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Receptors, Mediators, and Mechanisms Involved in Bacterial Sepsis and Septic Shock

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INTRODUCTION 380
SEPSIS AND SEPTIC SHOCK 380
BACTERIAL CELL WALL ARCHITECTURE 381
Lipopolysaccharide 381
Lipoteichoic and Teichoic Acids 383
Peptidoglycan 383
Purification and Aggregate Structure 383
HOST RESPONSE TO CELL WALL CONSTITUENTS 384
Cellular Defense 384
Humoral Defense 385
The Liver 385
Liver cell types 386
Experiments with Radiolabeled Lipopolysaccharide In Vivo 386
Macrophages and the Response to Lipopolysaccharide and Lipoteichoic Acid 386
Detoxification of Lipopolysaccharide 387
LIPOPOLYSACCHARIDE AND LIPOTEICHOIC ACID RECEPTORS 387
Lipopolysaccharide-Binding Protein 388
CD14 388
sCD14 389
Toll-Like Receptors 390
β_2-Integrins 392
Selectins 393
Scavenger Receptors 393
Moesin 394
Heptose-Specific Lipopolysaccharide Receptor 394
LIPOPOLYSACCHARIDE- AND LIPOTEICHOIC ACID-BINDING PROTEINS 394
Neutrophilic Lipopolysaccharide-Binding Molecules 394
Bactericidal/permeability-increasing protein 394
CAP18 394
CAP37 395
Lactoferrin 395
Lysozyme 395
Other Lipopolysaccharide-Binding Proteins 395
Development of Bactericidal and Lipopolysaccharide-Neutralizing Peptides 395
LIPOPROTEINS 395
Metabolism 395
Apolipoprotein E 396
Anti-Inflammatory Role 396
Lipid Metabolism and Infection 398
CLINICAL AND EXPERIMENTAL SEPSIS THERAPIES 399
Immunosuppression and Neutralization of Proinflammatory Cytokines 400
CONCLUDING REMARKS 400
REFERENCES 401

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INTRODUCTION

Throughout the ages, mankind has suffered from diseases caused by microorganisms. These microorganisms often caused severe disease and significantly reduced life expectation. The era of modern microbiology started with the observations by Antonie van Leeuwenhoek at the end of the seventeenth century. Later, Klebs indicated the presence of bacteria in lesions, whereas Koch established that "each infectious disease stems from a specific microbe" and made a pure culture of *Bacillus anthracis*. During these years the first exotoxins, heat-sensitive substances secreted actively by many bacteria and causing illness, were isolated (453). In 1892, Pfeiffer's discovery of a heat-stabile toxin synthesized by *Vibrio cholerae* initiated lipopolysaccharide (LPS) research.

Under normal circumstances, many bacteria live in coexistence with humans. The skin, digestive tract, upper respiratory tract, external urogenital organs, and conjunctiva all contain commensal bacteria that do not cause disease. In particular, the intestinal tract contains billions of bacteria such as *Escherichia coli* that contribute to the function of the intestine. Similarly, bacteria such as *Lactobacillus acidophilus* are involved in maintaining an acidic climate in the vagina while bacteria such as *Staphylococcus epidermidis* on the skin aid in the defense against invading microorganisms through production of several bactericidal substances. The presence of bacteria on or in these organs is not a threat to the body because the nasal and oral cavities, respiratory and digestive tracts, and urogenital organs are connected to the "external environment" and are thus separated from the normally sterile "internal environment."

Pathogenic as well as commensal microorganisms evoke an immune response if they, or their constituents, pass the barrier between the external and internal environment. After recognition of the bacteria or their products, the body launches an attack, kills the bacteria, and repairs putative damage. This sequence of events is highly regulated, enabling the body to combat infection by a tailor-made attack that is fierce enough to eradicate the bacteria but not so fierce as to cause unnecessary damage to the body.

As some of the first living organisms on Earth, bacteria evolved and have been endowed with an enormous capacity to adapt to changes in environment. Bacteria are the result of millions of years of evolution and are—despite their simplicity compared to multicellular organisms—highly refined.

The scope of the review is to discuss the different components of the various bacteria that are involved in the process of sepsis and/or septic shock. The interactions of the various bacterial components with receptors and other proteins are discussed in detail. The consequences of binding of the bacterial components to these receptors and other proteins for the process of sepsis and septic shock is discussed in terms of cellular activation and production of pro- and anti-inflammatory proteins. Finally, some newer therapies for the treatment of sepsis are reviewed.

SEPSIS AND SEPTIC SHOCK

Until the beginning of the 20th century, reports describing infections other than those due to *Salmonella enterica* serovar Typhi (typhoid fever) and *Yersinia pestis* (plague) were rare. Sepsis and septic shock, caused by gram-negative and gram-positive bacteria, fungi, viruses, and parasites, have become increasingly important over the past decades (168). In the United States, the septicemia rates more than doubled between 1979 and 1987 causing up to 250,000 deaths annually (403, 413). In three distinct studies, the proportion of infections due to gram-negative bacteria varied between 30 and 80% and that of infections due to gram-positive bacteria varied between 6 and 24% of the total number of cases of sepsis, with the remainder being accounted for by other pathogenic organisms (168). However, the contribution of gram-positive bacteria to sepsis has increased, and in the early 1990s it accounted for more than 50% of all cases of septicemia (27, 161), with *Staphylococcus aureus* and *S. epidermidis* being responsible for more than half of the cases of sepsis due to gram-positive bacteria (27, 161). The increasing septicemia rates are probably caused by the increasing use of catheters and other invasive equipment, by chemotherapy, and by immunosuppression in patients with organ transplants or inflammatory diseases. Furthermore, improvements in medical care have resulted in longer life spans for the elderly and patients with metabolic, neoplastic, or immunodeficiency disorders. These groups remain at increased risk for infection (42, 44).

Due to differences in interpretation of the clinical condition "septic shock," reported mortality rates in patients with septic shock vary from 20 to 80% (42). The mortality is related to both the severity of sepsis and the underlying disease that is nearly always present (42, 43, 413). In many cases of sepsis, the presence of microorganisms (bacteremia) or LPS in the blood (endotoxemia) cannot be established, which has prompted modification of the definitions of sepsis and septic shock (42, 43, 561). The definitions are as follows: bacteremia, positive blood cultures; sepsis, clinical evidence of infection, tachypnea (>20 breaths/min), tachycardia (>90 beats/min), hyperthermia, or hypothermia; sepsis syndrome, sepsis plus hypoxemia or elevated plasma lactate levels or oliguria; and septic shock, sepsis syndrome plus hypotension (despite adequate volume resuscitation).

The clinical phenomena preceding the development of sepsis and septic shock are highly complex. Paradoxically, as mentioned above, persons with a weakened immune system are most likely to develop sepsis, but the detrimental processes that may ultimately lead to the death of the patient are mostly caused by an exaggerated, systemic response to an infection. The widespread activation of cells responsive to bacteria or bacterial components results in the release of an array of inflammatory mediators, such as cytokines, chemokines, prostaglandins and lipid mediators, and reactive oxygen species. These compounds induce vasodilatation and upregulation of adhesion molecules, resulting in extravasation of neutrophils and monocytes; activation of leukocytes, lymphocytes, and endothelial cells; and myocardial suppression (218, 251, 413, 570). Besides stimulation of coagulation by cytokines, bacterial components may directly interact with the coagulation system. The resulting disseminated intravascular coagulation causes hypoperfusion and hypoxia. Together with the damage caused by the intra- and extravascular phagocytic cells, these conditions lead to organ failure (338, 551). This may initiate the often lethal stage of sepsis, in which multiple-organ failure,

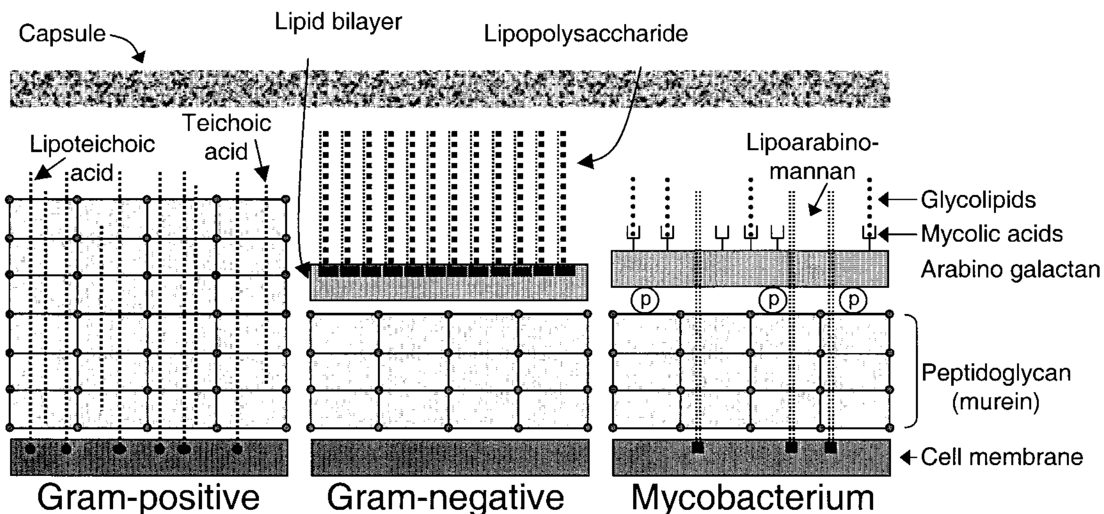

FIG. 1. Cell wall structure of bacteria. All types of bacteria contain a cell membrane surrounded by a PGN-containing layer. LTA and LAM are inserted into the cell membrane of gram-positive bacteria. LPS forms the outer layer of the outer membrane of gram-negative bacteria. The mycobacteria also contain a carbohydrate shell, but not all bacteria contain a capsule.

mostly involving the lungs (acute respiratory distress syndrome), liver, and kidneys, develops (42, 413, 585). In addition, the hypoperfusion caused by disseminated intravascular coagulation may impair the gut mucosal barrier and result in translocation of bacteria to the mesenteric lymph nodes and, under conditions of ongoing stress, to several organs and the circulation. The released bacteria will "feed" the multiple-organ failure and significantly worsen the prognosis (608).

There are marked differences in the responses to gram-positive and gram-negative bacteria. Whereas gram-negative bacteria all contain LPS as their major pathogenic determinant, gram-positive bacteria contain a number of immunogenic cell wall components besides the highly deleterious exotoxins (403, 495). The immunological response to gram-negative bacteria mainly involves leukocytes and the production of cytokines such as tumor necrosis factor alpha (TNF-α), interleukin-1 (IL-1), and IL-6. The release of exotoxins, many of which are superantigens, by gram-positive bacteria activates T cells, resulting in a different cellular response and different cytokine profile, with relatively low levels of TNF-α, IL-1, and IL-6 and increased levels of IL-8 (44, 403, 495).

BACTERIAL CELL WALL ARCHITECTURE

LPS and lipoteichoic acid (LTA) are the main building blocks of the outer leaflets of bacterial cell wall membranes and as such contribute to and are essential for stability and growth. Often they are not directly exposed to the external environment because many naturally occurring gram-positive and gram-negative bacteria are fitted with a thick polysaccharide capsule (455). In Fig. 1, schematic representations of the gram-positive and gram-negative cell walls are shown.

Lipopolysaccharide

LPS is a major constituent of the outer membrane of gram-negative bacteria and is the only lipid constituent of the outer leaflet; a single *E. coli* cell contains approximately 3.5×10^6 LPS molecules (454). Other componentsof the bacterial outer membrane are glycerolphospholipids in the inner leaflet and inner membrane and proteins (e.g., pore proteins such as OmpA in *E. coli*), some of which are firmly associated with the LPS molecules (328). LPS is an essential compound of the cell wall and is a prerequisite for bacterial viability. The LPS molecules is not toxic when it is incorporated into the bacterial outer membrane, but after release from the bacterial wall, its toxic moiety, lipid A, is exposed to immune cells, thus evoking an inflammatory response. LPS and other cell wall constituents are released from the bacterial cells when they multiply but also when bacteria die or lyse (209,209,454). Various endogenous factors like complement and bactericidal proteins can cause disintegration of bacteria, resulting in the release of LPS (82). In addition, some antibiotics are known to cause the release of LPS from bacteria (71).

The LPS molecule consists of four different parts (Fig. 2) (328,443,454). The first and most essential part is lipid A, the covalently linked lipid component of LPS. Six or more fatty acid residues are linked to two phosphorylated glucosamine sugars. Four of these fatty acids carry a hydroxyl group on the third carbon, whereas the other two are not hydroxylated. All bacterial species carry unique LPS, and some of the variations reside in the lipid A moiety: (i) acylation pattern, which is commonly asymmetric (4 + 2), or a symmetric (3 + 3) configuration (e.g., in *Neisseria meningitidis*); (ii) length of the fatty acid residues; typically three or four different fatty acids are present, with a length between 10 and 16 C atoms (average, 14 C atoms); (iii) the presence of 4-amino-deoxy-L-arabinose and/or phosphoethanolamine linked to the phospho groups on the glucosamine sugars; and (iv) The number of fatty acids (most common bacteria contain six fatty acid residues). Experiments with synthetic lipid A have shown that this part of the LPS molecule represents the toxic moiety (274). A number of synthetic derivatives of lipid A (dephosphorylated or deacylated) have been tested in vivo and in vitro, and the potency of these molecules was 10- to 1,000-fold reduced with respect to

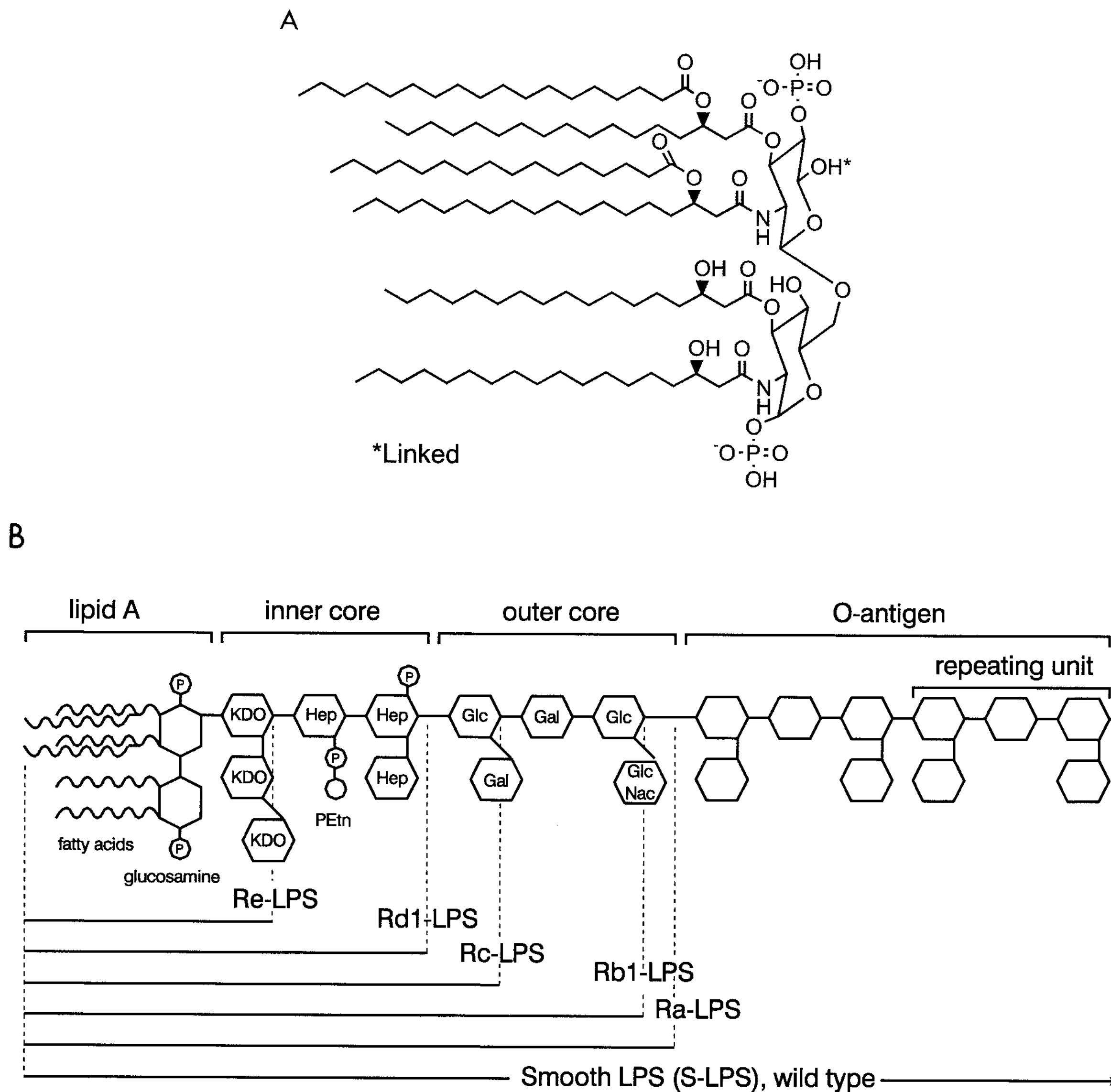

FIG. 2. Structure of lipid A (443) (A) and whole LPS (B). The composition and length of several LPS serotypes are indicated.

