The vascular endothelium is a key target of circulating bacterial lipopolysaccharide (LPS). LPS elicits a wide array of endothelial responses, including the up-regulation of cytokines, adhesion molecules, and tissue factor, many of which are dependent on NF-κB activation. In addition, LPS has been demonstrated to induce endothelial apoptosis both in vitro and in vivo. Although the mechanism by which LPS activates NF-κB has been well elucidated, the signaling pathway(s) involved in LPS-induced apoptosis remains unknown. Using a variety of dominant negative constructs, we have identified a role for MyD88 and interleukin-1 receptor-associated kinase-1 (IRAK-1) in mediating LPS pro-apoptotic signaling in human endothelial cells. We also demonstrate that LPS-induced endothelial NF-κB activation and apoptosis occur independent of one another. Together, these data suggest that the proximal signaling molecules involved in LPS-induced NF-κB activation have a requisite involvement in LPS-induced apoptosis and that the pathways leading to NF-κB activation and apoptosis diverge downstream of IRAK-1.

Gram-negative bacterial sepsis is a life-threatening event that affects ~200,000 patients annually in the United States (1). A deleterious outcome of sepsis is the development of septic shock. Endothelial cell (EC) injury and/or dysfunction is a commonality among several key complications associated with septic shock, including systemic vascular collapse, disseminated intravascular coagulation, and vascular leak syndromes (2, 3). The pathogenesis of septic shock and its attendant vascular complications is believed to be mediated, at least in part, by lipopolysaccharide (LPS), a component of the outer envelope of all Gram-negative bacteria (4–6).

LPS directly activates the vascular endothelium and elicits an array of EC responses including the up-regulation of pro-inflammatory cytokines, adhesion molecules, and tissue factor. Many of these responses are mediated by NF-κB (7). The signaling pathway by which LPS activates NF-κB in EC has only recently been elucidated (8). Circulating LPS binds to the acute phase protein, LPS-binding protein (LBP), and this complex is recognized by soluble CD-14 (sCD14) (9). Although the exact mechanism of interaction remains unknown, this LPS-LBP-binding protein-soluble CD14 complex is recognized by the transmembrane receptor, Toll-like receptor (Tlr)-4 (10). The extracellular domain of Tlr-4 contains repeating leucine-rich motifs, and the cytoplasmic portion contains a Toll receptor-interleukin-1 receptor (TIR) domain with homology to the intracellular signaling domain of the type 1 interleukin-1 receptor (11). After Tlr-4 activation, another TIR domain-containing protein, MyD88, is recruited to Tlr-4 through respective TIR-TIR interactions (12, 13). MyD88 also contains a death domain (DD), a highly conserved protein binding domain that facilitates its interaction with another DD-containing signaling molecule, interleukin-1 receptor-associated kinase-1 (IRAK-1) (11). IRAK-1 subsequently autophosphorylates, dissociates from MyD88, and interacts with TNF receptor-associated factor-6 (14, 15). This activates a downstream kinase cascade involving NF-κB-inducing kinase and IκB kinase, resulting in the phosphorylation and degradation of the NF-κB inhibitor, IκB, and the nuclear translocation of NF-κB (11).

Several reports indicate that LPS elicits vascular endothelial apoptosis both in vitro (2, 16–20) and in vivo (21–23). We have previously elucidated an anti-apoptotic signaling pathway involving FLICE-like inhibitory protein (FLIP) that protects human EC from LPS-induced apoptosis (17). FLIP is a cytoprotective protein that is rapidly degraded by the proteosome. In the absence of new protein synthesis, FLIP levels decrease, resulting in sensitization of human EC to LPS-induced apoptosis. Recently, Tlr-4 has been reported to have a requisite involvement in LPS pro-apoptotic signaling (24), similar to its role in mediating LPS-induced NF-κB activation. However, the intracellular signaling pathway through which LPS activates apoptosis remains unknown. We, therefore, decided to investigate whether downstream signaling molecules involved in Tlr-4-mediated activation of NF-κB were similarly involved in mediating apoptosis.

