pathogens Borrelia burgdorferi and Treponema pallidum subsp. pallidum, respectively (15, 16). Both spirochetes lack LPS (17, 18); however, they do possess abundant membrane lipoproteins (19). There now exists a large body of evidence that spirochetal lipoproteins and synthetic lipohexapeptide analogs are potent activators of monocytes/macrophages, neutrophils, lymphocytes, endothelial cells, and fibroblasts and that acyl modification of the peptides is essential for these proinflammatory activities (20–29). More recent observations suggest that the mechanisms underlying monocyte cell activation by motile B. burgdorferi and T. pallidum are identical to those employed by their purified membrane constituents (30). These results support the notion that lipoproteins are the principle component of intact spirochetes driving the host immune response during Lyme disease and syphilis. Similarly, lipoproteins and lipopeptides derived from the human pathogen Mycoplasma fermentans are also potent activators of monocytes/macrophages and may play

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1 The abbreviations used are: IL, interleukin; TLR, Toll-like receptor; LPS, lipopolysaccharide; Osp, outer surface protein; nOspA, native OspA; CHO, Chinese hamster ovary; sMALP-2, synthetic macrophage-activating lipopeptide-2; TNF, tumor necrosis factor; NF-κB, nuclear factor-κB; FBS, fetal bovine serum; PBMC, peripheral blood mononuclear cells.
an important role in the inflammatory response during infection (31–33).

The cellular activation induced by the lipopeptides or lipoprotein-derived lipopeptides from B. burgdorferi and T. pallidum resembles that of the LPS signaling pathway, as CD14 appears to facilitate cellular activation by both types of pathogenic membrane structures (21, 25). However, several differences have been observed between LPS and lipoprotein cellular activation, indicating the utilization of different signaling elements. For example, siphonocal and mycoplasma lipopolysaccharides and lipopolysaccharides activate macrophages from LPS hyporesponsive C3H/HeJ mice (23, 24, 27, 31). In addition, whereas Chinese hamster ovary (CHO)-K1 cells become remarkably sensitive to LPS after transfection with CD14 (34–36), they remain insensitive to the lipopolysaccharides, lipopolysaccharides, and motile B. burgdorferi (21, 30, 32). These observations led us to hypothesize that differences in the main signaling components exist between lipopolysaccharides and LPS.

We have recently found that CHO-K1 cells do not express an mRNA transcript for full-length and functional TLR2 (37). This observation raised the possibility that the lack of functional TLR2 might account for the failure of CHO/CD14 cells to respond to bacterial structures other than LPS. To test this hypothesis, we engineered stable CHO/CD14 fibroblast cell lines that express TLR2. The transfected cells were highly susceptible to activation by lipopolysaccharides and lipopolysaccharides from B. burgdorferi, T. pallidum, and M. fermentans, as well as to activation by live motile B. burgdorferi. In contrast, cells expressing TLR1 or TLR4 did not acquire responsiveness to bacterial lipopolysaccharides. Moreover, we observed a TLR2-mediated cell activation by Mycobacterium avium, an important pathogen in AIDS. Similar studies have documented inducible responses to other bacteria as well, including staphylococci, listeria, tuberculosis, and the pneumococcus, suggestive of widespread recognition of bacteria by TLR2 (10, 11, 38).3, 4 We propose that TLR2 mediates cellular responses to structures from numerous microbial cell wall constituents and may thus be central in host recognition of diverse bacterial pathogens. Therapies directed at the TLRs may be useful anti-inflammatory agents for a large variety of chronic and acute bacterial infections.

MATERIALS AND METHODS

Reagents—PBS, Ham's F-12 medium, RPMI 1640 medium, and trypsin-versene mixture (trypsin-EDTA) were from BioWhittaker (Walkersville, MD). Low endotoxin FBS was from Summit Biotechnologies (Greeley, CO), and ciprofloxacin was a gift from Miles Pharmaceuticals (West Haven, CT). Hygromycin B was purchased from Calbiochem (San Diego, CA), and puromycin was from Sigma, and G418 was from Life Technologies, Inc. Protein-free LPS from Salmonella minnesota Re595 was a gift from N. Qureshi (Midleton Veterans Affairs Hospital, Madison, WI). Antibodies for flow cytometry were purchased from Becton Dickenson, and human IL-1β and tumor necrosis factor α (TNFα) were from Genzyme (Cambridge, MA).