the original lipid A molecule (99,325,378). In addition, the lipid a Precursor, lipid IV_A, dose dependently inhibits the effects of lipid A, as shown by reduced TNF-α and prostaglandin E_2 (PGE_2) production in vitro (169). Another lipid A precursor, lipid X, has limited lipid A antagonist activity (169). This illustrates that lipid A-induced cell activation requires a stricter structure than lipid A binding to the receptor per se.

The second part of the LPS molecule is the inner core, which consists of two or more 2-keto-3-deoxyoctonic acid (KDO) sugars linked to the lipid A glucosamine and two or three heptose (L-glycero-D-manno-heptose) sugars linked to the KDO. Both sugars are unique to bacteria. The smallest LPS molecule produced by gram-negative bacteria under natural conditions is Re-LPS (lipid A with one or two KDO sugars), but longer LPS molecules are more common. The Rd1- and Rd2-LPS serotypes contain a complete inner core and an inner core lacking two heptose sugars, respectively.

The outer core, the third part of the LPS molecule, consists of common sugars and is more variable than the inner core. It is normally three sugars long with one or more covalently bound sugars as side chains. LPS serotypes consisting of lipid A and the complete inner and outer core are denoted Ra-LPS, whereas the Rb- and Rc-LPS serotypes only contain a part of the outer core.

The fourth moiety of the LPS molecule is the O antigen. This part of the LPS molecule is attached to the terminal sugar of the outer core, extends from the bacterial surface, and is highly immunogenic. It is composed of units of common sugars, but there is a huge interspecies and interstrain variation in the composition and length. In a single LPS preparation, the length of the O antigen may vary from 0 to as many as 40 repeating units, but it generally consists of 20 to 40 repeating units. Each unit is composed of three sugars with a single sugar connected to the first and third sugar of the unit. LPS mole-

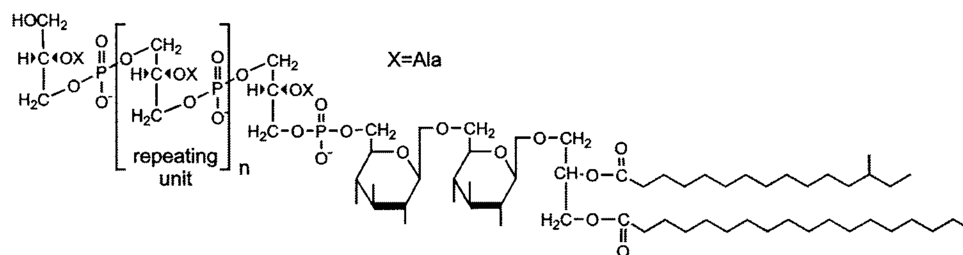

FIG. 3. Structure of LTA from *S. aureus* (131). Ala, alanine.

cules with O antigen are denoted S-LPS. Colonies from bacteria with O-antigen-containing LPS have a smooth (S) appearance on the plate, while bacteria that express an O-antigen-lacking LPS have a rough (R) appearance.

Lipoteichoic and Teichoic Acids

LTA resembles LPS in certain respects and can therefore be considered the gram-positive counterpart of LPS (Fig. 3). It contains a diacylglycerol lipid moiety instead of a phospholipid-like structure as well as highly charged glycerophosphate repeating units, in contrast to the oligosaccharide-repeating units in LPS. Like LPS, LTA is essential for bacterial growth (131). It may be involved in the regulation of the Ca^{2+} and Mg^{2+} ion concentration in the cell wall and in the regulation of the activity of autolytic enzymes, and it may function as a carrier in cell wall teichoic acid synthesis (132, 460). The architecture of the gram-positive cell wall is markedly different from that of gram-negative bacteria, since it contains only a single cell membrane in which LTA molecules are inserted. The outside of the gram-positive cell wall is covered with a thick layer consisting of peptidoglycan (PGN) and teichoic acid (Fig. 1) (95).

The gram-positive bacterial cell membrane contains, in addition to LTA, other lipid constituents such as diglucosyldiacylglycerol, phosphatidylglycerol, diacylglycerol, and lysylphosphatidylglycerol (131, 132). In *Staphylococcus aureus* LTA, two acyl chains (the first generally unbranched and 16, 18, or 20 C atoms in length and the second shorter and often branched) are linked to the 1 and 2 positions of the glucosylglycerol moiety (Fig. 3) (133). Comparison of the basic structure of LTAs from various species has revealed that all LTAs contain a single unbranched polyglycerophosphate chain phosphodiester-linked to the nonreducing hexapyranosyl residue of the diacylglycerol moiety (133). Marked interspecies differences were observed in the length of the acyl chains and in length and the carbohydrate composition of the glycerophosphate tail (130, 212).

A long tail of repeating 1,3-linked glycerophosphate units is connected to the glucoside moiety (131–133). The number of repeating units varies widely, depending on the species, strain, and growth conditions, but generally ranges between 4 and 30 for *S. aureus* (130, 465). D-Alanine may be incorporated at the 2 position of the glycerophosphate tail, but the extent of alanine substitution depends on factors, such as species, strain, growth conditions, and growth stage (130, 131, 272). Various conditions may lead to the release of LTA from the cell wall, including the presence of certain antibiotics (352, 552).

In *S. aureus*, about 50% of the total mass of the cell wall consists of teichoic acid (165). Teichoic acid is composed of long chains of ribitol phosphate units that are partially replaced by ester-linked D-alanine. Teichoic acid is linked to the muramic acid of the cell wall PGNs via phosphodiester bonds (165).

Peptidoglycan

A major component of the cell wall of gram-positive bacteria is PGN, which is—although to a much lesser extent—also found in gram-negative bacteria. The glycan strands of the cell wall consist of repeating disaccharide *N*-acetylmuramic acid-(β1–4)-*N*-acetylglucosamine (MurNAc-GlcNAc) units (165, 384). The glycan strands may vary in length between 5 and 30 subunits, depending on the bacterial species. In most cases, the D-lactyl moiety of each MurNAc is amide linked to the short peptide component of PGN. The tetrapeptides, consisting of L-alanine, D-glutamine, L-lysine, and D-alanine, are cross-linked with other peptides that are attached to neighboring glycan strands, thereby generating a three-dimensional molecular network that surrounds the cell and provides the desired exoskeletal function (165, 384).

Purification and Aggregate Structure

Due to their lipophilic and hydrophilic moieties, LPS and LTA form aggregates in solution. Purified LTA forms simple, spherical micelles with a diameter of approximately 22 nm and consisting of around 150 LTA molecules (131). Due to its conical shape, LTA does not have the capacity to form membranes and therefore needs to be inserted in membranes formed by other lipids like those present in the bacterial cell membrane (131). In contrast, LPS aggregates may form several types of micellar structures due to a larger number of acyl residues in lipid A than in LTA. This results in an increased cross-sectional area of the lipophilic and hydrophilic moieties and a more cylindrical shape. For every LPS serotype, the temperature and ionic strength define its micellar structure that shifts from lamellar to cubic and/or hexagonal (51, 52). The capacity of different LPS serotypes to exert their endotoxic activity (e.g., cell activation) appears to be related to their micellar structure and fluidity (52, 329, 472). The data from Schromm and coworkers provide an explanation for the fact that several LPS serotypes, such as that from *Rhodobacter sphaeroides*, are poor activators or, rather, are LPS antagonists: these LPS serotypes are in the lamellar state under physiolog-

ical conditions which has been shown to correlate with poor agonistic activity (329, 472).

LPS and LTA can be purified using a number of isolation procedures employing phenol and—depending on the LPS serotype—chloroform and petroleum ether, yielding LPS and LTA preparations that may be contaminated with minor amounts of protein, phospholipids, divalent anions, and DNA (66, 152, 367). In particular, the protein contaminants may affect the physiological behavior of LPS, including cellular binding, endotoxic potency, and lipoprotein binding (339, 340, 435, 504, 508). However, bacterial DNA is also able to activate macrophages (483). Similarly, the presence of a minor nonprotein constituent of LTA preparations with stimulatory capacity has been described (283, 284). Most of the contaminants in LPS and LTA preparations can be removed only by reextraction, reversed-phase chromatography, or electrodialysis (151, 340, 488). Under physiological conditions, the LPS or LTA and their contaminants may behave as inseparable complexes impeding the analysis of the contribution of these contaminants to physiological processes (504).

Due to their numerous peptide cross-links, PGNs are isolated from rough cell wall preparations as insoluble fragments that can be broken down to soluble PGN by trypsin-mediated hydrolysis of the peptide bonds (334). Different levels of bioactivity have been described for isolated PGNs, which are up to 1,000 times less active than LPS. However, using the PGN hydrolase of *Streptococcus pneumoniae*, soluble PGN was obtained with bioactivity in the same range as that of LPS (334).

HOST RESPONSE TO CELL WALL CONSTITUENTS

As soon as a bacterium enters the body, it is confronted with two lines of defense: a humoral line and a cellular line. The humoral factors comprise complement, antibodies, and acute-phase proteins. In the cellular line of defense, in particular the mononuclear cells (monocytes and macrophages) and the neutrophils are of great significance since these cells may recognize bacterial cell wall constituents directly or indirectly after complement and antibody bind to the bacterium and its constituents.

Under physiological conditions, the immune cells are continuously exposed to low levels of LPS derived from gastrointestinal bacteria that enter the body via the portal vein. This LPS is taken up by macrophages and may be essential to maintain a basal level of attentiveness of the immune system. At the end of the 19th century, LPS was mainly regarded as an "endotoxin," although Coley showed that heat-killed *Serratia marcescens* caused necrosis and hemorrhage of various tumors as well as causing fever (588). About 40 years later, Shear identified LPS as the agent responsible for the necrosis and hemorrhage. Buchner discovered that the immunological defense system could be nonspecifically activated against infection by injection with bacterial extracts (565, 588). It is now thought that continuous challenges with small amounts of bacterial constituents may be necessary to keep the immune system alert to infections. Indeed, low levels of LPS are present in healthy individuals without causing disease (137, 512, 565).

Cellular Defense

As described in more detail below, LPS and other bacterial (surface) components are recognized by complement and antibodies, leading to opsonisation and lysis of the bacterium. Phagocytes (monocytes, macrophages, and polymorphonuclear leukocytes [PMN]) are able to recognize opsonized bacterial components by complement receptors and Fc receptors (which bind immunoglobulin G [IgG] antibodies) (140). Furthermore, they express receptors that recognize bacterial components. In the host response to bacteria, the mononuclear phagocytes (monocytes and macrophages) are of major importance (365). This was further illustrated in a mouse strain unresponsive to LPS: C3H/HeJ mice. When bone marrow from LPS-responsive C3H/HeN mice was injected into irradiated C3H/HeJ recipients, they became responsive to LPS (363). In addition, C3H/HeJ mice could be rendered sensitive to LPS after injection of macrophages from C3H/HeN mice (147). Recognition of LPS or other bacterial components by these cells initiates a cascade of release of inflammatory mediators, vascular and physiological changes, and recruitment of immune cells. An LPS-activated macrophage becomes metabolically active and produces intracellular stores of oxygen free radicals and other microbicidal agents (lysozyme, cationic proteins, acid hydrolases, and lactoferrin) and secretes inflammatory mediators (214, 353, 456). One of the key mediators is TNF-α (39). After exposure to LPS, TNF-α is one of the first cytokines released by macrophages. TNF-α mRNA is constitutively transcribed in Kupffer cells, allowing rapid release of TNF-α after an inflammatory challenge (175). IL-1 and IL-6 are not constitutively expressed, but the mRNAs of these cytokines, as well as that of TNF-α, are immediately transcribed after a challenge, and maximum mRNA levels have been found 40 min post-challenge in mouse liver macrophages (175, 331).

The release of TNF-α, IL-1, IL-6, IL-8, IL-12, platelet-activating factor (PAF), chemokines, and eicosanoids has profound effects on the surrounding tissue (179, 252, 330, 438). In concert with the complement pathway-derived anaphylatoxins C3a and C5a, several of these inflammatory mediators attract PMN from the circulation and activate them. The extravasation of PMN is enabled by vasodilatation and upregulation of adhesion molecules on endothelial cells, PMN, and macrophages (242, 258, 556). The PMN react to these stimuli by intravascular aggregation, adherence to the endothelium, diapedesis, and the production of inflammatory mediators like TNF-α, leukotriene B_4, and PAF (370, 550). The (activated) PMN express CD14, CD11/CD18, and several complement and Fc receptors and are thus able to recognize and phagocytose LPS, bacterial fragments, and whole bacteria. As specialized phagocytes, PMN produce an impressive series of microbicidal agents, such as lysozyme, bactericidal/permeability-increasing protein (BPI), enzymes, and oxygen free radicals (62, 457). These agents are used mainly for lysosomal killing of microorganisms. However, adherence of the PMN to endothelial cells and the presence of high concentrations of stimuli may also result in the release of microbicidal agents; much of the endothelial damage observed in sepsis is caused by these agents (42). Endothelial cells respond to LPS (via soluble CD14) and to the circulating cytokines by the release of IL-1, IL-6, eicosanoids, the vasoactive agents endothelium derived

relaxation factor and endothelin-1, chemokines, and colony-stimulating factors (CSF) (332). The inflammatory mediators secreted by the different cell populations attract and activate B and T lymphocytes. In turn, the latter release mediators such as IL-2, gamma interferon (IFN-γ), and granulocyte-macrophage (GM)-CSF (42). IL-2 and GM-CSF are involved in proliferation and activation of PMN and mononuclear cells, whereas IFN-γ enhances the effects of LPS on mononuclear cells (4, 42, 206, 241, 610). The actions of the activated immune cells combined with the effects of the inflammatory mediators cause symptoms such as fever, endothelial damage, capillary leakage, peripheral vascular dilatation, coagulation disorders, microthrombi, and myocardial depression. These phenomena may finally result in multiple organ dysfunction, shock, and death (42).