Experimental Procedures

Materials—LPS from Escherichia coli serotype 0111:B4 and polymyxin B were purchased from Sigma. Recombinant human TNF-α was purchased from R&D Systems, Inc. (Minneapolis, MN). The caspase inhibitor peptide, z-VAD-FMK (zVAD) and the protein synthesis inhibitor, cycloheximide, were purchased from Calbiochem-Novabiochem.

Cell Culture—The human dermal microvascular EC line (developed and generously provided by F. J. Candal and Dr. E. Ades, Centers for Disease Control, and Dr. T. Lawley, Emory University, Atlanta, GA) (25) was cultured in RPMI medium (BioWhittaker, Inc., Walkersville, MD) enriched with 10% fetal bovine serum (HyClone Laboratories, Logan, UT) and 100 U/ml penicillin and 100 μg/ml streptomycin.

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*Dedicated to Dr. W. H. Kehoe in honor of his 80th birthday.

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§The abbreviations used are: EC, endothelial cell; LPS, lipopolysaccharide; Tlr, Toll-like receptor; TIR, Toll receptor-interleukin-1 receptor domain; DD, death domain; IRAK, interleukin-1 receptor-associated kinase; FLICE, Fas-associated death-domain-like interleukin 1β-converting enzyme; FLIP, FLICE-like inhibitory protein; zVAD, benzoyloxycarbonyl-Val-Ala-Asp-fluoromethyl ketone; EGFP, enhanced green fluorescent protein; IκBαM, IκBα mutant; D/N, dominant negative; FADD, Fas-associated death domain; TNF, tumor necrosis factor.

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Logan, UT), endothelial cell growth factor provided from bovine hypothy-alamus, l-glutamine (2 mM), sodium pyruvate (1 mM), and nonessential amino acids in the presence of penicillin (100 units/ml) and streptomycin (100 μg/ml) (all purchased from BioWhittaker).

**Cloning and Stable Expression of cDNA Constructs—**cDNA encoding either the DD or TIR domain of MyD88, the DD of IRAK-1 (generous gifts of Dr. Marta Muzio, Mario Negri Institute, Milan, Italy), or the DD of Fas-associated death domain (FADD) (generous gift of Dr. Vishva Dixit, Genentech, Inc., South San Francisco, CA) was cloned into the bicistronic retroviral expression plasmid, pBMMN-IRES-enhanced green fluorescent protein (EGFP) (kindly provided by Dr. Gary Nolan, Stanford University, Stanford, CA) (26). High-titer retrovirus was prepared from the Phoenix amphotropic packaging cell line (ATCC, Manassas, VA) transfected with 24 μg of the expression plasmid by calcium phosphate precipitation. Recombinant retroviral supernatants were collected 48 h after transfection and filtered through a Millex-HV 0.45-μm filter (Millipore Corp., Bedford, MA). For infection, 4 × 10^5 EC were seeded/well of a 6-well plate for 24 h to achieve ~80% confluence. The growth medium was replaced with 2.5 ml of retroviral supernatant supplemented with 32 μg/ml Polybrene and 100 mM HEPES, and the plate was centrifuged for 2 h (1430 g, 37 °C), after which the retroviral supernatant was replaced with normal growth medium. Cells were analyzed and sorted on the basis of EGFP expression using a FACSVantage SE cell sorter (Becton Dickinson Corp., Franklin Lakes, NJ).