Lipopolysaccharides and Lipopeptides—Native OspA (nOspA) was immunoaffinity purified from B. burgdorferi strain TH-1 (40). Hexapeptides similar to the N termini of B. burgdorferi OspA (CKQVNS1), OspC (CNNSK), and T. pallidum 47-kDa major lipoprotein (CGSSH8) were synthesized on an Applied Biosystems (Foster City, CA) peptide synthesizer. Lipopeptides (OspAL, OspCL, and 47L) corresponding to the acetylated N termini of natural OspA, OspC and 47-kDa lipoprotein were synthesized using tripalmitoyl-S-glyceryl-cysteine in a solid-phase procedure (41). A synthetic (s) lipopeptide based upon the full-length MALP-2 membrane lipoprotein from M. fermentans (sMALP-2; CGNNDESSIFKKE) was prepared using dipalmitoyl-S-glyceryl-cysteine as described (42). An unlipidated version of sMALP-2 was also synthesized (32). Lipoprotein-derived lipopeptides from B. burgdorferi were synthesized using tripalmitoyl-

Flow Cytometry Analysis—Cells were plated at a density of 1 × 10^6 cells/well in 24-well dishes. The following day, the cells were stimulated with 2 μg/ml of lipopolysaccharides or lipopoly peptide for 5 h. After incubation, the cells were washed with PBS and stained with fluorescein isothiocyanate anti-CD25 in PBS, followed by flow cytometry using a FACScan (Becton Dickinson). For TLR2 expression, the cells were incubated with 2 μg/ml lipopolysaccharides or lipopeptides for 1 h. After incubation, the cells were washed with PBS and stained with fluorescein isothiocyanate anti-CD25. The cells were analyzed by flow cytometry using a FACScan fluorometer and FACSwin software (Becton Dickinson).
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10^6 cells/well in a 96-well dish. Immediately before stimulation with the indicated compounds, 1:5 (v/v) dilutions of a hybridoma supernatant containing the TLR2-specific antibody TL2.1^2 or a control antibody (mouse IgG, Sigma, diluted in hybridoma medium), to a final antibody concentration of 5 μg/ml, was added. The cells were stimulated for 12 h, and cell-free supernatants were harvested and analyzed for TNFα release by enzyme-linked immunosorbent assay (matching antibody pair from Roche Molecular Biochemicals).

RESULTS

TLR2, but Not TLR4 or TLR1, Imparts Cellular Activation by B. burgdorferi, T. pallidum, and M. fermentans Lipoproteins and Lipopeptides—In order to test the potential role of TLRs in B. burgdorferi and T. pallidum infections, we constructed several TLR-expressing reporter cell lines in a CHO fibroblast background that contained an inducible NF-κB-dependent promoter driving the surface expression of membrane CD25 (43). Thus, the induction of proinflammatory activity could be quantified by flow cytometry. We exposed CHO/CD14, CHO/CD14/TLR1, CHO/CD14/TLR2, and CHO/CD14/TLR4 reporter cell lines to the purified native B. burgdorferi outer surface protein A (nOspA), a synthetic lipohexapeptide based upon the N-terminus of the 47-kDa major T. pallidum lipoprotein (47L), and a synthesized version of the sMALP-2 full-length M. fermentans lipoprotein. All of the cell lines were engineered to express CD14, thereby conferring responsiveness to LPS, as indicated by increased membrane expression of the CD25 reporter transgene. Cells expressing TLR2 were activated by lipoprotein or lipopeptide structures (Fig. 1A). In contrast, CHO/CD14, CHO/CD14/TLR1, and CHO/CD14/TLR4 cells were not activated by any of the spirochetal molecules. These results also illustrate an important point concerning the purity of our preparations. Lack of stimulation of the highly LPS-sensitive CHO/CD14 line is strong evidence against the possibility that environmental endotoxin contaminated our preparations.

The N terminus of mature B. burgdorferi and T. pallidum lipoproteins consists of a diacylglycerol moiety in thioether linkage to a cysteine residue and a third fatty acid amide-linked to the α-amino group of the cysteine (19). In contrast, M. fermentans MALP-2 possesses an N-acetyl-S-diacylglycerol cysteine with a free N terminus (31). Several reports demonstrate dependence on lipid modification for both in vivo and in vitro cellular activation by B. burgdorferi, T. pallidum, and M. fermentans lipoproteins and synthetic lipopeptides (22, 23, 29, 32). As shown in Fig. 1B, only lipided peptides (B. burgdorferi OspC1, OspAL, T. pallidum 47L, and M. fermentans sMALP-2) activated the CHO/CD14/TLR2 reporter cell line, whereas the nonlipided peptides completely lacked stimulatory activity. These data demonstrate that TLR2 mediates cellular activation by lipoproteins/lipopeptides and that the N-acetyl-S-diacylglycerol moiety appears to be more important than the amide/linked fatty acid for their biological activity.