Compared to LPS, relatively little is known about the actions of LTA in vivo and in vitro. In contrast to gram-negative bacteria, in which LPS is the major biologically active moiety, in gram-positive bacteria LTA, PGNs, and exotoxins are highly relevant with respect to the immunological response (403). LTA and PGNs are able to induce the release of nitric oxide (NO), IL-1, IL-6, and TNF-α by monocytes and macrophages and to activate the oxidative burst in vitro (40, 100, 259, 263, 518, 574). Furthermore, the effects of LTA and PGNs may be synergistic (90). Like LPS, the bacterial species largely determines the potency of the biological actions of LTA (40, 259, 261). In vivo both LTA and PGNs cause the release of NO, TNF-α, and IFN-γ and induce circulatory failure (89, 90, 261), which indicates that gram-positive bacterial components such as LTA and PGNs induce similar effects to LPS both in vitro and in vivo.

In vivo challenges with viable and killed bacteria reveal marked differences between gram-positive and gram-negative bacteria in the kinetics of bacterium-induced TNF-α release, and similar differences were observed in vitro (73, 491). In contrast, LPS and LTA exhibit similar kinetics of TNF-α release in vivo (90). Despite the differences between bacteria and LPS, it has recently been shown that *S. enterica* serovar Typhimurium and its LPS induce similar changes in macrophage-gene expression in vitro, confirming the early observations that LPS mimics whole gram-negative bacteria in many respects (462). The pathogenesis of gram-positive bacteria depends to a large extent on the production of powerful exotoxins. Gram-positive bacterial sepsis differs from gram-negative bacterial sepsis in that the gram-positive bacteria often arise from skin, wounds, soft tissue structures, and catheter sites rather than enteric or genitourinary sources. Additionally, gram-positive organisms require a highly orchestrated host response, with intracellular killing by neutrophils and macrophages (403). This is often not the case for gram-negative pathogens, which may be readily killed in the extracellular space by antibody and complement (424, 495). Exotoxins may act as bacterial superantigens, which are potent T-cell-stimulatory protein molecules, produced by for instance *S. aureus* and *S. pyogenes*. These superantigens are able to induce toxic shock syndrome and can sometimes cause multiple organ failure (25, 44). The superantigenic activity of the bacterial exotoxins can be attributed to their ability to cross-link major histocompatibility complex class II molecules on antigen-presenting cells outside the peptide groove with T-cell receptors to form a trimolecular complex (312). Each superantigen is known to interact with a specific V(beta) element of the T-cell receptor. This trimolecular interaction leads to uncontrolled release of a number of proinflammatory cytokines, especially IFN-γ and TNF-α, the key cytokines causing toxic shock syndrome (58). Besides the highly deleterious exotoxins, gram-positive bacteria contain a number of immunogenic cell wall components, such as LTA and PGNs (403, 495).

Humoral Defense

Bacteria activate both complement pathways: *E. coli* polysaccharide surface components (O antigen, capsule, and LPS) trigger the alternative pathway by binding to complement factor 3 (C3) (246, 436, 521). Lipid A binds C1q and activates the classical pathway (609). The classical complement pathway is also activated in the presence of specific antibodies (IgG and IgM) against gram-negative bacterial constituents. In all three cases, C3b is deposited on the molecule or cell surface, which promotes phagocytosis by macrophages and neutrophils and leads to insertion of C5–C9 (membrane attack complex) into the cell surface, in many cases leading to lysis of the bacterium (83, 140). However, long O-antigen chains in gram-negative bacteria or the thick PGN layer of gram-positive bacteria may protect the bacteria from complement-mediated lysis (180). Similar to LPS. LTA activates the classical pathway by interacting with C1 and C1q (324). In addition, erythrocyte bound-LTA activates the alternative complement pathway resulting in lysis of the erythrocytes (229, 578).

With the cleavage of C3 and C5, the chemoattractive and vasoactive agents C3a and C5a are released. They cause increased vascular permeability, upregulate adhesion molecule expression on endothelial cells and neutrophils, and attract and activate these phagocytes. Furthermore, they activate basophilic granulocytes and mast cells: these cells release a variety of vasoactive compounds (such as histamine), facilitating the invasion of phagocytes (116, 223, 280, 370, 434, 457, 521, 550).

During infection, liver parenchymal cells are stimulated by TNF-α, IL-1, and IL-6 to produce acute-phase proteins. These proteins comprise C-reactive protein, serum amyloid A, lipopolysaccharide-binding protein (LBP), serum amyloid P, hemopexin, haptoglobin, complement C3 and C9, α_1-acid glycoprotein, α_2-macroglobulin, and some proteinase inhibitors (129, 476, 498). The expression is differentially upregulated from severalfold (C3 and C9) to even 1,000-fold (C-reactive protein) (129). Some of the acute-phase proteins, like LBP modulate the immune response reactions by activation of phagocytes and antigen-presenting cells, but basically the acute-phase response is considered to alleviate the damage caused during infection (129, 280, 444). Albumin is a so-called negative acute-phase protein since its production is down regulated during inflammation (129).

The Liver

The liver is the largest solid organ in the body, constituting 2 to 5% of the body weight in adults. Via the portal vein, the liver is provided with nutrients from the gastrointestinal tract. A major function of the liver is the uptake of these nutrients

and their subsequent storage, metabolic conversion, and distribution to blood and bile. Of interest for this review, the liver is considered to be of major importance in the body's defense mechanism against bacteria and foreign macromolecules derived from bacteria and microorganisms (92, 270).

Liver cell types. The liver consists of five kinds of cells: liver parenchymal cells (hepatocytes), endothelial cells, fat-storing cells, pit cells, and Kupffer cells. The liver parenchymal cells represent 60% of the liver cells (423). Parenchymal liver cells are metabolically highly active and contain huge numbers of lysosomes, peroxisomes, Golgi complexes, and mitochondria (92). Important and specific metabolic pathways are the urea cycle, regulation of lipid metabolism, production of bile acid in relation to bile secretion, and hormonally regulated glycogenolysis and gluconeogenesis (423). Furthermore, liver parenchymal cells are major producers of plasma proteins (e.g., albumin) and, as mentioned above, acute-phase proteins (129). Sinusoidal endothelial cells account for approximately 19% of all liver cells. In contrast to vascular endothelial cells, these cells have no basement membrane and possess slender processes containing fenestrae, allowing direct contact between the plasma and the cells behind the endothelial barrier. Liver endothelial cells express several receptors that allow the endocytosis of (foreign) ligands, and during a bacterial infection, they produce several cytokines and eicosanoids (82, 278, 452). Fat-storing cells are characterized by the presence of vitamin A-rich fat droplets in the cytoplasm. Some specific functions are uptake and storage of retinoids, as well as synthesis and secretion of extracellular matrix proteins (162). Pit cells are located in the sinusoids and exert natural killer (NK) activity (92). Kupffer cells are the liver macrophages; they are stellate and are situated in the sinusoids, where they are attached to endothelial cells (and parenchymal cells) by their pseudopodia. They constitute 80 to 90% of the fixed tissue macrophages (reticuloendothelial system) and account for approximately 15% of the liver cells. Kupffer cells remove all kinds of old, unnecessary, and damaged material from the circulation (immune complexes, erythrocytes, tumor cells, cellular debris, and apoptotic cells) (485, 530, 571). In addition, they remove foreign materials from the blood with high efficacy (92, 278). In relation to the defense against bacteria and bacterial components, Kupffer cells are highly relevant (270, 530), playing a major role in both clearance and detoxification of LPS from the circulation (especially the portal vein) and the production of inflammatory mediators in response to LPS (85, 139, 482, 530, 571).

Experiments with Radiolabeled Lipopolysaccharide In Vivo

Klein et al. injected radiolabeled, live *E. coli* into the femoral vein of rats (270). At 5 min after injection, 80% of the bacteria had already been taken up by liver cells and the rest of the bacteria could be found in the lungs, spleen, and blood. Uptake was followed by degradation, which was almost complete after 24 h (270). However, the clearance of bacteria is species and strain specific, with generally higher residual levels for virulent strains than for avirulent strains (41). Mathison and Ulevitch injected rabbits intravenously (i.v.) with 250 μg of either *E. coli* O111:B4 S-LPS or *S. enterica* serovar Minnesota Re595 Re-LPS and observed a rapid serum decay ($t_{1/2} < 30$ min) and high clearance capacity of the liver (346). In an electron microscopy study by Van Bossuyt et al., at 5 min after the injection of radioactive *S. enterica* serovar Abortus-equi S-LPS into the portal vein, maximal association with Kupffer cells was observed (542). The association gradually decreased over 3 days, but increasing association with liver parenchymal cells was detected several hours after injection of the LPS and was paralleled by excretion of radioactivity into the bile. Mathison et al. obtained similar results (346). Freudenberg et al. observed that injected *S. enterica* serovar abortus-equi S-LPS bound to Kupffer cells and granulocytes (145, 149). Also in these experiments, LPS was redistributed from Kupffer cells to liver parenchymal cells. Although in general the decay of LPS in serum was rapid, with $t_{1/2}$ varying between 15 min and 3 h depending on the route of administration, dose, and animal used, bioactive LPS could be recovered from plasma for a long time (346, 432, 466). Using radioiodinated Re595-LPS, we found rapid decay in serum ($t_{1/2} < 5$ min) and a high liver uptake predominantly due to uptake by the liver Kupffer and endothelial cells (75%), showing that the liver binding and decay in serum may vary with the LPS serotype and preparation used (146, 557).

Macrophages and the Response to Lipopolysaccharide and Lipoteichoic Acid

Macrophages play a pivotal role in the cellular response to LPS. The reticuloendothelial system consists of specialized tissue macrophages responsible for the primary response to microorganisms in most tissues. As described above, an immune reaction is aimed at eradicating the invading microorganism (lysis, phagocytosis) and preventing the spread of microorganisms and their toxic components or products (coagulation) to the rest of the body. It has been shown that macrophages are able to remove endotoxin and bacteria from the lymph and blood circulation and respond to the binding of LPS by the production of inflammatory mediators. The cells of the reticuloendothelial system have acquired tissue specific characteristics, which result in differences in their response to LPS. On challenge with LPS, LTA, or other bacterial components, macrophages release a series of inflammatory mediators such as TNF-α, IL-1, IL-6, eicosanoids, PAF, NO, and reactive oxygen. Not only free LPS, LTA, and PGN but also live and killed bacteria can elicit the release of TNF-α (21, 73, 178, 262, 400, 491). The lipid mediators—eicosanoids and PAF—released by the macrophages and liver sinusoidal endothelial cells have important functions as well (197, 230, 254, 279). Besides the vasoactive functions of these agents (368, 369), PGE_1 and PGE_2 inhibit the transcription of TNF-α mRNA in macrophages, resulting in a long-term inhibition of TNF-α release (175, 317, 389, 458). The last group of products released in response to LPS are the reactive oxygen species. Activation of macrophages and infiltrating PMN by bacterial components and by TNF-α and other inflammatory mediators induces the intracellular production of O_2^-, H_2O_2, and other potent microbicidal products (32, 361). Although these compounds are responsible for killing phagocytosed microorganisms, they are released at high concentrations of activators and cause extensive tissue damage. Nitric oxide (NO) is a microbicidal product which is produced by macrophages, endothelial

cells, and hepatocytes. Once secreted, it is rapidly converted to nitrate and nitrite and has a wide range of physiological effects (74, 298, 406, 493). Besides its (beneficial) microbicidal and tumoricidal effects, NO causes vasodilation, endothelial damage, damage to hepatocytes, inhibition of acute-phase protein production, and increased leukocyte adhesion in liver and lungs (85, 213, 237, 575).

Gadolinium chloride ($GdCl_3$) causes a transient depletion of the large, ED2-positive Kupffer cell fraction in rats (81, 192). Administration of $GdCl_3$ reduces death and hepatic damage in rats treated with a lethal dose of LPS but does not prevent TNF-α production (231). Bautista et al. described a similar technique with liposome-encapsulated dichloromethylene biphosphonate (Cl_2MBP); this reagent eliminated 90% of the largest Kupffer cell fraction and 50% of the smaller Kupffer cells (33). In addition, macrophages in the spleen are depleted after injection of these liposomes whereas circulating monocytes are spared (558). After i.v. injection of LPS into Cl_2MBP-liposome treated rats, serum TNF-α levels were significantly reduced (33). Similar decreases in TNF-α, IL-1, and IL-6 production in liver slices from Cl_2MBP-liposome treated mice were observed (331).

An in vitro study with splenic macrophages and Kupffer cells has shown that splenic macrophages produce significantly more LPS-induced TNF-α than do Kupffer cells but that the latter phagocytose more latex beads in vitro and in vivo (486). In addition, Lichtman et al. showed that there are major differences in the activation pathway between peritoneal macrophages and Kupffer cells (316). Whereas the response of peritoneal macrophages to LPS was dependent on CD14 (see the section on LPS and LTA receptors, below), a mainly CD14-independent activation pathway was utilized in Kupffer cells. The route of LPS entry into the body may also alter the immune response. Asari et al. have shown that the peak TNF levels and the kinetics of TNF release after intraperitoneal (i.p.) versus i.v. injection differ, confirming that the macrophages from relevant organs respond differently (13).

Detoxification of Lipopolysaccharide

There are several lines of evidence that LPS is processed after uptake by macrophages and PMN. Several investigators observed the displacement of LPS from Kupffer cells to hepatocytes after incubation times varying from several hours to days, indicating preferential binding of native LPS to Kupffer cells and preferential binding of Kupffer cell-released LPS to liver parenchymal cells (139, 148, 543). Indeed, the observation that LPS, both modified and unmodified, binds to liver parenchymal cells may indicate that these cells are involved in the clearance of LPS from the circulation (94, 412). This is confirmed by the observations that LPS or LPS metabolites are excreted in bile and feces (138, 542). One of the intracellular degradation pathways may be the removal of fatty acids by acyloxyacyl hydrolase. This enzyme is present in the lysosomes of PMN and macrophages (253, 327, 373). Deacylated LPS probably has decreased biological activity (148, 188, 426, 450, 543) and actually antagonises the actions of native LPS (268, 316). A second method of processing may be digestion of the O antigen. LPS released by Kupffer cells showed a decreased sugar/lipid ratio compared to native LPS (138, 139). Hampton and Raetz described the dephosphorylation of LPS after binding to the scavenger receptor (186). Like deacylated LPS, dephosphorylated LPS appears to have a decreased biological activity (99). Poelstra et al. proposed that alkaline phosphatase is involved in detoxification of LPS (425). Treatment of LPS with alkaline phosphatase results in dephosphorylation in vitro, whereas blocking of alkaline phosphatase in vivo causes an enhanced sensitivity to *E. coli* in mice (425). Treon et al. isolated LPS that was released by Kupffer cells (531a). The Kupffer cell-released LPS exhibited a higher binding to liver parenchymal cells and a markedly reduced induction of TNF-α production by peritoneal macrophages. Furthermore, binding to the liver hepatocytes could not be inhibited by excess amounts of LPS, indicating that the LPS structure had been changed significantly (139). However, the nature of the changes and the receptors responsible for the uptake of the modified LPS were not identified.