**Immunoblotting—**Cell monolayers were washed once with phosphate-buffered saline, lysed with ice-cold modified radioimmunoprecipitation assay lysis buffer (50 mM Tris-HCl (pH 7.4), 1% Nonidet P-40, 0.25% sodium deoxycholate, 150 mM NaCl, 1 mM EDTA, protease inhibitor mixture tablet (Roche Molecular Biochemicals), 1 mM vanadate, 50 mM NaF), scraped, transferred to microcentrifuge tubes, and centrifuged (16,000 × g, 10 min, 4 °C). Total protein was determined using the BCA protein assay (Pierce). The supernatants were combined with 5× sample buffer (Genomic Solutions Inc., Chelmsford, MA) and boiled for 3 min, and 20 μg of protein/lane were resolved by SDS-PAGE on a 20% Tris-glycine gradient gel (Novex Inc., San Diego, CA). A recombinant adenovirus (KZ142) system (gift of Dr. C. B. Wilson (University of Washington, Seattle, WA), The IBeM (S122/S122A) cDNA was generously provided by Drs. J. DiDonato and M. Karin (University of California, San Diego, CA) (30). Construction and purification of IBeM and control (β-galactosidase) recombinant adenovirus were performed as previously described (20). For adenoviral transduction, ECs were seeded into 96-well plates at a density of 50,000 cells/well for 24 h, washed once with medium, and incubated for 48 h at a multiplicity of infection of 1000 with control or IBeM adenovirus in complete EC medium. ECs were washed once with complete medium and subjected to experimental treatment.

**Statistical Methods—**A t test or analysis of variance was used to compare the mean responses between a single experimental group or multiple experimental groups, respectively, and the control group. For experiments analyzed by analysis of variance, the Tukey post hoc comparison test was used to determine between which groups significant differences existed. All statistical analyses were performed using GraphPad Prism version 3.00 for Macintosh (GraphPad Software, Inc., San Diego, CA). A p value of <0.05 was considered significant.

**RESULTS**

**Polymyxin B Inhibits LPS-induced EC Apoptosis—**As the name implies, LPS is comprised of both a polysaccharide and a lipid moiety. It is well established that the lipid A moiety of LPS is responsible for its pro-inflammatory properties (31). Furthermore, this portion of LPS alone activates the Tlr-4 receptor, resulting in NF-κB activation and the up-regulation of pro-inflammatory cytokines (32). To determine whether LPS-induced apoptosis is similarly mediated by lipid A, ECs were exposed to medium or LPS preincubated with or without polymyxin B (Fig. 4). Polymyxin B, derived from the bacterium Bacillus polymyxa, binds and neutralizes the lipid A moiety of LPS (33, 34). Consistent with a role for lipid A in cell activation, neutralization with polymyxin B completely inhibited LPS-induced NF-κB activation (Fig 1A). Similarly, polymyxin B was able to completely block LPS-induced apoptosis (Fig. 1B), suggesting that the pro-apoptotic properties of LPS are local-
Expression of MyD88 D/N inhibits LPS-induced apoptosis. EC were stably transfected with either EGFP vector alone or cDNA encoding either the TIR domain or DD of MyD88 (A–C). An antibody raised against MyD88, which recognizes the TIR domain of MyD88, and an anti-AU1 antibody were used to confirm expression of the TIR-containing MyD88 D/N (A). An anti-hemagglutinin antibody was used to detect hemagglutinin (HA)-tagged MyD88 D/N comprised of the DD alone (A). To confirm the functional efficacy of the D/N constructs, these cells were treated for 4 h with either medium or LPS (100 ng/ml), lysed, and assayed for luciferase activity (B). In other experiments, ECs expressing EGFP vector, the TIR domain of MyD88, or the DD of MyD88 were treated for 8 h with medium, LPS (100 ng/ml), or TNF-α (10 ng/ml) and assayed for caspase activity (C). The vertical bars represent the mean ± S.E. of NF-κB (B) or caspase (C) activity relative to simultaneous media controls. * = significantly decreased compared with EGFP vector-transfected ECs exposed to identical treatment. IB, immunoblot.