The Lack of TLR4 Activity after Lipoprotein/Lipopeptide Exposure Is Due to the Lack of Ligand-specific Recognition—Although the inability of the CHO/CD14/TLR4 cell line to respond to lipoproteins and lipopeptides may reflect the fact that TLR4 is not involved in lipoprotein recognition, it is possible that these cell lines expressed a nonfunctional TLR4. Control conditions were difficult to establish, because LPS already activates CHO/CD14 cells through the endogenous hamster TLR4. Therefore, an alternative approach was employed to confirm the functionality of the transfected TLR4 protein before concluding that bacterial lipoproteins and lipopeptides were not TLR4 ligands.

Our laboratory has recently described CHO/CD14 cells with a genetic defect in LPS, but not in IL-1- or TNF-induced signal transduction (43). These cells respond to LPS after transfection with TLR2 or TLR4, as these Toll proteins bypass their genetic lesion. As shown in Fig. 2, transfection with TLR2 enabled the cells to respond to lipopeptides, lipoproteins, and LPS. In stark contrast, TLR4-transfected cells responded to LPS only, demonstrating that the transfected TLR4 is functional in CHO/CD14 cells but will not transduce a signal in response to lipoproteins/lipopeptides. These data suggest that TLR2 is able to serve as a receptor for a broad repertoire of bacterially derived ligands, whereas TLR4 appears to be a more specific receptor for LPS.

TLR2 Mediates Cellular Responses upon Exposure to Live B. burgdorferi—Similar to spirochetal lipoproteins/lipopeptides, live B. burgdorferi and T. pallidum activated monocytic cells but failed to stimulate CHO/CD14 cells (30). These findings are one of several pieces of evidence supporting the hypothesis that live spirochetes and their constituent lipoproteins activate cells by similar, if not identical, mechanisms. In light of these results and the above observations it was of interest to test whether motile spirochetes signal through TLR2. We found that only TLR2-transfected cells were activated upon exposure to B. burgdorferi (Fig. 3A), whereas CHO/CD14/TLR4 cells remained insensitive to spirochetal challenge (data not shown). Experiments with fluorescein isothiocyanate-labeled B. burgdorferi showed a similar high degree of binding of the spirochete to all cell lines (data not shown), indicating that membrane attachment was not sufficient to initiate cellular responses. Again, motile B. burgdorferi stimulated the TLR2-transfected LPS nonresponder mutant CHO/CD14 cells, whereas TLR4-transfected cells were enabled to respond to LPS, but not to the spirochetes (Fig. 3B). Thus, the recognition of lipopeptides and lipoproteins by TLR2 appears to be relevant to the responses observed during natural infection in man. These results demonstrate that TLR2 but not TLR4 mediates responses to whole B. burgdorferi and that TLR4 is unlikely to be involved in responses to spirochetes.

TLR2 Is a Pattern Recognition Receptor—Many microbial infections induce similar clinical symptoms, which may reflect similarities in host responses to invasion. Recent observations suggest that bacterial cell wall structures, such as peptidoglycan from Gram-positive organisms (38, 39), are able to signal through TLR2. M. avium is an opportunistic pathogen, which leads to serious complications in HIV-1 disease; patients with M. avium experience profound fevers, diffuse pains, and generalized wasting (44). Recent observations suggest that structures from M. avium activate the LPS signaling pathway by utilizing CD14 (45). We exposed the transfected fibroblasts to live M. avium and killed S. aureus and E. coli in order to determine whether there were similarities in utilization of TLR2 by bacteria containing different membrane constituents. The patterns of response demonstrated the following (Fig. 4): CHO cells required expression of CD14 in order to respond to Gram-negative cell wall products. However, cells that co-expressed CD14 with TLR2 were capable of responding to stimulation by all the bacteria tested, including the atypical mycobacterium M. avium and the Gram-positive bacterium S. aureus. Hence, although they are phylogenetically diverse and contain a variety of proinflammatory constituents, M. avium, S. aureus, B. burgdorferi, T. pallidum, and M. fermentans all appear to activate cells through the same receptor system.

TLR2-null Chinese Hamster Macrophages Fail to Respond to Lipoproteins/Lipopeptides—Chinese hamster macrophages respond to LPS, although they do not express mRNA for a full-length TLR2 (37). Sequence analysis of TLR2 from the Chinese hamster, compared with human and mouse TLR2, revealed a single base pair deletion that resulted in a frameshift mutation; this mutation encodes a protein fragment devoid of transmembrane and intracellular domains. In contrast, CHO/CD14
cells and macrophages from Chinese hamsters appear to have a full-length and functional TLR4. We isolated peritoneal macrophages from Chinese hamsters in order to test the action of lipoproteins/lipopeptides toward TLR2-null primary phagocytes. We found that the hamster macrophages responded to LPS, but not to nOspA or 47L, as measured by nuclear translocation of NF-κB (Fig. 5A). In contrast, macrophages from C3H/OuJ mice responded to LPS, nOspA, and 47L. These results suggested that the lack of TLR2 in primary Chinese hamster macrophages made them unable to recognize bacterial lipoproteins and lipopeptides.