TABLE 1. LPS and LTA receptors and some of their ligands

Receptor	Ligand(s)
CD14 and TLR	LPS, LTA, PGN, other microbial constituents, apoptotic cells
β_2-Integrins	C3bi, C3b, ICAM-1, LPS
SR-A	Oxidized LDL, apoptotic cells, LPS, LTA
MARCO	Bacteria
L-selectin	GlyCAM-1, CD34, MAdCAM-1, Sgp200, LPS, LTA
P-selectin	PSGL-1 (Sialyl Lewis^x moiety), LPS
Heptose receptor	LPS

LIPOPOLYSACCHARIDE AND LIPOTEICHOIC ACID RECEPTORS

Over the past 20 years, one of the major aims in LPS research has been the elucidation of the sequence of events between the binding of LPS to a cell and the response of the cell. One of the first LPS receptors to be characterized was the CD11b/CD18 or CR3 receptor (593). Binding of LPS-coated erythrocytes to PMN is mediated through this receptor. However, it turned out that the cells were not sufficiently activated through the CD11b/CD18 receptor, and the quest for identification of the cell-activating LPS receptor was continued. In 1990, CD14 (previously known only as a monocyte-specific antigen) was identified as the receptor involved in cellular activation (596). However, because CD14 lacks a transmembrane signaling domain, the involvement of an accessory receptor was proposed. Quite recently, the Toll-like receptors (TLR) were identified as the putative signaling receptor for LPS, LTA, and a variety of other microbial constituents (428). Although the precise nature of the CD14-TLR interactions has not been clarified, the events occurring after binding to the TLR are now being unraveled. In this section the various receptors involved in the uptake of, and in some cases activation by, LPS and LTA are described in further detail. The serum proteins LBP and soluble CD14 function as accessory receptors and are therefore also described in this section. Other LPS- or LTA-binding serum constituents are described in the next section. LPS and LTA receptors are listed in Table 1, along with some of their ligands.

Lipopolysaccharide-Binding Protein

LBP was first isolated from rabbit acute-phase serum by Tobias et al. (526). They observed differences in the binding of LPS to high-density lipoprotein HDL in normal and acute-phase serum and discovered that LPS in acute-phase serum was mainly complexed with a protein. The LBP was recovered from serum as a 58- and 60.5-kDa protein, the difference in molecular mass reflecting different degrees of glycosylation (444, 526).

LBP is an acute-phase protein (473, 476) and is induced by IL-6 and IL-1 (176, 444, 572). Besides the liver, the lungs, kidneys, and heart are also involved in the production of LBP (506). The constitutive levels of LBP in serum are low (1 to 15 μg/ml) but increase greatly during infection (155, 289, 474, 476, 528). In humans during the acute phase of trauma or sepsis, LBP levels are at a maximum on days 2 to 3 (476). Most of the LBP in serum is associated with lipoproteins, and LBP in serum is mainly associated with low-density lipoprotein (IDL), very-low-density lipoprotein (VLDL), or HDL (414, 569, 600).

LBP binds to smooth and rough LPS, lipid A, and lipid IV_A. The affinity of LBP for lipid A is high, with the K_d varying from 1 to 58 nM (158, 527). The binding site for lipid A is situated in the N-terminal part between amino acids (aa) 91 and 108, with positively charged arginine and lysine residues within this region fulfilling an essential role (290, 519). The C-terminal part of the LBP molecule, however, mediates the transfer of LPS to CD14 (187, 522). The binding of LBP to killed bacteria is markedly higher than the binding to living bacteria (307).

LBP catalyses the transfer of LPS to CD14, thus enhancing the LPS-induced activation of monocytes, macrophages, and PMN by 100- to 1,000-fold (475). The CD14-mediated activation of peritoneal macrophages by heat-killed *Staphylococcus aureus* bacteria, LTA, cell wall PGN, or mycobacterial lipoproteins is not enhanced by LBP (345, 357, 478, 524). In the presence of LBP, LPS induced an enhanced intracellular killing and secretion of TNF-α and NO by murine macrophages (68), increased adherence of human PMN to endothelial cells (590), LBP and CD14 release by HepG2 human hepatoma cells (383), and release of tissue factor by THP-1 cells in vitro (500), whereas the addition of anti-LBP or anti-CD14 antibodies abrogated the effect of LBP (154, 500, 590). Application of anti-LBP antibodies together with LPS protected D-galactosamine-sensitized mice from death (155, 156, 307a).

Besides its proinflammatory role, LBP may also have anti-inflammatory actions, such as the LBP-mediated catalysis of LPS and LTA transfer to HDL and other lipoproteins (see the section on lipoproteins below). (177, 526, 600, 602). Recently, LBP was shown to be involved in the neutralization of LTA by HDL, extending the anti-inflammatory role of LBP to gram-positive organisms (177). Interestingly, as mentioned above, LBP is not essential for binding of gram-positive cell wall components to CD14 while promoting the neutralization of LTA by lipoproteins, suggesting a solely anti-inflammatory function in the response to gram-positive organisms. The injection of LBP into D-galactosamine-sensitised mice decreased LPS-induced TNF and IL-6 release and significantly reduced mortality, and LBP was also found to be protective during an infection with live *E. coli* (289). Interestingly, Jack et al. observed that LBP knockout mice were less susceptible to a challenge with LPS but more susceptible to live *S. enterica* serovar Typhimurium (240), which is in line with the putative protective effect of LBP during bacterial infection. Wurfel et al. observed the absence of a response to LPS in whole blood from LBP knockout mice (601).

LBP binds certain phospholipids, which relates to its structural homology to other lipid-binding proteins like phospholipid transfer protein (PLTP), which is able to transfer LPS to HDL (182, 414, 612). By analysis of sequence homologies, it was found that LBP belongs to a family of lipid-binding proteins also containing BPI, PLTP, and cholesteryl ester transfer protein (3, 224, 266, 287).

CD14

LPS binding to and activation of mononuclear cells from CD18-deficient patients indicated the presence of additional receptors on macrophages and PMN (592, 597). The addition of anti-CD14 antibodies prevented binding of the LPS-coated erythrocytes to macrophages and decreased LPS-induced TNF-α release (596). Transfection of CD14-negative CHO and 70Z/3 cells with CD14 conferred responsiveness to LPS and positively identified CD14 as an LPS receptor (170, 302). Kirkland et al. determined the binding affinity of the LPS-LBP complex to CD14-transfected CHO cells and THP-1 cells and found K_d values of 2.7×10^{-8} to 4.8×10^{-8} M (265). The mechanism of LPS binding to CD14 is shown in Fig. 4.

Mice transgenic for human CD14 are three times more sensitive to LPS than are wild-type mice (128). In contrast, CD14-deficient mice are highly resistant to a challenge with LPS (200). However, the CD14-deficient mice were less sensitive to a challenge with live gram-negative bacteria, due to the accelerated clearance of bacteria by PMN (200, 201). The clearance of live *S. aureus* and the TNF-α levels were even higher in CD14-deficient than in wild-type mice after a challenge with live *S. aureus*, indicating that CD14 is not of great importance in the in vivo defense against these gram-positive bacteria (202). Anti-CD14 antibodies applied to LPS-treated rabbits and cynomolgus monkeys decreased hypotension, neutropenia, TNF-α release, and organ damage, indicating that blocking of CD14 in severe endotoxemia could protect against the detrimental effects (308, 468).

Because CD14 is a glycosylphosphatidylinositol-linked receptor that lacks a transmembrane domain, it probably needs an accessory molecule for signal transduction (499). This hypothesis was confirmed using different anti-CD14 antibodies that either blocked LPS binding to CD14, or did not block LPS binding while preventing LPS-induced cell activation (163, 303). The accessory receptor has been identified as being a member of the TLR family.

Binding of LPS to a cell does not result in an immediate response. A time lapse of 15 to 30 min between LPS binding and LPS-induced responses such as cytokine release and adhesion was observed, which suggests that a time-consuming process such as internalization is necessary to enable signaling (93, 315). Indeed, several, but not all, studies have revealed that blocking internalization or endosome fusion also blocks LPS-induced signaling (93, 315, 427, 431). Although the precise mechanisms are not completely understood, it has been shown that monomeric LPS is transported into the cell to the

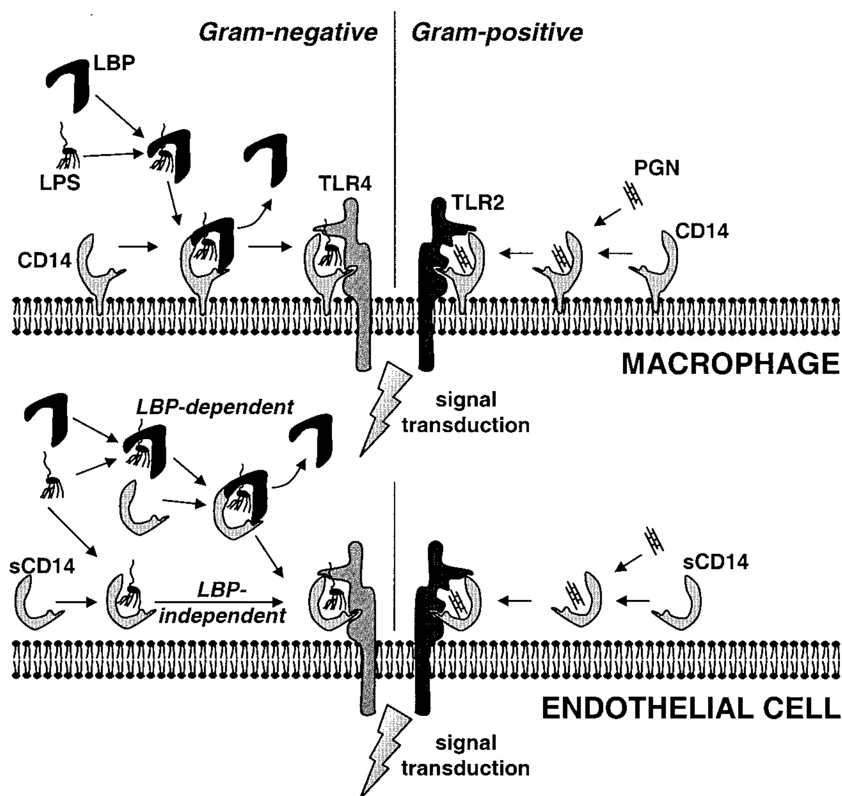

FIG. 4. Binding of bacterial ligands to CD14 and sCD14. The involvement of LBP, (s)CD14, and TLR2 and TLR4 in the activation of CD14-expressing cells (e.g., macrophages) and of cells that do not express CD14 (e.g., endothelial cells) is shown. LPS (left) and PGN (right) represent TLR4- and TLR2-specific ligands, respectively.

Golgi complex, thus activating the cell. In contrast, particulate (bacterium) or aggregated (micelles) LPS is transported through a CD14-dependent pathway to the lysosomes without activating the cell (461).

Although LPS was the first CD14 ligand discovered, many other microbial ligands for CD14 were later identified. These are also ligands for the TLRs, and these are discussed below. Molecular cloning of the CD14 gene revealed a 1.4-kb transcript encoding a 356-aa protein (126). CD14 is glycosylphosphatidylinositol linked and has a high leucine content (17.7% human CD14, 15.5% murine CD14) (484). A repeating leucine-rich, 24-residue motif (LxxLxLx) can be recognized (127, 484). The LPS-binding site and the sites involved in the interaction of CD14 with the putative accessory receptors have been identified in the N-terminal part of CD14 (250, 613). Two putative LPS-binding sites were mentioned: aa 39 to 44 (501) and aa 57 to 64 (248, 355). Stelter et al. also measured the LPS- or *E. coli*-induced activation and found that the substitution mutant with substitution at aa 39 to 44 was not capable of inducing activation (501). Two other regions essential for sCD14-mediated signaling of endothelial and smooth muscle cells were also identified: aa 9 to 13 and aa 91 to 101 (249, 502).

CD14 is expressed by cells of the myeloid lineage (monocytes, macrophages, and PMN), B cells, liver parenchymal cells, gingival fibroblasts, and microglial cells (9, 322, 383, 421, 507, 616). Differential expression of CD14 is observed: peritoneal and pleural macrophages have a high level of constitutive CD14 expression, whereas (murine) Kupffer cells, alveolar macrophages, monocytes, and PMN have a low level of constitutive CD14 expression (9, 341, 350, 617). CD14 is absent from early progenitor (myeloid) cells, but CD14 expression increases with maturation (164). In vivo challenge of mice with LPS results in up regulation of CD14 on Kupffer cells but also in the heart, lungs, spleen, and kidneys (119, 350). Human PMN express low levels of CD14, but the expression can be upregulated by TNF-α, granulocyte (G) CSF, GM-CSF and fMLP (formyl-Met-Leu-Phe) within 20 min, indicating that the CD14 originates from intracellular stores (205, 595).

sCD14

In 1986, the excretion of the MY-4 antigen (CD14) by monocytes was observed (36). The glycoprotein was later found to be the soluble form of CD14: sCD14 (98, 285). In addition to macrophages, liver parenchymal cells are involved in the release of sCD14 (322, 383, 505). The release of sCD14 by mononuclear cells and PMN is dose dependently induced by LPS and TNF-α, whereas IFN-γ and IL-4 inhibit the release of sCD14 (291, 477). In the steady state, the concentration of sCD14 is 2 to 6 μg/ml in human serum (528). In septic shock patients, sCD14 levels are increased, the levels have been found to correlate with mortality (292). Active soluble CD14 was also found in human milk at 10-fold-higher concentrations than in serum. The milk sCD14 may play a role in the bacterial colonization of the gut (286).

Endothelial and epithelial cells do not express membrane

CD14 and become up to 10,000-fold more sensitive to LPS in the presence of serum (Fig. 4). The LPS sensitivity can be blocked by anti-CD14 or by immunodepletion of sCD14 from the serum (150, 566). Presentation of sCD14-LPS to endothelial or epithelial cells results in up regulation of adhesion molecules, excretion of IL-6 and IL-8, and endothelial damage (150, 433, 566, 616) The role of LBP in the transfer of LPS to sCD14 is unclear (433).

In addition to its proinflammatory actions, sCD14 exerts anti-inflammatory actions. First, it accelerates the LBP-mediated transfer of LPS to HDL, but it has been found to be inessential in this process (599, 612). Second, injection of sCD14 into LPS-challenged mice is protective against LPS-induced death (204), although in a similar experiment by Stelter et al., sCD14 provided less protection, with significant decreases in mortality but not in cytokine release and organ damage (503). In both experiments, the amount of sCD14 injected was approximately 25-fold greater than the endogenous sCD14 levels. In vitro experiments revealed that moderate concentrations of sCD14 enhanced the LPS-induced activation of monocytes, macrophages, and PMN (183, 533) whereas inhibition of LPS-induced activation was observed at higher sCD14/LBP ratios (203, 477, 533).