Expression of Dominant Negative (D/N) MyD88 Inhibits LPS-induced Apoptosis in EC—MyD88, by virtue of its direct recruitment to Tlr-4, is one of the most proximal intracellular signaling molecules involved in LPS-induced activation of NF-κB. MyD88 contains two distinct protein interaction domains, a TIR domain and a DD, which mediate its ability to bind to Tlr-4 and IRAK, respectively (12). The expression of either domain alone blocks Tlr-4 and mediated NF-κB activation in a dominant negative fashion (8, 12). To determine whether MyD88 mediates LPS-induced apoptosis, ECs were stably transfected with cDNA encoding either the TIR domain or the DD. Expression of these two D/N forms of MyD88 was confirmed by Western blot analysis (Fig. 2A). Furthermore, the functional efficacy of these D/N constructs was confirmed by assaying for the ability of each to inhibit LPS-induced NF-κB activation (Fig. 2B). Expression of either the TIR domain or the DD alone inhibited LPS-induced NF-κB activation by >80%. In experiments conducted in parallel, expression of either MyD88 D/N also inhibited LPS-induced caspase activity, albeit to a lesser extent (Fig. 2C). EC expressing either the TIR domain or the DD demonstrated a ≥30% reduction in caspase activity after LPS exposure than EC-expressing vector alone.

Similar to LPS, TNF-α is a well described activator of EC NF-κB (35). Distinct receptor membrane complexes and proximal intracellular signaling molecules mediate LPS- and TNF-α-induced NF-κB activation; farther downstream, however, the signaling pathways leading to NF-κB activation converge at the level of NF-κB-induced kinase and IkB kinase (36). Consistent with the role of MyD88 in mediating signaling elicited by LPS, but not TNF-α, expression of the MyD88 D/N encoding the TIR domain had no effect on TNF-α-induced apoptosis (Fig. 2C). ECs expressing the MyD88 D/N encoding the TIR domain, however, demonstrated ~15% less caspase activity after TNF-α exposure than ECs expressing vector alone. Although this decrease in caspase activity was subtle, it was statistically significant.

IRAK-1 D/N Inhibits LPS-induced EC Apoptosis—After Tlr-4 activation and MyD88 recruitment, IRAK-1 transiently binds MyD88 and undergoes an autophosphorylation step leading to its activation (12, 14, 15). Optimal activation of NF-κB by LPS is dependent upon functional IRAK-1 (8, 12, 15). To determine whether IRAK-1 has a similar involvement in promoting LPS apoptotic signaling, a truncated form of IRAK-1, reported to function as a D/N, was expressed in EC. Consistent with previous reports (12, 20), expression of the DD alone of IRAK-1 significantly blocked LPS-induced NF-κB activation (Fig. 3A). Expression of this IRAK-1 D/N construct blocked >60% of the
NF-κB activation elicited by LPS. Similarly, the IRAK-1 D/N was able to abrogate LPS-induced caspase activation by ~50% (Fig. 3B). In contrast, the IRAK-1 D/N failed to block TNF-α-induced apoptosis (Fig. 3B).

**FADD Is Not Required for LPS Pro-apoptotic Signaling**—FADD is a pro-apoptotic signaling molecule that couples death receptors to initiator caspases. FADD has been clearly established to mediate apoptosis initiated by several receptors, including those for TNF (37, 38), TRAIL (TNF-related apoptosis-inducing ligand (39, 40)), and CD95L (37, 41). FADD has also been implicated in mediating Tlr-2-induced apoptosis (42). Both Tlr-2 and Tlr-4, which recognize bacterial lipoproteins and LPS, respectively, are highly homologous receptors belonging to the larger family of Toll-like receptors (43). Although each recognizes distinct ligands, Tlr-2 and Tlr-4 utilize a common intracellular signaling pathway that activates NF-κB. To determine whether FADD is required for LPS-induced apoptosis, ECs were transduced with cDNA encoding a truncated form of FADD that has previously been demonstrated to function in a D/N manner (37, 38). Western blot analysis confirmed efficient expression of the FADD D/N construct (Fig. 4A). ECs expressing the FADD D/N displayed equivalent amounts of caspase activity after LPS stimulation as EC-expressing vector alone (Fig. 4B). Consistent with previous studies (37, 38), expression of the FADD D/N construct significantly inhibited TNF-α-induced apoptosis.