The anti-TLR2 mAb TL2.1 Inhibits Lipoprotein/Lipopeptide and M. avium-induced Release of TNF from Human Peripheral Blood Mononuclear Cells—In order to determine whether our findings in transfected cell lines reflect the signal transduction systems used by native phagocytes, we stimulated freshly isolated human PBMC with nOspA, 47L, and M. avium in the presence of the TLR2 antibody TL2.1. As shown in Fig. 5B, TL2.1 inhibited TNF production from PBMC after exposure to nOspA, 47L, and live M. avium by 40–70%. These data support the hypothesis that TLR2 may play an important role in vivo responses to various bacterial structures. In the presence of TL2.1, LPS-induced responses in primary cells were only minimized.

5 H. Heine, E. Lien, B. Monks, and D. T. Golenbock, unpublished observations.

58 peptides are represented by thin lines, and unstimulated cells are represented by dotted lines. Shown is one representative experiment out of four performed.
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**DISCUSSION**

The severity of clinical symptoms associated with bacterial diseases varies according to the type of infectious agent, bacterial burden, affected tissue, and co-existing illness. Nevertheless, in many aspects, similar host responses are observed. For example, several clinical and immunological similarities can be seen between therapy-induced Jarisch-Herxheimer reaction during infection with *Treponema* and *Borrelia* spp. (46, 47) and Gram-negative and Gram-positive sepsis (48). Hence, one is tempted to speculate that the pathophysiological similarities observed with these diverse infections are due to the activation of analogous signaling pathways in response to bacterial exposure. The present study implicates TLR2 in host interactions with *B. burgdorferi*, *T. pallidum*, *M. fermentans*, and *M. avium*, as well as components of Gram-negative and Gram-positive bacteria. Thus, this receptor can mediate host inflammatory reactions to a variety of microbial pathogens, indicating a remarkable spectrum of bacterial recognition.

Previous reports have identified mechanisms of cellular activation by many microbial structures that are similar, yet never identical, to the LPS signaling pathway. In most cases, the reported observations concerned the ability of the microbes to utilize CD14. In addition to being a high-affinity receptor for LPS, CD14 has been implicated in the responses to several bacteria and their microbial products, including *Borrelia* and

![TLR2 mediates cellular activation upon exposure to live *B. burgdorferi*.](http://www.jbc.org/content/385/14/33423/F3)

**Fig. 3.** TLR2 mediates cellular activation upon exposure to live *B. burgdorferi*. A, CHO/CD14 or CHO/CD14/TLR2 cells were left untreated (dotted lines) or exposed to motile *B. burgdorferi* (thick lines) (1000 spirochetes/cell) for 8 h. The cells were harvested, stained for reporter gene expression, and analyzed by flow cytometry, as in Fig. 1. Indicated in insets is the fold increase of median fluorescence relative to unstimulated cells. From left to right: untreated cells (0, open bars), cells exposed to different doses of live *B. burgdorferi* (black bars) (1, 10, 100, and 1000 spirochetes/cell, respectively) and LPS (hatched bars) (100 ng/ml). B, LPS nonresponder mutant CHO/CD14 cells transfected with TLR2 or TLR4 were exposed to medium (dotted lines), 1000 spirochetes/ml (thick lines), or LPS (thin lines) (100 ng/ml). Shown is one representative experiment out of three performed.

![Microbial pattern recognition via CD14 and TLR2.](http://www.jbc.org/content/385/14/33423/F4)

**Fig. 4.** Microbial pattern recognition via CD14 and TLR2. CHO control, CHO/CD14, or CHO/CD14/TLR2 reporter cell lines were exposed to the following stimuli (from left to right): medium (0, open bars), live *M. avium* (black bars), heat-killed *S. aureus* (gray bars), *E. coli* bioparticles (light gray bars), or LPS (hatched bars) (100 ng/ml). Numbers indicate the density of the bacteria per ml. After 20 h, the cells were harvested, stained for reporter gene expression, and analyzed by flow cytometry, as in Fig. 1. The y axis indicates fold increase of median fluorescence compared with unstimulated cells. Shown is one representative experiment out of three performed.