Toll-Like Receptors

Due to the absence of a transmembrane signaling domain in CD14 and the necessity for a signaling receptor for sCD14, the presence of an additional molecule involved in LPS binding and signaling was expected. This putative signaling receptor was found after the cloning of the defective gene in the LPS-unresponsive C3H/HeJ and C57BL/10ScCr mice (428, 430, 441). This molecule turned out to be Toll-like receptor 4 (TLR4), named after the homologous Toll protein in *Drosophila melanogaster* (359, 439). The putative signaling pathway components in mammals and *Drosophila* are CD14 → TLR4 → MyD88 → IRAK → TRAF6 → IκB → NF-κB for inflammatory mediators and Spàtzle → Toll → Tube → Pelle → dTRAF → Cactus → Dorsal for antimicrobial peptides, where IRAK is IL-1R-associated kinase and TRAF6 is TNF receptor-associated factor 6 (49, 439). To date, TLR1 to TLR10 have been identified and are all expected to be involved in immune responses (63, 376, 400a). The TLRs, the IL-1 receptor, the IL-18 receptor, and a number of mammalian and nonmammalian proteins exhibit a striking similarity with respect to the Toll/IL-1 receptor domain (TIR); hence, this family of receptors is called the TIR superfamily (400a). Three major groups can be determined: the immunoglobulin domain subgroup, containing the IL-1RI and the IL-18R; the leucine-rich-repeat subgroup, containing the TLRs; and the adaptor subgroup, which includes the MyD88 protein essential for TLR2 and TLR4 mediated signaling (400a).

So far, the specificities of TLR2, TLR3, TLR4, TLR5, and TLR9 (partially) have been shown to be involved in recognition of microbial components. A substantial amount of data suggests that TLR4 is involved mainly in the recognition of LPS from gram-negative bacteria. TLR2 recognizes gram-positive cell wall constituents such as PGN and LTA but also recognizes microbial lipoproteins and lipopeptides and yeasts. In addition, TLR3 recognizes viral double-stranded RNA

TABLE 2. Microbial ligands of the TLRs

Receptor	Origin	Microbial ligands
TLR2	Gram-positive bacteria	Peptidoglycan (478, 611) and LTA (478)
	Gram-negative bacteria	LPS proteins (216, 301), LPS from *Leptospira interrogans* (587) and *Porphyromonas gingivalis* (22)
	Mycobacteria	Lipoarabinomannan (356), cell wall (538) and lipoproteins/lipopeptides (53)
	Borrelia burgdorferi	Lipoproteins/lipopeptides (215, 320)
	Treponema spp.	Glycolipids (405, 471) and lipoproteins/lipopeptides (320)
	Mycoplasma spp.	Lipoproteins (320) and lipopeptides (515)
	S. aureus	Phenol-soluble modulin from *S. aureus* (184)
	S. pneumoniae	Cell wall (611)
	Group B streptococci	Soluble factor (GBS-F) (211)
	Neisseria meningitidis	Porins (344)
	Yeast (zymosan)	Complete cells (537)
	Human protein	Heat shock protein 70 (14, 541)
TLR3	Virus	dsRNA (6)
TLR4	Gram-negative bacteria	LPS (221, 428, 441)
	Gram-positive bacteria	LTA (514)
	Mycobacteria	Heat-sensitive compound (357)
	Chlamydia pneumoniae	Heat shock protein 60 (55)
	Respiratory syncytial virus	F protein (282)
	Treponema brennaborense	Glycolipids (471)
	Human protein	Heat shock protein 60 (396)
	Human protein	Heat shock protein 70 (14, 541)
TLR5	Bacteria with flagella	Flagellin (199)
TLR9	Bacteria	CpG DNA (210)

dsRNA, TLR5 recognizes bacterial flagellin, and TLR9 recognizes bacterial CpG DNA (references are given in Table 2). Of the remaining TLRs identified, TLR1 may function as an accessory receptor for TLR2 in the recognition of *Neisseria meningitidis* cell wall components, whereas other investigators observed the heterodimerization of the signaling domain of TLR2 with either TLR1 or TLR6, enabling the recognition of zymosan, group B streptococcal soluble factor, or gram-positive lipopeptides and lipoproteins (211, 407, 516, 603). In the response to *S. aureus* modulin, however, TLR1 inhibited and TLR6 enhanced the TLR2-mediated response, indicating a modulatory role for these proteins (184). This is confirmed by the findings of Spitzer et al., who observed the inhibition of TLR4-mediated responses by TLR1 in endothelial cells (494). A similar role could be envisioned for some other TLRs for which no microbial specificity has been determined.

Some contradictory results with regard to receptor specificities were obtained. The LTA-induced activation through TLR4 instead of TLR2 was also reported (349, 513), as well as the LPS-induced activation through TLR2 instead of TLR4 (267, 606). The latter has been clarified, because repurified

LPS, totally devoid of associated endotoxin protein, activated cells through TLR4 but lacked TLR2 binding (216). However, LPS from *Leptospira interrogans* (587) and *Porphyromonas gingivalis* (22) have been found to act exclusively through TLR2. LPS from the LTA-induced activation through TLR2 was observed in overexpression experiments (478). In contrast, the lack of a response to LTA was observed in TLR4-deficient mice, whereas TLR2-deficient mice were responsive to LTA (513). Unidentified cofactors in the overexpression experiments may hamper the accurate characterization of ligand specificity, which is not the case for the knockout models (5).

The activation of cells by microbial components is dependent on CD14 (myeloid cells) or sCD14 (endothelial and epithelial cells). It has now been shown that the microbial components interact primarily with CD14 and subsequently with the TLRs. In fact, by using photoactivated cross-linking, it was shown that LPS becomes cross-linked to TLR4 and MD-2 only if the latter are coexpressed with CD14 (79). The extracellular protein MD-2 is closely associated with TLR4 and is essential for LPS binding to this receptor (487).

The role of sCD14 in TLR-mediated signaling has not been specifically addressed. In several of the TLR-overexpression studies in vitro, however, serum was found to enhance activation by the microbial components and the activation could be (partially) inhibited by the addition of anti-CD14 antibodies (118, 215, 320). This reveals that sCD14 in serum can replace surface-bound CD14 and that CD14-mediated signaling is not significantly different in myeloid cells expressing membrane CD14 and other cell types that are dependent on sCD14. However, in deletion and substitution studies with membrane, CD14 and sCD14, the same binding site for LPS, but different sites for mCD14 and sCD14-mediated signaling were found (502, 563). Whether these differences actually reflect the involvement of distinct accessory receptors (e.g., TLRs) remains to be determined.

Human TLR4 is an 841-aa protein with a molecular mass of 92 kDa, whereas TLR2 is an 85-kDa protein (359, 614). A structural similarity between CD14 and the TLRs is the presence of a leucine rich-repeat (LRR) in the extracellular domain. CD14 and TLR4 contain 10 and 21 of these LRR moieties, respectively, which suggests that both receptors may contain a similar binding site for LPS (127, 359). In contrast to TLR4, the binding site in CD14 is only partially situated in the LRR region (248, 250). An acyclic LPS agonist exhibited TLR4-mediated binding which was independent of LBP and (s)CD14, although sCD14 strongly enhanced the cellular response (318). In addition, the proximity of LPS-CD14-TLR4 prior to signaling has been illustrated (244). Poltorak et al. showed that C3H/HeJ macrophages (expressing a nonfunctional TLR4) transfected with either human or murine TLR4 responded differently to LA-14-PP (deficient in secondary acyl chains): whereas the cells transfected with murine TLR4 produced TNF-α, the cells transfected with human TLR4 were not activated (429). The authors proposed that LPS physically interacts with TLR4, enabling this molecule to discriminate between lipid A and the partially deacylated LA-14-PP. Similarly, human THP-1 ($CD14^+$) cells transfected with hamster TLR4 responded to *Rhodobacter sphaeroides* LPS whereas the same cells transfected with human TLR4 did not (319).

Several approaches using knockout mice or cell lines transfected with mutated putative signaling proteins have pinpointed important participants in the signaling pathway. Defective proteins such as MyD88 (255, 513, 515, 614), IRAK (607, 614), TRAF (607, 614), and NIK (NF-κB-inducing kinase) (607), resulted in blocked or muted responses to gram-positive and/or gram-negative cell wall constituents. In addition, similar experiments with knockout mice have identified MD-2 as essential accessory molecules in TLR4-mediated signaling and intracellular trafficking (379, 487), whereas MD-1 is instrumental in the LPS-induced B-cell proliferation and antibody production through RP105 (380, 394). A substantial part of the TLR2 and TLR4 signaling pathways coincides, but there is now increasing evidence that alternative pathways also exist. This is exemplified by the observation that Kupffer cells from MyD88-deficient mice release IL-18 but do not produce IL-1β and IL-12 while Kupffer cells from TLR4-deficient mice do not produce any of these cytokines after stimulation with LPS (481) (the signaling pathways of TLR2 and TLR4 are shown in Fig. 5).

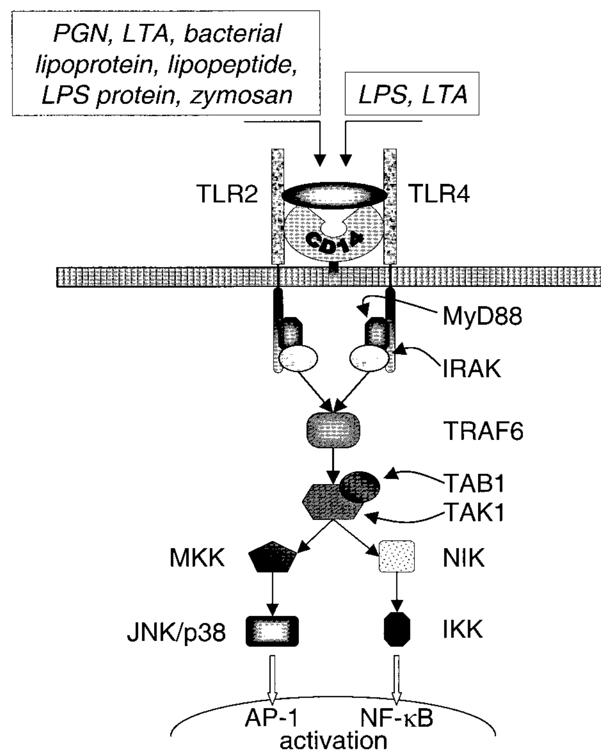

FIG. 5. TLR signaling pathways. The shared signaling pathway for TLR2 and TLR4 is depicted. IRAK, IL-1R-associated kinase; TRAF6, tumor necrosis factor receptor-associated factor 6; TAK1, transforming growth factor β-activated kinase; TAB1, TAK1-binding protein; NIK, NF-κB-inducing kinase; MKK, mitogen-activated protein kinase kinase; JNK, c-Jun N-terminal kinase; IKK, IκB kinase; AP-1, activator protein 1.

The expression patterns of the TLRs vary widely, but whereas TLR1 transcripts are present in almost all myeloid and lymphoid cells, the TLR3 mRNA is present at substantial levels only in NK cells (Table 3) (219). TLR2 and TLR4 exhibit comparable expression patterns and in steady state are represented mainly on PMN, monocytes, macrophages, and dendritic cells (376, 377). However, both receptors are also present

TABLE 3. Constitutive TLR mRNA expression patterns in human leukocytes[a]

Receptor	Expression of receptor in[b]:				
	T-lymphocytes	B-lymphocytes	NK cells	Monocytes	Dendritic cells
TLR1	+	+	+	+	+
TLR2	±	−	−	+	−
TLR3	−	±	+	−	−
TLR4	−	−	−	+	−
TLR5	+	−	+	±	−
TLR6	±	+	+	±	±
TLR9	−	−	−	−	+

[a] Data from reference 219.
[b] All levels within one cell type are related to the highest level of TLR expression for that particular cell type. Of the listed cell types, T cells have the lowest expression levels and monocytes have the highest.

on various other cell types including epithelial and endothelial cells (59, 118, 614); TLR2 is also present on hepatocytes (323). In comparison to CD14, the number of TLR4 molecules on monocytes is small: CD14 is expressed at ca.115,000 molecules per monocyte whereas TLR4 is present at ca.1,300 molecules per monocyte, which has led some investigators to propose that TLR4 expression may be a limiting factor in the response to LPS (9, 564). The expression levels of TLR2 and TLR4 are modulated by LPS and other microbial components. During infection, TLR2 and TLR4 are expressed on cells otherwise expressing very low levels of these receptors. The treatment of rats with LPS, IL-1, or TNF results in a marked upregulation of TLR2 mRNA on macrophages, monocytes, liver parenchymal cells, and a variety of cells in other tissues (323, 348, 349, 564). TLR4 mRNA levels on liver parenchymal cells, kidneys, and spleen was unchanged after an LPS challenge, whereas the levels were increased in the heart and lungs and decreased in the brain (349). Although LPS induces an increase in TLR4 mRNA in a number of cell types, surface expression of TLR4 is decreased on murine macrophages (348, 390) and human monocytes (47).

Recently, the expression of a splice variant of TLR4 in mice was observed, resulting in the presence of a soluble TLR4 in serum (239). The soluble TLR4 inhibited TNF-α release and NF-κB activation in macrophages, possibly representing a novel component involved in immunomodulation. Although the TLR4 is a link in a highly sensitive signaling pathway, the absence of this receptor corresponds to a decreased response to LPS, as expected, but also in an increased sensitivity to live gram-negative bacteria (440). However, Haziot et al. have shown that CD14- and TLR4-deficient mice and TLR2-deficient hamsters exhibit a highly efficient LPS- or *E. coli*-induced PMN infiltration into the peritoneum, resulting in increased clearance of bacteria (201). They propose a novel CD14-, TLR4-, TLR2-, complement-, and coagulation factor-independent pathway for the PMN response.

In addition to a direct role in innate immunity, several investigators have revealed a modulating role of the TLR pathway in the development of adaptive immune responses. MyD88-deficient mice were defective in the activation of antigen-specific Th1 immune responses (469), whereas the absence of TLR4 affected Th2 responses (77).

These data, taken together, indicate an important role for TLRs in discrimination between a variety microbial components. Additional research must reveal the precise interactions between (s)CD14 and the TLRs, as well as the functions of the remaining TLRs in the innate immune response.

β_2-Integrins

The CD18 antigens, or β_2-integrins, comprise a family of three closely related cell surface glycoproteins with a varying CD11 α-chain and an identical CD18 β-chain: (i) $\alpha_1\beta_2$-integrin, LFA-1 or CD11a/CD18; (ii) $\alpha_2\beta_2$-integrin, CR3 (complement receptor), MAC-1, or CD11b/CD18; and (iii) $\alpha_3\beta_2$-integrin, CR4, p150,95, or CD11c/CD18. LFA-1 is expressed on all leukocytes; CR3 is expressed on monocytes, macrophages, PMN, and lymphocytes; while CR4 is expressed abundantly on monocytes and macrophages (591). LFA-1 recognizes the adhesion molecules ICAM-1 and ICAM-2, CR3 recognizes surface-bound C3bi and surface-bound fibrinogen, and CR4 binds surface-bound fibrinogen as well (591, 598).