**LPS-induced EC Apoptosis Is Independent of NF-κB Activation**—To determine whether NF-κB activation is required for LPS-induced apoptosis, ECs were transduced with a gene encoding mutations in the inhibitor of NF-κB, IκBo, that render it resistant to phosphorylation and degradation (20, 30). Accordingly, expression of the IκBoM significantly inhibited LPS-induced NF-κB activation compared with expression of a vector control encoding β-galactosidase (Fig. 5A). ECs expressing the IκBoM, however, demonstrated equivalent levels of caspase activity after LPS exposure as those ECs expressing vector alone (Fig. 5B). To determine whether caspase activation contributes to NF-κB signaling, ECs were exposed to LPS in the presence or absence of the caspase inhibitor, zVAD. At a concentration that could block 100% of the LPS-induced caspase activity (Fig. 5C), zVAD failed to inhibit LPS-induced NF-κB activation (Fig. 5D). Interestingly, zVAD actually enhanced LPS-induced NF-κB activation by ~40%.

**DISCUSSION**

We have previously established that LPS induces human EC apoptosis by several different criterion including poly(ADP-ribose) polymerase cleavage, nuclear histone release, and DNA laddering (17, 44). To quantify relative changes in apoptosis, we have used a caspase activity assay. Caspases are highly specific effector proteases that are activated during apoptosis and cleave cellular substrates (45). The observed increase in caspase activity after LPS exposure is consistent with previous reports that LPS-induced EC apoptosis is mediated, in part, by caspase-dependent proteolysis of key EC substrates (16, 17, 44).

In the present report, we have established that the lipid A moiety of LPS is responsible for its pro-apoptotic signaling properties. Consistent with its role in activation, neutralization of the lipid A moiety of LPS with polymyxin B inhibited LPS-induced EC apoptosis (Fig. 1A). Similarly, polymyxin B was able to completely abrogate LPS-induced apoptosis (Fig. 1B), suggesting that the lipid A portion of the molecule is responsible for its pro-apoptotic signaling properties. It has previously been reported that LPS-induced apoptosis is dependent on Tlr-4 signaling (24). In that study, the authors demonstrate that macrophages derived from C3H/HeJ mice, which have a missense mutation in the third exon of Tlr-4 (46), were resistant to LPS-induced apoptosis. It has further been established that the domain of LPS recognized by Tlr-4 has a missense mutation in the third exon of Tlr-4 (46), suggesting that the lipid A portion of the molecule is resistant to phosphorylation and degradation (20, 30). Accordingly, expression of the IκBoM significantly inhibited LPS-induced NF-κB activation (Fig. 5A).
lipid A moiety (32). Together, these data imply that the lipid A moiety confers pro-apoptotic signaling through a Tlr-4-dependent pathway. This is consistent with our finding that neutralization of lipid A completely protects against LPS-induced apoptosis.

There has been some controversy in the past regarding whether Tlr-2 or Tlr-4 mediates LPS-induced apoptosis. The genetic evidence clearly indicates that Tlr-4 is the putative receptor for LPS (46). Other studies using overexpression conclude that Tlr-2 recognizes LPS (47, 48). It was later ascertained that certain commercial preparations of LPS were contaminated with bacterial lipoproteins, the latter of which activate Tlr-2 signaling (49). In the present report, highly purified LPS, which was phenol-extracted and purified by ion exchange chromatography, was used for all experiments. The finding that polymyxin B completely blocks LPS-induced NF-κB activation and apoptosis rules out that the EC responses studied were influenced by contaminating lipoproteins.