![TLR2 mediates responses to lipoproteins/lipopeptides in primary cells.](http://www.jbc.org/content/385/14/33423/F5)

**Fig. 5.** TLR2 mediates responses to lipoproteins/lipopeptides in primary cells. A, TLR2-null peritoneal macrophages from Chinese hamsters and C3H/OuJ mice were stimulated with nOspA, 47L, and LPS for 1 h in RPMI 1640 medium containing 10% FBS. Nuclear extracts were isolated and analyzed for binding to a NF-κB specific probe by electrophoretic mobility shift assay. Shown is the NF-κB band, in one representative experiment out of two performed. B, human PBMC were isolated by gradient centrifugation, resuspended in RPMI 1640 medium containing 10% human serum, and plated at a density of 10^6 bacteria/ml, 47L (1 μg/ml), or nOspA (300 ng/ml) in a total volume of 0.2 ml for 12 h. The supernatants were harvested and assayed for TNF by immunoassay. The antibody did not block activation induced by phorbol ester (not shown). Data are from one representative experiment out of three performed. Shown is the mean of duplicate wells ± S.D.
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| Organisms          | Reference                                  | Stimulus tested                                                      |
|--------------------|--------------------------------------------|                                                                      |
| Gram-negative      | Yang et al. (10)                           | LPS (various sources), lipid A                                      |
| bacteria           | Kirschning et al. (11)                     | LPS (various sources), lipid A                                      |
| Gram-positive      | Yoshimura et al. (38)                      | *S. aureus, S. pneumoniae; peptidoglycan                            |
| bacteria           | Schwandner et al. (39)                     | *S. aureus, B. subtilis, Streptococcus sp.; peptidoglycan, lipoteichoic acid |
|                    | Footnote 2                                 | *Listeria monocytogenes*                                            |
|                    | Present study                              | *S. aureus*                                                        |
| Mycobacteria       | Footnote 3                                 | *Mycobacterium tuberculosis; ara-lipoarabinomannan*                 |
|                    | Present study                              | *M. avium*                                                         |
| Spirochetes        | Aliprantis et al. (60)                     | *B. burgdorferi; lipoproteins from T. pallidum and Borrelia*        |
|                    | Hirschfeld et al. (61)                     |                                                                      |
| Mycoplasmas        | Present study                              | Lipopeptide from *M. fermentans*                                   |

Table I: Bacterial strains and compounds reported to activate cells via TLR2

Toxoplasma sp. (21, 25), peptidoglycan, and other cell wall components of *S. aureus* (14, 49), group B streptococci (50), structures from mycobacteria (14, 45, 51, 52), and mannuronic acid polymers from *Pseudomonas aeruginosa* (53). Because it can facilitate responses to all of these bacterial structures listed, CD14 has been termed a pattern recognition receptor by Pugin et al. (14). Yet CD14 lacks specificity in bacterial product recognition, and some controversy exists about whether CD14 is a true pattern recognition receptor (54). The identification of TLR2 in the recognition of most of these pathogens adds another layer of complexity to our understanding of the mammalian response to microbes. In contrast to CD14, TLR2 contains all of the characteristics that one would expect from a true pattern recognition receptor, including the presence of a true signal-transducing intracellular domain. Although only recently described, the list of putative ligands for TLR2 is already impressively large (Table I). Of particular interest is the observation that despite the apparent interactions of TLR2 with many Gram-positive bacteria, group B streptococci do not seem to stimulate cells through this receptor. This highlights the fact that we cannot exclude the involvement of additional receptors, functioning either alone or as part of a receptor complex, in host responses to the microbial structures described.

Although TLR2 has the features of a pattern recognition receptor, it is difficult to define a common microbial pattern among all of these putative ligands. The list of TLR2 ligands is still not complete, and there is no evidence yet that TLR2 is required for sensitive responses to LPS, whereas TLR4 is. Furthermore, the present data do not rule out the possibility that TLR2 may have a more important function in LPS recognition by nonphagocytic cells.

The downstream signaling molecules involved in TLR2-mediated cellular activation have not been definitively defined. However, both TLR2 and TLR4 have a cytoplasmic domain that is homologous to the IL-1 receptor. Thus, it is likely that both TLRs activate the NF-κB pathway, and perhaps other proinflammatory pathways as well, via their interactions with IL-1 receptor signaling genes, including MyD88, TRAF6, and IRAK (11, 58, 59). The similarities in the signal transduction process that appear to constitute the inflammatory response to invasion by a variety of bacteria suggest the exciting possibility that novel therapies directed against the harmful proinflammatory response to nearly all forms of infectious illnesses can one day be developed.

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