Many strains of *E. coli* are recognized by macrophages without the intervention of antibodies and complement. CD18 on the surface may be responsible for recognition of the bacteria: (i) Spreading of macrophages on a surface coated with anti-CD18 antibodies prevents the binding of *E. coli* (593); (ii) spreading of macrophages on a surface coated with Re-LPS or lipid IV_A prevents the binding of bacteria and C3bi-coated erythrocytes (593); (iii) LPS-coated erythrocytes (E-LPS) bind to macrophages in the absence of LBP, and the binding is proportional to the amount of LPS bound to the erythrocytes (593); and (iv) monocytes from CD18-deficient patients are unable to bind E-lipid IV_A, E-LPS, and unopsonized bacteria (594). Furthermore, all three members of the CD18 family are capable of binding LPS. The part of the LPS recognized by CD18 resides in the lipid A region because Re-LPS and the lipid A precursor lipid IV_A are recognized. Since the acyl moieties of the LPS are embedded in the outer cell wall of the bacteria, only the phosphorylated glucosamines of lipid IV_A are exposed; therefore, this is probably the moiety of the LPS molecule that is recognized by CD18 (593, 594). This hypothesis is strengthened by the observation that *Leishmania mexicana* lipophosphoglycan, rich in phosphosugars, binds to the same site as LPS on CD18 (517). In addition, *Blastomyces dermatidis* yeasts, an acylpolygalactosyl from *Klebsiella pneumoniae*, and group A and B streptococci bind to CD11b/CD18, while *S. aureus* and *Listeria monocytogenes* bind CD11c/CD18 (76, 217, 358, 388). The binding site on the CD18 antigens for LPS is distinct from the binding site for endogenous ligands (594).

In several studies it was shown that the activation of mononuclear cells by several microbial antigens, including LPS, is partially inhibited by antibodies to CD18, CD11b, or CD11c, which may indicate that the β_2-integrins are involved in cellular activation (76, 358). CD11/CD18 and CD14 may have a common signaling pathway (170, 232, 234). There are indications that CD11/CD18 also utilizes the TLR4 pathway for LPS-induced activation, albeit with substantially lower efficiency, as shown by the differences in activation kinetics (233, 420). Due to the lower efficiency of CD11/CD18-TLR4 than of CD14-TLR4, the physiological relevance of the former is probably limited. Whether CD11/CD18 contributes to gram-positive

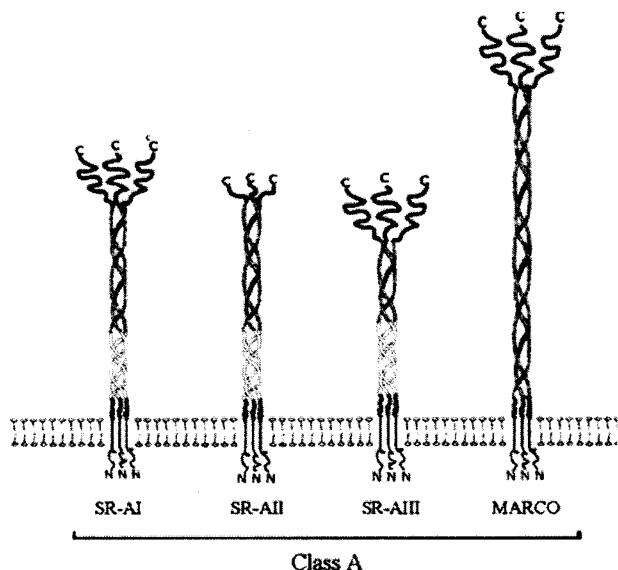

FIG. 6. Structure of the SR-As.

bacterium-induced activation through TLR2 remains to be determined.

Selectins

The β_2-integrins are not the only adhesion molecules involved in the binding of LPS. Recently, Malhotra et al. showed that P-selectin and L-selectin are able to bind LPS (335, 337). In addition, L-selectin mediated the binding of LTA (395). In the absence of serum, anti-P-selectin antibodies almost fully inhibited the binding of fluorescein isothiocyanate-LPS to platelets, whereas antibodies to P-selectin and L-selectin significantly reduced the binding of fluorescain isothiocyanate-LPS to PMN and the LPS-induced superoxide production by these cells (335, 337, 395). It was proposed that L-selectin may represent the low-affinity serum-independent signaling receptor involved in the response to high concentrations of LPS (336).

Scavenger Receptors

Hampton et al. demonstrated that lipid IV_A can bind to a class A scavenger receptor (SR-A). Binding to the SR-A resulted in uptake but not in activation of the cells and uptake was followed by dephosphorylation, which renders the lipid IV_A less toxic (185, 186). The SR competitor polyinosinic acid, poly(I), reduced liver uptake of lipid IV_A by approximately 35%, indicating a considerable SR mediated binding to the liver (185). Besides LPS and *E. coli*, SR-A binds LTA and whole gram-positive bacteria like *S. aureus, L. monocytogenes*, and *Mycobacterium tuberculosis* (97, 173, 236, 416, 509, 619). The MARCO SR (for "macrophage receptor with collagenous structure"), which also belongs to the SR-A class, recognizes gram-negative and gram-positive bacteria (107, 544).

SR-A are trimeric transmembrane glycoproteins that are expressed by tissue macrophages (including Kupffer cells) and liver sinusoidal and aortic endothelial cells (80, 227, 382). They consist of three extracellular C-terminal cysteine-rich domains connected to the transmembrane domain by a long fibrous, collagen-like stalk (Fig. 6). Three SR-A types have been identified, of which SR-AI and SR-AII are expressed on the plasma membrane (15). SR-AI contains a 110-aa C-terminal cysteine-rich sequence that is lacking in SR-AII (273). The C-terminal end of the collagenous domain is responsible for the binding of polyanionic ligands (96, 604). Besides the bacteria and bacterial components, SR-A recognize a broad range of ligands, including acetylated LDL, oxidized LDL, maleylated bovine serum albumin, poly(I), and poly(G) (277, 520). MARCO is very similar to SR-Al, hence its designation as an SR-A (Fig. 6). MARCO is homotrimeric and contains an extracellular collagenous domain and a C-terminal cysteine-rich domain (107). It lacks the α-helical coiled coil present in SR-A and contains a much longer collagenous domain. The bacterium-binding domain has been located immediately proximal to the cysteine-rich domain, which is similar to the analogous domain in SR-A (108).

Cross-competition studies with LPS and several other SR ligands have shown that there are also other SRs expressed on Kupffer cells and liver sinusoidal endothelial cells involved in the binding of LPS (489, 557). Little is known about the relative contribution of the SRs in the liver for the uptake of bacterial components. In in vivo experiments, blocking antibodies against MARCO did not affect the clearance of bacteria in mice, but this may partially be explained by the low constitutive expression levels of MARCO in the liver (544). The liver uptake of i.v.-injected LPS in SR-A-deficient mice was almost equal to that in control mice (E. S. van Amersfoort et al., unpublished results), but increased LPS levels were found in SR-A-deficient mice after i.p. injection (271). The in vitro binding of LPS to Kupffer cells, liver sinusoidal endothelial cells, and peritoneal macrophages from SR-A-deficient mice is significantly reduced compared to that to cells from wild-type mice, which shows that the SR-A does recognize LPS and does contribute to the binding and uptake of LPS (van Amersfoort et al., unpublished). Binding by scavenger receptors may actually form a protective mechanism by removing excess microorganisms or components, thus preventing binding to the highly sensitive CD14 receptor and the development of septic shock. Possibly, the constitutive expression levels of SR-A are not sufficient to unequivocally reveal the protective effect under normal, noninflammatory conditions. Injection of LPS into SR-A knockout and wild-type mice revealed no differences in the production of TNF-α (van Amersfoort et al., unpublished) (271). However, Haworth et al. showed that *M. bovis* BCG-infected SR-A knockout mice are more susceptible to LPS (198). In addition, Suzuki et al. and Ishiguro et al. observed that compared to wild-type mice, SR-A knockout mice were markedly more susceptible to live *L. monocytogenes* bacteria and to herpes simplex virus (236, 509). Besides a reduced phagocytosis of *L. monocytogenes* by SR-A knockout macrophages, the intracellular killing of the facultative, intracellular bacteria was also reduced, resulting in larger granulomas and increased mortality in the SR-A knockout mice (236).

Although the incubation of macrophages with LPS did not result in SR-mediated activation, several other studies reveal that SR ligands such as modified LDL or poly(I) may induce the release of IL-1 and TNF-α, up regulation of urokinase-type

plasminogen activator on macrophages, and up regulation of adhesion molecules on endothelial cells (185, 222, 247, 410, 411). In addition, Kobayashi et al. observed reduced IL-1 production in SR-A knockout mice after an LPS challenge and proposed that binding of LPS to SR-A induces the release of IL-1 (271). However, no additional (in vitro) data to support this hypothesis were provided.

Based on available data, SR-A can be considered anti-inflammatory due to the uptake of LPS or other bacterial compounds, circumventing the CD14-TLR signaling pathway. LPS affect the expression of the SR-A. On human macrophages, the expression of SR-A decreases after stimulation with LPS (553). Similarly, the SR-A mRNA is transiently down regulated after an in vivo challenge with LPS in mice (461). However, treatment of mice with inflammatory stimuli like BCG or heat-killed *Corynebacterium parvum* results in increased expression on liver Kupffer cells (181, 198, 523). Also, the expression of MARCO can be upregulated by inflammatory stimuli; in mice, treatments with BCG, *C. parvum, K. pneumoniae*, and LPS all resulted in a marked upregulation of MARCO expression in the liver (181, 544, 545). Moreover, a similar pattern of high MARCO expression was observed in the livers of two newborns who died of sepsis (108).

Moesin

A 78-kDa LPS-binding protein was shown to be identical to moesin (membrane-organizing extension spike protein) (529). An anti-moesin antibody completely inhibited the LPS-induced TNF release by monocytes, but LPS binding was not blocked (529). Due to the complete inhibition of LPS-mediated signaling by the anti-moesin antibody, whereas an anti-CD14 antibody only partially blocked responses, it is tempting to speculate that moesin may represent an element in the CD14-TLR4 signaling pathway. The fact that the anti-moesin antibody does not inhibit *S. aureus*-mediated inhibition precludes the binding of the antibody to TLR2 but not to TLR4.

Heptose-Specific Lipopolysaccharide Receptor

A receptor on liver parenchymal cells was identified that specifically recognized heptose residues in the inner core of LPS (412). This receptor may be involved in the transfer of LPS from the circulation to bile as proposed by Van Bossuyt et al. (542).

LIPOPOLYSACCHARIDE- AND LIPOTEICHOIC ACID-BINDING PROTEINS

Neutrophilic Lipopolysaccharide-Binding Molecules

Bactericidal/permeability-increasing protein. In 1978, Weiss et al. reported the isolation of a potent bactericidal protein, BPI, from human PMN (583). The cationic, 55-kDa protein resided in the azurophilic granules of PMN and, to a lesser extent, in monocytes and macrophages. It binds highly specifically to gram-negative bacteria and kills bacteria by increasing the permeability of the outer membrane and by activating cell wall-degrading outer membrane enzymes (110, 583). No bactericidal activity of BPI against gram-positive bacteria was observed (583). The initial effect of the decreased integrity of the outer membrane of gram-negative bacteria is growth arrest (<1 min) followed by changes in the cytoplasmic membrane, resulting in impaired energy metabolism, irreversible growth arrest, and, finally, death (109, 583). The bactericidal activities of other granule constituents such as the p15s and defensins are synergistic with that of BPI (311, 577), but the serum protein LBP may also enhance the bactericidal activity of BPI (220). PMN may also excrete BPI, and excreted BPI has identical bactericidal effects to intracellular BPI (109). Binding of BPI to gram-negative bacteria is mediated by LPS. The initial interaction probably involves negatively charged groups in the inner core and lipid A and additional interactions with the hydrophobic moieties of lipid A, resulting in a high-affinity binding (K_d = 2 to 5 nM) (159, 160, 401). In vitro experiments with BPI have shown that the sensitivity of various gram-negative species to the bactericidal effect of BPI varies considerably. Strains expressing rough LPS are more sensitive than strains expressing smooth LPS. Limited proteolysis of BPI yields a C-terminal 30-kDa fragment and an N-terminal 25-kDa fragment (401). The latter contains the LPS-binding and bactericidal capacity (401, 402). The 25-kDa fragment, a recombinant 23-kDa N-terminal fragment ($rBPI_{23}$), and holo-BPI have comparable affinities for free LPS, irrespective of the serotype (401).

Binding of BPI to LPS neutralizes the biological activity of LPS in vitro. BPI attenuates LPS-mediated endothelial damage and IL-6 production as well as LPS-mediated NO, TNF-α, IL-1, IL-6, and IL-8 production by macrophages and whole blood (11, 67, 91, 362, 584). In vivo, BPI or $rBPI_{23}$ reduced LPS- or bacterium-induced TNF-α release, liver damage, NO production, and mortality and protected against cardiovascular depression (7, 117, 275, 321). Combining rBPI with antibiotics enhances its protective effect (7). BPI causes a significant reduction in serum LPS, TNF, IL-6, IL-8, and IL-10 levels and in several other parameters in healthy volunteers (567). The results of a clinical study of children with meningococcal sepsis were promising: of 26 patients only 1 died (4%), which was favorable compared to the predicted mortalities, which varied between 15 and 49% based on various parameters such as LPS levels, serum IL-6 levels, etc. (167). However, in a larger placebo-controlled study, the mortality in the $rBPI_{21}$-treated patients was not significantly reduced, although there was a trend toward improved outcome in the primary outcome variables (309). The feasibility of the use of BPI for the treatment of sepsis and septic shock in humans may be restricted due to the limited half-life of approximately 10 min in vivo (28, 29).

CAP18. Like BPI, CAP18 was isolated from PMN, but the 18-kDa protein bears no structural and sequence similarity to BPI and other LPS-binding proteins (297). CAP18 binds LPS but is also bactericidal to bacteria such as *E. coli* and *S. aureus* (381). Defensins, lactoferrin, and lysozyme synergistically enhance the bactericidal activity of CAP18 (23, 381). The production of CAP18 by human lung epithelial cells and the release of CAP18 onto the airway surface of the cells indicate that it may also have a function in mucosal defense (23). Intratracheal instillation of CAP18-adenovirus reduced the response to *Pseudomonas aerigunosa*, whereas i.v.-injected virus protected against LPS and *E. coli* (24). The LPS-binding site resides in the C-terminal 36-aa part of the molecule, and pep-

TABLE 4. Physical properties and composition of human plasma lipoproteins[a]

Property	Chylomicrons	VLDL	LDL	HDL
Density (g/ml)	0.95	0.95–1.006	1.019–1.063	1.063–1.21
Mol mass (/10^6 Da)	±400	10–80	2.3	0.17–0.36
Diam (nm)	75–1200	30–80	18–25	5–12
Composition (%, wt/wt)				
Triglycerides	80–95	55–80	5–15	5–10
Phospholipid	3–9	10–20	20–25	20–30
Total cholesterol	2–7	5–15	40–50	15–25
Apolipoproteins	A-I, A-II, A-IV			A-I, AII, A-IV
	B48	B100	B100	
	C-I, C-II, C-III	C-I, C-II, C-III		C-I, C-II, C-III
	E	E		E

[a] Data from reference 166.

tides containing this region show similar anti-inflammatory effects to intact CAP18 (264, 295, 296, 545a).

CAP37. CAP37 is a glycoprotein with a molecular mass of 29 to 37 kDa (418); it is bactericidal to gram-negative and gram-positive bacteria such as *E. coli, S. enterica* serovar Typhimurium, *S. aureus, and S. pneumoniae* (418). In addition, CAP37 (also called heparin-binding protein) binds LPS, is chemotactic to monocytes, opsonizes *S. aureus* for phagocytosis by monocytes, enhances the LPS-induced activation of monocytes, and stimulates protein kinase C activity in endothelial cells (207, 208, 418, 419). A $CAP37_{20-44}$ peptide, containing the bactericidal and LPS-binding site, inhibited the LPS-induced hemodynamic changes, leukopenia, TNF-release, and mortality in rats (50).