To investigate whether signaling molecules that link Tlr-4 to NF-κB activation are also involved in mediating LPS-induced apoptosis, D/N versions of MyD88 and IRAK-1 were expressed in EC, and apoptosis was assayed. LPS-induced apoptosis was significantly inhibited by expression of either one of two MyD88 D/N constructs (Fig. 2C) or an IRAK-1 D/N (Fig. 3B). These constructs had minimal or no inhibitory effect on TNF-α-induced apoptosis, consistent with previous reports that TNF-α signaling occurs independently of MyD88 and IRAK-1 (50, 51). Expression of a D/N form of FADD, a pro-apoptotic adapter molecule that links death receptors to initiator caspases, failed to block LPS-induced apoptosis (Fig. 4B). In accordance with the well described role of FADD in promoting TNF-α-induced apoptosis (37), FADD D/N expression significantly inhibited TNF-α-induced caspase activation. It has previously been reported that both MyD88 and FADD contribute to Tlr-2-induced apoptosis. Because LPS has been shown to initiate apoptosis via Tlr-4 (24), the present data suggest differences in pro-apoptotic signaling between different members of the Tlr family. Similar to Tlr-2, MyD88 promotes Tlr-4-induced apoptosis; in contrast, Tlr-4-induced apoptosis occurs independently of FADD.

The MyD88 and IRAK-1 D/N constructs were able to inhibit ≥30 and 50% of the LPS-induced caspase activation, respectively. Expression of the FADD D/N, which has been demonstrated to have a requisite involvement in TNF-α-induced apoptosis (37), inhibited ~50% of the caspase activity elicited by TNF-α. The inability to completely inhibit apoptosis using any of the D/N constructs is not surprising considering endogenously expressed full-length MyD88, IRAK-1, and FADD are still expressed. There is evidence suggesting that Tlr-4 activation of NF-κB can occur through a MyD88- and IRAK-1-independent pathway. First, LPS-induced NF-κB DNA binding activity in macrophages derived from either MyD88 or IRAK-1 knockout mice was delayed, but not inhibited, indicating that cellular activation by LPS can occur in the absence of these signaling molecules (15, 52). Second, a MyD88-like protein has been recently described by two independent groups named MyD88-adaptor-like protein (MAL) or TIR domain-containing adapter protein (TIRAP), which can promote LPS-induced NF-κB signaling through IRAK-2 (53, 54). Whether MAL/TIRAP and/or IRAK-2 mediate LPS-induced apoptosis remains unknown. The existence of alternative activation pathways, which may also be involved in LPS pro-apoptotic signaling, could explain the lower efficacy of the MyD88 D/N in abrogating LPS-induced caspase activation.

Because both MyD88 and IRAK-1 contribute to LPS-induced NF-κB activation and apoptosis, we investigated whether these two events were mutually dependent. NF-κB activation has been classically viewed as a cytoprotective event based on its ability to up-regulate anti-apoptotic proteins (55, 56); however, there are reports that NF-κB signaling has a role in pro-apoptotic signaling as well (57, 58). In the present study, inhibition of NF-κB activation had no effect on LPS-induced apoptosis, and inhibition of caspases failed to down-regulate LPS-induced NF-κB activation, suggesting that these two responses occur independent of one another (Fig. 5). Interestingly, caspase inhibition augmented LPS-induced NF-κB activation. Recently, the p65 subunit of NF-κB has been identified as a substrate of EC caspases (59). Because zVAD-exposed EC demonstrated 30% less caspase activity than EC exposed to medium alone, it is possible that zVAD prevents the degradation of NF-κB under basal conditions, thus increasing the amount of functional NF-κB in the cell. This may account for the enhanced LPS-induced NF-κB activation in EC pretreated with the caspase inhibitor.

In summary, we have identified a pro-apoptotic signaling pathway involved in LPS-induced apoptosis. First, the lipid A moiety of LPS was identified as the portion of the molecule that confers pro-apoptotic signaling. Second, a role for MyD88 and IRAK-1 in mediating LPS-induced apoptosis was established. Third, LPS-induced apoptosis was determined to occur through a FADD-independent pathway. Finally, despite the involvement of MyD88 and IRAK-1 in promoting both LPS-induced NF-κB signaling and apoptosis, these cellular responses were determined to occur independent of one another. We propose that LPS-induced apoptosis is mediated through Tlr-4 and involves the recruitment of MyD88 and IRAK-1. Furthermore, the data presented here suggest that the signaling pathways leading to NF-κB activation and apoptosis diverge downstream of IRAK-1.

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