Lactoferrin. Lactoferrin is an 80-kDa glycoprotein that is present in neutrophilic granules, milk, and mucosal secretions (35). It binds LPS and is bacteriostatic to bacteria, indirectly through chelation of iron ions and directly through destabilization of the gram-negative bacterial cell membrane (35, 106). Lactoferrin is a major LPS-neutralizing compound produced and excreted by stimulated PMN (10, 56, 573). Lactoferrin peptides containing the LPS-binding site prevent the LBP-mediated binding of LPS to CD14, which results (105) in a reduction of TNF and IL-6 release by THP-1 cells in vitro (104, 351). However, Baveye et al. demonstrated that lactoferrin binds to sCD14 and sCD14-LPS complexes, inhibiting the activation of endothelial cells and the resultant expression of adhesion molecules (34). A peptide containing the N-terminal first 33 aa of lactoferrin potently inhibited TNF release by RAW264.7 in vitro, TNF release in vivo, and LPS lethality (615). Germ-free piglets that were fed lactoferrin were less sensitive to LPS, as shown by reduced mortality and hypothermia (304).

Lysozyme. Ohno and Morrison have shown that LPS binds to lysozyme and that the binding inhibits the immunostimulation of B cells. All LPS serotypes were shown to bind to lysozyme. However, conflicting data were obtained on the ability of lysozyme to affect cytokine release (397, 398, 510, 511).

Other Lipopolysaccharide-Binding Proteins

A number of other LPS-binding proteins have been characterized. Surfactants A and D bind to LPS and whole bacteria and may thus inhibit the binding of LPS to alveolar macrophages (46, 467, 559). Serum amyloid P (SAP) binds LPS and inhibits the LPS-induced activation of PMN in vitro (87). In addition, SAP peptides that bind LPS inhibit cell activation in whole blood (87). In contrast to these anti-inflammatory actions, SAP prevents the LPS-induced complement activation through the classical pathway and dose-dependently inhibits the neutralization of LPS by HDL, suggesting that under physiological conditions in the presence of serum, SAP mainly plays a proinflammatory role (86, 88). Other naturally occurring LPS-binding proteins are albumin (153), transferrin (37), and hemoglobin (464). Several apolipoproteins have been reported to bind LPS. These are addressed in the section on lipoproteins (see below).

Development of Bactericidal and Lipopolysaccharide-Neutralizing Peptides

Many investigations of LBP have been performed with the ultimate goal of creating a neutralizing LPS-binding structure applicable in the clinic to treat septic patients. Therefore, structural similarities between LBP have been studied, enabling the identification of specific requirements for LPS and LTA binding (260). Two similarities between lipid A-binding proteins are rather consistent: a net positive charge and a hydrophobic region in the LPS- or LTA-binding pocket (260). Peptides based on BPI (172), LBP (78), CAP18 (264), CAP37 (50), lactoferrin (615), SAP (87), *Limulus* anti-LPS factor (LAL) (451), bee melittin (479, 480), silk moth cecropin (479, 480), and the antibiotic peptide polymyxin B (238) have been constructed and tested on bactericidal, LPS- or LTA-binding, and neutralizing potency in vitro and in vivo. The results with these peptides with respect to binding, neutralization, and bactericidal activity are promising, but it was shown that the spatial organization of the positive and hydrophobic moieties largely determines the binding affinity of the peptides for the bacterial compounds (238, 354). Further investigations are needed to determine an optimal structure and may lead to the construction of a potent and highly specific peptide-based antibiotic and LPS- and LTA-neutralizing peptide.

LIPOPROTEINS

Metabolism

Lipoproteins are spherical macromolecular particles composed of a core containing hydrophobic cholesteryl esters and

triglycerides surrounded by a shell of phospholipids, unesterified free cholesterol, and one or more proteins called apolipoproteins. The cholesterol and apolipoproteins stabilize the particles, but the apolipoproteins are also involved in lipid recruitment, modulation of enzyme activity, and modulation of receptor-mediated binding and endocytosis. In human blood, four major lipoprotein classes can be distinguished according to their density: chylomicrons, VLDL, LDL, and HDL. These lipoprotein classes differ with respect to size, electrophoretic mobility, and lipid and apolipoprotein composition (Table 4) (166). Two major metabolic routes can be distinguished: an exogenous pathway is involved in the transport and metabolism of intestinally derived dietary lipids, and an endogenous pathway is involved in the transport and metabolism of processed lipids. In short, dietary lipids that are absorbed in the intestines are packaged into chylomicrons, large triglyceride-rich particles, and transported from the lymph to the blood circulation (333). On entering the circulation, lipoprotein lipase (LPL) processes the chylomicrons, delivering free fatty acids to peripheral tissues (fat and muscle tissue), whereas the cholesterol-rich core remnants are taken up mainly via ApoE-specific recognition sites on liver parenchymal cells (333). The liver secretes ApoB100-containing VLDL that in the circulation becomes enriched in ApoC and ApoE. These particles are also rich in triglycerides and serve as a source of free fatty acids for extrahepatic tissues. LPL and hepatic lipase (HL) process these particles, resulting in a loss of triglycerides, phospholipids, ApoC, and ApoE. The remnants (also called intermediate-density lipoproteins [IDL]) are further processed to become LDL with ApoB100 as its sole apolipoprotein. These cholesterol-rich particles are taken up in the liver and peripheral tissues through the LDL receptor. To maintain cholesterol homeostasis, excess cholesterol in extrahepatic tissues must be returned to the liver, which is the only organ capable of disposing of cholesterol via the bile. This process is known as reverse cholesterol transport and involves the last lipoprotein particle, HDL. The enzyme lecithin:cholesterol acyltransferase promotes the esterification of cholesterol in HDL, creating a concentration gradient and thus facilitating the efflux of free cholesterol from extrahepatic tissues to HDL. In exchange for triglycerides, cholesteryl ester transfer protein-mediated transfer of cholesteryl esters to LDL and VLDL occurs. Subsequently, these particles are taken up by the liver. In addition, direct transfer of cholesteryl esters from HDL to the liver occurs through recognition by SR-BI. In contrast to the receptor-mediated uptake of VLDL and LDL, SR-BI promotes only the selective transfer of cholesteryl ester without causing the uptake of the HDL particle (2).

Apolipoprotein E

ApoE was identified in 1973 as a component of triglyceride-rich VLDL and was initially referred to as arginine-rich protein due to its relatively high arginine content compared to other apolipoproteins known at that time (490, 540). The ApoE molecule is synthesized as a 317-aa prepeptide after cotranslational cleavage yielding a 299-aa protein with a molecular mass of 34.2 kDa. ApoE is synthesized in a wide variety of tissues, including the liver, central nervous system, kidneys, adrenal glands, testes, and ovaries, but not the intestines (111, 496). However, the highest levels of ApoE mRNA are found in the liver parenchymal cells and the second highest are found in the astrocytes in the brain. Furthermore, ApoE is also produced by macrophages from the liver, lungs, and spleen (12, 26). In the absence of lipids, ApoE self-associates to form tetramers over a wide concentration range (580). In contrast, self-association does not occur on lipid surfaces. ApoE contains two domains that are joined by a protease-susceptible hinge region. Thrombin digestion of ApoE yields two fragments, of which the 10-kDa C-terminal fragment harbors the lipid-binding domain whereas the LDL receptor (LDLr)-binding domain is situated in the 22-kDa N-terminal fragment (235, 581). The N-terminal domain contains four antiparallel helices, of which helix 4 contains the LDLr-binding domain. This helix is unusually rich in basic amino acids (Arg, Lys, and His). ApoE contains two heparin-binding sites, of which one is located within the LDLr-binding site (582). Similarly, ApoE interacts with heparan sulfate proteoglycans (HSPG). HSPG are abundantly present on many different cell types, including vascular endothelial cells and liver parenchymal cells within the space of Disse (605). In the liver, HSPG may be involved in both the secretion of ApoE and the binding of lipoprotein-bound ApoE (243).

Several physiological and pathological functions for apoE have been proposed. These include the role of ApoE in lipid metabolism (as described above), intracellular lipid redistribution (281, 448), atherogenesis (75, 463, 549), neurobiology (nerve regeneration, association of the ApoE4 serotype with neuropathologic lesions in Alzheimer's disease) (342, 580), and immunomodulation (inhibition of proliferation of peripheral blood mononuclear cells and lymphocyte activation; inhibition of TNF secretion by glial cells) (20, 228, 299, 364, 399, 417).

Anti-Inflammatory Role

Ulevitch et al. were the first to observe that if LPS is mixed with serum or plasma, a decrease in buoyant density results. Preincubation of LPS with plasma decreased the ability of LPS to induce neutropenia and a pyrogenic response in rabbits. Further investigations showed that the LPS was bound to HDL and that a plasma protein aided in the binding (525, 534, 536). In rabbits, the uptake of LPS by the adrenal glands was increased after LPS binding to HDL, which indicates that binding of LPS to HDL results in a decreased recognition by LPS receptors (347, 372). Since then, in vivo and in vitro experiments have shown that LPS and LTA bind to and are neutralized by lipid emulsions (177, 445), chylomicrons (194, 195, 447), VLDL (102, 194, 459, 464, 576), LDL (102, 177, 366, 459, 464, 554, 576), Lp(a) (385), HDL (102, 144, 177, 374, 459, 464, 535, 576), ApoA-I (112, 135, 539), ApoB (112, 464), and ApoE (449, 555).

In vivo experiments have shown that the injection of LPS-HDL complexes may affect the decay of LPS in serum (144, 375) and inhibits the LPS-induced release of cytokines compared to LPS alone (194, 536). In addition, in several experiments the infusion of recombinant HDL (rHDL), VLDL, or lymph-derived chylomicrons and lipid emulsion also resulted in inhibition of LPS-induced physiological changes (120, 195, 226, 310, 445). Pajkrt et al. infused rHDL into humans, who

TABLE 5. Inhibitory effects of lipoproteins on LPS and LTA toxicity

LPS and LTA property	Effect of:							Reference(s)
	HDL	rHDL	LDL	VLDL or chylomicrons	Emulsion	Total lipoprotein	ApoE	
In vivo								
Inhibition of cytokine release		↓		↓		↓	↓	60, 72, 120, 195, 225, 226, 437, 555[a]
Decreased pyrogenicity	↓					↓		534, 535
Decreased mortality after LPS challenge	↓	↓	↓	↓	↓	↓	↓	120, 194, 195, 310, 445, 555
Decreased mortality and TNF release after CLP[b]				↓				446
Increased excretion of ^{125}I-LPS into bile				↓				447
Decreased Kupffer cell binding							↓	449
In vitro								
Inhibition of macrophage or monocyte activation (cytokine release)	↓	↓	↓	↓	↓	↓		30, 60, 61, 135, 136, 177, 196, 306, 415, 545, 554, 579
Inhibition of PMN priming	↓							568
Inhibition of VCAM-1 expression by HUVEC[c]		↓						57
Inhibition of LAL activation	↓		↓	↓				103,112,193

[a] E. S. van Amersfoort et al., unpublished results.
[b] CLP, cecal ligation puncture; this experimental procedure results in polymicrobial peritonitis and sepsis.
[c] HUVEC, human umbilical vein epithelial cells.

were subsequently challenged with a low dose of LPS and observed a significant reduction in the release of proinflammatory cytokines and a partial reduction in the activation and/or release of components involved in coagulation (408, 409). The in vitro data mainly parallel those found in vivo. These data confirm that binding of LPS to lipoproteins decreases its ability to activate macrophages and endothelial cells (30, 57, 60, 196, 306, 366, 415, 554, 579) (Table 5). Recently, Grunfeld et al. have shown a similar inhibitory effect of lipoprotein binding on LTA-induced activation of macrophages (177). The inhibition of LPS-induced activation is dependent largely on the concentration of lipoproteins: in the presence of low concentrations of lipoproteins, cells become activated before neutralization by lipoproteins occurs (386). It has been shown that a 5-min exposure to LPS is sufficient to maximally bind and stimulate monocytes in whole blood, which implies that in the circulation neutralization by (infused) lipoproteins is a rapid process (157). However, Kitchens et al. illustrated that lipoproteins can remove LPS bound to the cell surface. This transfer is dependent on the presence of sCD14 and further enhances the protective effect of lipoproteins (269).

Mice with high HDL levels due to overexpression of human ApoA-I levels and rats rendered hyperlipidemic by estradiol treatment are less sensitive to LPS compared to the respective controls (120, 310). Hypercholesterolemic rabbits exhibited higher TNF- levels and mortality than did the normolipidemic controls (54). LDL receptor knockout mice, with cholesterol levels twice those in C57BL/6 mice, are less susceptible to LPS than are wild-type mice, as shown by decreased mortality and reduced release of TNF, IL-1, and IL-6 (387). In contrast, the severely hypercholesterolemic ApoE knockout mice were more sensitive to LPS (84). It is likely that the lack of ApoE is the cause of this increased sensitivity.

The binding of LPS to HDL is mediated by LBP and sCD14, although only the first has been shown to be essential (600, 602). Wright et al. showed that most LBP is associated with ApoA-I-containing particles, which may explain the preferential binding of LPS to HDL (414, 600). PLTP may also aid in the transfer of LPS to HDL (182). This was confirmed by observations that both LBP and PLTP could extract LPS from gram-negative bacterial cell membranes and mediate the transfer to lipoproteins (mainly HDL) (562). However, experiments by Vreugdenhil et al. indicated that LBP is associated mainly with ApoB-containing lipoproteins (e.g., LDL) (569). They have shown that the association of LBP with ApoB is stronger than with ApoA-I, that LBP in serum is present mainly on LDL and VLDL, and that LDL- and VLDL-associated LBP enhanced LPS binding to these lipoproteins. Using a solid-phase binding assay, they also observed that in the absence of LBP, LPS preferentially bound to LDL and VLDL. The discrepancies in the results of Wright et al. (600) and Vreugdenhil et al. (569) may be explained by the differences in the methods used. Whereas the first group used affinity chromatography with either anti-ApoA-I or anti-LBP antibodies to coprecipitate ApoA-I and LBP, Vreugdenhil et al. employed agarose gel electrophoresis in combination with immunoblotting to detect LBP-containing lipoproteins. In our in vivo and in vitro experiments, we have observed LPS and LTA binding to all lipoproteins in the serum, which may indicate that LBP transfers LPS and LTA to all lipoproteins (van Amersfoort et al., unpublished). However, although we observed binding to all lipoprotein classes, based on lipid or protein contents LTA seemed to exhibit preferential binding to HDL (Van Amersfoort et al., unpublished). Other investigators have also observed either preferential binding of LPS to HDL (375, 464, 535), to LDL and/or VLDL (102, 554), or to all lipoproteins (102, 459, 554, 562, 576) depending on the lipid and/or protein distribution in the distinct lipoprotein fractions. A correlation between the cholesterol contents of the lipoprotein fractions and LPS association was proposed by Van Lenten et al. (554), but with rHDL the neutralizing potency correlates with the phospholipid contents of the particle (72). Using the synthetic LPS-like antagonist E5531, it was found that association with the different lipoproteins did correlate with protein (HDL), cholesterol (VLDL, LDL), and triglyceride (VLDL) contents, which may imply that factors other than the composition of the li-

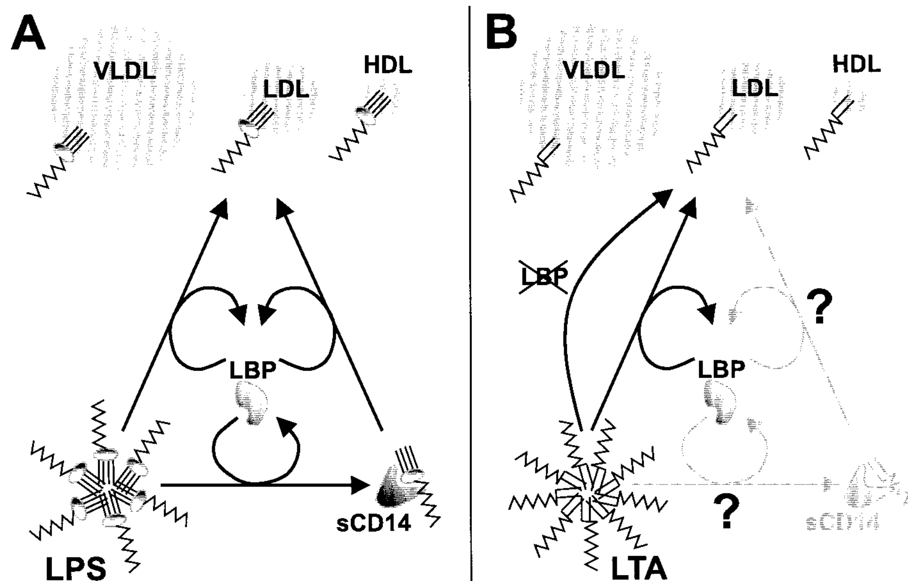

FIG. 7. LPS and LTA transfer to lipoproteins. Black arrows indicate established pathways. In contrast to LPS (left), LTA may also associate with lipoproteins in the absence of LBP (extra arrow in right panel).

poproteins are also involved (459, 576). The association with the lipoproteins in sera from mouse strains with various lipoprotein profiles correlates with the cholesterol contents of LDL and VLDL but not of HDL (van Amersfoort et al., unpublished). The increased binding of LTA to HDL that we have observed may be caused by the involvement of LBP in the transfer of LTA to HDL, as proposed by Grunfeld et al. (177). The proposed LPS and LTA neutralization pathways are depicted in Fig. 7.

The lipoprotein distribution of LPS may depend on the type of LPS used, the origin of the serum (animal species and lipoprotein status), or, when using plasma, the type of anticoagulant used (e.g., citrate, EDTA, or heparin) (101, 102, 554). Furthermore, as mentioned above, the use of a density gradient, agarose gel electrophoresis, or column chromatography may introduce additional variations.

So far, only the binding of LPS to lipoproteins has been discussed, but binding to apolipoproteins has also been reported. Emancipator et al. and Usynin et al. have shown that both ApoB and ApoA-I are able to bind and neutralize LPS (112, 539). Our group has shown that LPS binds ApoE and causes a redistribution in vivo, reducing the uptake by Kupffer cells and promoting the binding to liver parenchymal cells (449). In addition, we have shown that ApoE binds LTA, resulting in a similar redistribution from Kupffer cells to liver parenchymal cells and in a strongly decreased TNF release in vivo (Van Amersfoort et al., unpublished).

Lipid Metabolism and Infection

Injection of LPS or bacteria leads to a marked hyperlipidemic response, caused primarily by an increase in the level of VLDL triglycerides (470). Remarkably, the underlying mechanisms differ with the dose of LPS administered to the animal. With low doses, an increase in hepatic triglyceride production occurs, whereas at high doses of LPS (>500 μg/kg of body weight), a decrease in the clearance of triglyceride-rich lipoproteins occurs (125). Experiments with IL-1 receptor antagonist (IL-1ra) and TNF antibodies showed that these phenomena could be only partially mimicked by administration of IL-1 or TNF-α (125). Subsequently, it was shown that α_1-adrenergic receptors were involved in the low-dose-LPS-induced increase in triglyceride production whereas the α_2-adrenergic receptors were involved in the high-dose-LPS-induced inhibition of LPL activity, confirming a partial cytokine-independent pathway (391). LPS and the proinflammatory cytokines induced by LPS affect a wide range of enzymes and receptors involved in lipid metabolism, which include LPL, hepatic lipase, PLTP, LRP, and LDL receptor (Table 6).

However, the extent and kinetics of the effects differed widely among these species and in some cases were even contradictory. This is not surprising since there are substantial species-specific differences in lipid metabolism, resulting in marked differences in lipoprotein profiles. For instance, in mice almost all serum cholesterol resides in HDL, whereas in humans a significant portion of the serum cholesterol can be recovered from the VLDL and LDL. However, a TNF-induced increase in triglyceride levels was also observed in humans, which was paralleled by an increased rather than decreased lipolysis (497). The increased LPS- and LTA-induced triglyceride levels, along with the evidence that LPS and LTA are neutralized by lipoproteins, led to the hypothesis that these metabolic changes may be protective during bacterial infection (189, 293, 313). To test this hypothesis, rats were treated with estradiol or 4-aminopyrolo-(3,4-D)-pyrimide to induce hypolipidemia, after which they were challenged with LPS. The TNF-α levels and mortality were significantly increased in the hypolipidemic animals (120). However, these animals could be rescued by the injection of lipoproteins prior to the challenge with LPS, confirming that hypolipidemic animals are more sensitive to LPS. Fraunberger et al. collected serum from sep-

TABLE 6. Effects of inflammation and inflammatory mediators on lipid metabolism

Lipid undergoing metabolism	Effect of[a]:						Reference(s)
	LPS	LTA	TNF-α	IL-1	IFN-γ	GM-CSF	
Serum or plasma							
TG	↑§	↑	↑	↑			19, 121, 124, 276, 391, 392, 497
TC	↓↑		↑	↔			121, 122, 124
LCAT	↓						19
PLTP	↓						245
CETP	↓		↓	↓			190
Tissue							
LPL	↓	↓					256, 257, 392
Liver							
HL	↓		↔	↓			123
LDL receptor	↓						314
Monocytes/macrophages							
LRP receptor	↓				↓		288
ApoE							
Serum ApoE	↑						19, 314, 555[a]
Liver ApoE	↓						122, 532[b]
Macrophage ApoE	↓		(↓)			↓	360, 586, 620

[a] ↑, increase; ↓, decrease; ↔, no change; ↓ ↑, increased as well as decreased levels were observed.
[b] E. S. van Amersfoort et al., unpublished results.

tic patients and measured lipoprotein and apolipoprotein contents. In the septic patients, there was a marked increase in triglyceride levels, whereas cholesterol, ApoB and ApoA-I levels were reduced. They also observed an inverse relationship between serum cholesterol and TNF-α levels. A similar inverse relationship could be established between mortality and serum cholesterol levels (141–143). However, they did not show data on the serum triglyceride levels in this group of patients, which precludes a final conclusion about whether cholesterol or triglyceride levels may be protective in septic shock.

We have shown that serum ApoE levels are increased in mice which were injected with LPS, LTA, or live bacteria (555; van Amersfoort et al., unpublished). Along with the finding that ApoE is able to bind LPS and LTA, this also indicates that ApoE may be protective against LPS and LTA (449; van Amersfoort et al., unpublished). Fraunberger et al. observed an increase in HDL- and LDL-associated ApoE levels in human serum, whereas an increase in the HDL-associated ApoE level in LPS-treated African green monkeys was observed by Auerbach and Parks (19, 141). In contrast, decreased amounts of ApoE were detected in VLDL and LDL from septic rats (293). Administration of LPS to Syrian hamsters caused a reduction in liver ApoE mRNA levels but also a decreased release of ApoE and ApoB by the perfused rat liver (122, 532). In LPS-treated Syrian hamsters, the levels of ApoE mRNA were also reduced extrahepatically (191). LPS also caused a decrease in the release of ApoE by macrophages (Table 6) (294).

CLINICAL AND EXPERIMENTAL SEPSIS THERAPIES

Due to the complexity of immunologic defense and sepsis, the development of pharmacologic interventions is difficult (1, 218). One approach would be to prevent infection in patients at high risk. However, timely treatment to prevent sepsis or septic shock is often not possible, or the prevention of infection is simply insufficient. The standard treatment of bacterial sepsis often consists of administration of fluid and vasopressors to restore blood pressure and organ blood flow, oxygenation, and administration of antibiotics (65, 442, 589). Although eradication of the microbial organism and treatment of the pathophysiological changes are essential, alternative approaches actively suppressing the deleterious effects of inflammation while retaining the antimicrobial defense are needed. In this section, some approaches to the treatment of sepsis and septic shock are briefly described.

The first alternative approach to treatment of sepsis was through antibody preparations to LPS. Three anti-lipid A IgM preparations were used, HA-1A and E5 and a polyclonal antiserum against the LPS core of *E. coli* J5. The human anti-*E. coli* J5 (Rc-LPS) antiserum was first used to treat a small group of patients with septic shock. This cross-reactive antiserum barely significantly improved the overall prognosis in septic shock, but it was not possible to determine whether the antibodies or other compounds (e.g., inflammatory mediators) from the donor conferred protection (618). E5 decreased mortality in a first trial but provided no protection in successive trials (8, 174). HA-1A (Centoxin), was protective in one trial but had no effect in a second and tended to increase mortality in a subgroup of patients in a third trial (31, 69, 548). Very little is known about the mechanism of protection of these antibodies. Although it was expected that the HA-1A antibody recognized lipid A specifically, it was later discovered that it bound rather nonspecifically to hydrophobic substances (31). Other attempts to treat patients with an anti-LPS antibody have also failed (218). As listed in Table 7 a substantial number of patients have been treated with the various preparations, but no overall benefit was observed.

TABLE 7. Randomized controlled trials of immunotherapy in sepsis and septic shock[a]

Type of trial	No. of trials	Total no. of patients	Mortality (%) in patients receiving:	
			Placebo	Therapy
Anti-endotoxin	4	2,010	35	35
Anti-IL-1R	3	1,898	35	31
Anti-bradykinin	2	755	36	39
Anti-PAF	2	870	50	45
Anti-TNF	8	4,132	41	40
Soluble TNF-R	2	688	38	40
NSAIDS	3	514	40	37
Steroids	9	1,267	35	39
Activated protein C	1	1,690	31	25
All studies	33	13,824	38	37

[a] Adapted from reference 17.

The recombinant 23-kDa N-terminal part of BPI, which is a powerful LPS-neutralizing agent, has also been used to treat septic patients. Although the initial results of a small trial in children with meningococcal sepsis were promising, a larger trial showed no real benefit (167, 309). In addition to the disappointing results of these trials, the use of therapeutics effective only against gram-negative organisms may not be desirable due to the delay caused by the time-consuming identification of the pathogenic organism.

Both in vitro studies with whole blood from septic patients and in vivo studies of healthy volunteers challenged with LPS indicate that treatment with recombinant HDL could be effective in combating septic shock. However, no data are yet available from clinical trials with recombinant HDL (171, 408, 409).

Immunosuppression and Neutralization of Proinflammatory Cytokines

Although general immunosuppression seems to be an obvious choice in the treatment of sepsis, the overall mortality increased (70). Similarly, nonsteroidal anti-inflammatory drugs that suppress the COX enzymes were also proven ineffective. Since TNF-α is a key mediator in the pathogenesis of sepsis, a recombinant humanized murine anti-TNF antibody preparation (Remicade or infliximab) and a TNF-R:Fc fusion protein (Enbrel, or etanercept) have been tested for the treatment of sepsis (64, 134). In clinical trials these preparations proved ineffective. Paradoxically, these TNF antagonists are very effective against Crohn's disease (inflammatory bowel disease) and rheumatoid arthritis, while they are contraindicated for infection and sepsis (113–115). Another important cytokine in inflammation and sepsis is IL-1. A recombinant IL-1 receptor antagonist has been tested in two large phase III trials but was not effective (404, 531). In healthy human volunteers, LPS tolerance could be induced by the infusion of monophosphoryl lipid A, but no clinical trials with septic patients have been performed (18). Interestingly, cross-tolerance to gram-positive infection could be induced in mice, indicating that this therapy might be effective in gram-negative and gram-positive sepsis (16).

The use of corticosteroids has been a subject of debate for many years. Corticosteroids are known to regulate a number of immune responses. They inhibit a number of inflammatory processes, such as leukocyte infiltration and cytokine production, and have a positive effect on cardiac output by a blockade of NO synthesis (48, 371). Based on these effects, patients have been treated in two large clinical trials using corticoids in the early phase of sepsis (326). The results of these trials indicated eventually that there were no beneficial effects of corticoids in the early phase of sepsis. More recently, it was observed that patients with a so-called adrenocortical insufficiency may have a poor prognosis (45, 70, 305, 492). Based on this hypothesis, trials were started in which patients were treated with a lower dose of corticosteroids (300 mg of hydrocortisone per day) for a number of days at a later stage in sepsis. The outcome of this lower dose of steroids seems to be more promising than the higher dose of steroids in the early phase of sepsis (45, 70, 305, 492).

The latest success in the treatment of sepsis in adults was the PROWESS study (Human Activated PROtein C Worldwide Evaluation in Severe Sepsis) (38). In this large double-blind study, the effect of activated protein C was studied. After the treatment of 1,520 patients, the study was abrogated because of the significant survival advantage in the actively treated group (24.7% mortality versus 30.8% for placebo [$P = 0.005$]). The mode of action of activated protein C is most probably based on its ability to inhibit both thrombosis (lower levels of D-dimer) and inflammation (as seen in a reduced level of IL-6), whereas fibrinolysis is promoted. However, more studies are needed before activated protein C is widely introduced as a therapeutic in the treatment. Although the blocking or modulation of a number of other targets, including complement and coagulation factors, neutrophil adherence, and NO release, are promising in animals, it remains to be determined whether these therapeutic approaches will be effective in humans (1, 218, 547).

CONCLUDING REMARKS

Despite the extensive array of protective mechanisms employed by bacteria, in mammals an innate, sensitive system to detect and eradicate bacteria has evolved. The immune system is a double-edged sword: besides its ability to effectively detect bacteria and mount an immune response to eradicate them, it may also cause serious damage to the body, even leading to death. The rise and fall of an immune response is regulated by a complex, extensive system of pro- and anti-inflammatory receptors, cytokines, and other serum factors affecting the bacteria directly or modulating the cellular response to the bacteria. It is difficult to unequivocally attribute a fully pro- or anti-inflammatory role to inflammatory mediators and receptors. The experiments with TNF knockout mice and TNF receptor knockout mice, for instance, have shown that these mice exhibit a drastically reduced sensitivity to LPS but succumb to small amounts of live bacteria or yeast (343, 422).

In human patients with sepsis, several putative therapies have aimed at the neutralization of the proinflammatory cytokines TNF and IL-1. These therapies have proven ineffective or even counterproductive in some cases, leading to unchanged or increased mortality in the drug-treated patient groups (64, 134). This shows that treatment of sepsis or septic shock may not simply be a matter of administrating anti-inflammatory

agents or neutralizing their proinflammatory counterparts. Such therapeutic interventions may cause a shifted proinflammatory and anti-inflammatory balance, thus compromising the endogenous regulatory processes controlling the inflammatory cascade. Therapy of sepsis and septic shock will therefore have to simultaneously aim at maintaining homeostasis (part of the mechanism of action of the newly approved recombinant human activated protein C) and at eradication of the bacteria. Instead of combating the detrimental immune response during sepsis, an attempt should be made to restore the balance between the pro- and anti-inflammatory responses.

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