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Review

Lipopolysaccharide-Induced Immunological Tolerance in Monocyte-Derived Dendritic Cells

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Abstract: Bacterial lipopolysaccharides (LPS), also referred to as endotoxins, are major outer surface membrane components present on almost all Gram-negative bacteria and are major determinants of sepsis-related clinical complications including septic shock. LPS acts as a strong stimulator of innate or natural immunity in a wide variety of eukaryotic species ranging from insects to humans including specific effects on the adaptive immune system. However, following immune stimulation, lipopolysaccharide can induce tolerance which is an essential immune-homeostatic response that prevents overactivation of the inflammatory response. The tolerance induced by LPS is a state of reduced immune responsiveness due to persistent and repeated challenges, resulting in decreased expression of pro-inflammatory modulators and up-regulation of antimicrobials and other mediators that promote a reduction of inflammation. The presence of environmental-derived LPS may play a key role in decreasing autoimmune diseases and gut tolerance to the plethora of ingested antigens. The use of LPS may be an important immune adjuvant as demonstrated by the promotion of IDO1 increase when present in the fusion protein complex of CTB-INS (a chimera of the cholera toxin B subunit linked to proinsulin) that inhibits human monocyte-derived DC (moDC) activation, which may act through an IDO1-dependent pathway. The resultant state of DC tolerance can be further enhanced by the presence of residual E. coli lipopolysaccharide (LPS) which is almost always present in partially purified CTB-INS preparations. The approach to using an adjuvant with an autoantigen in immunotherapy promises effective treatment for devastating tissue-specific autoimmune diseases like multiple sclerosis (MS) and type 1 diabetes (T1D).

Keywords: immunological tolerance; LPS; cholera toxin B; indoleamine 2,3 dioxygenase

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1. Introduction

Understanding the role of LPS in both the toxicity of bacterial infections and effects on immune regulation has emerged as a critical objective due to the global importance of sepsis. The LPS bacterial surface molecule is produced by most Gram-negative bacteria. The attention LPS received in the early 20th century was due to its ability to stimulate the immune system, and was known as endotoxin glycolipids [1]. It was subsequently discovered that LPS created a permeable barrier on the cell surface and was the main driver of the innate resistance of Gram-negative bacteria to many antibacterial agents [1–4]. Unsurprisingly, these important properties of LPS have provided a vast and extensive literature for over 100 years.

The innate immune system's detection of microorganisms or microbial components is mediated by a special set of proteins called pattern recognition receptors (PRRs). One of the best studied PRRs is the bacterial LPS receptor, Toll-like receptor 4 (TLR4) [5,6]. TLR4 is an important driver of the immune response to bacterial infections and its dysregulation is thought to promote abnormal cytokine production, leading to bacterial sepsis [3,4,7,8].

Because sepsis remains one of the major conditions leading to acute morbidity and mortality, understanding the nature of TLR4 signaling will direct efforts towards understanding the basic mechanisms underlying inflammation and can lead to improved clinical outcome. Bacterial LPS is widely used in inflammation models because it induces many inflammatory effects by promoting the production and release of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 [8–10].

LPS signaling by PRR leads to the activation of intracellular signaling networks that promote the expression of inflammatory genes which stimulate the acute and sustained defense of the host [6,7]. TLR4 first encounters LPS in extracellular space when interacting with intact bacteria or when exposed to soluble LPS aggregates. Upon binding to LPS, TLR4 rapidly induces the assembly of supramolecular organization centers (SMOC) called myddosomes [11].

The intermediate consists of the MyD88 adapter protein and several serine-threonine kinases from the TIRAP and IRAK families [5–8]. This hub-like organizing center is a major subcellular site where TLR4 signaling activates the NF-κB and AP-1 pathways to promote the expression of inflammatory genes [12–14]. Subsequently, TLR4 is taken up by endosomes and promotes the production of IRF3-dependent interferon type I (IFN) via TRAM and TRIF adaptor proteins [15–17].

LPS acts as a proto-endotoxin and contributes to the inflammatory cascade because it binds to the CD14/TLR4/MD2 receptor complex in many cell types, but primarily to monocytes, dendritic cells, macrophages, and B cells. In these cell types, LPS stimulates the secretion of proinflammatory cytokines, eicosanoids, and nitric oxide [1,7]. Due to its role in the activation of several transcription factors, LPS activity has been experimentally investigated for many years [1,2,7,18].

Humans are more sensitive to LPS than other animals (e.g., mice). An LPS dose of 1 mcg/kg causes shock in humans, but mice can tolerate doses up to 1000 times that amount [19]. For this reason, LPS levels in pharmaceutical products and medical devices must be strictly monitored using the limulus amebocyte lysate (LAL) assay. This requirement may be due to differences in the amount of circulating natural anti-LPS antibodies between the two species [20,21].

Multiple pathways may be activated on engagement with LPS because it has been shown that LPS has both an immunostimulatory as well as immunosuppressive roles to play in immune activation of immune cells [22,23]. Consequently, despite LPS being recognized as a classical immune stimulating factor best characterized in bacterial infection, there is clear evidence of a far more complex role for LPS in the immune cascade.

Dendritic cells (DCs), considered the most potent APCs, are critical gateways of the immune system and have the unique ability to synthesize a wide range of input signals and transmit them to naive lymphocytes, thus directing immunization, or suppression of pathogenic microorganisms and tumors [24]. When confronted with pathogen-associated molecular structures, DCs "mature" by upregulating the expression of MHC class II receptors that exhibit antigen, cofactors, and processed cytokines and chemokines [25]. DCs contain TLRs which are major pattern recognition receptors that initiate and regulate immune responses via various signaling pathways [26]. Thus, the application and targeted regulation of DCs to control cancer and infectious diseases is being pursued in the development of clinical therapeutics [27]. However, DCs are also involved in the pathogenesis of diseases caused by immune cell dysfunction, such as chronic inflammation, autoimmunity, and cancer development and progression [28,29]. Uptake processing and presentation of self-antigens as foreign proteins is considered fundamental to the development of autoimmune conditions such as type 1 diabetes. Thus, targeting the downregulation of DC activation may be a useful strategy for treatment of these diseases.

Monocytes are also important in the early acute inflammatory phase of the immune response to an infectious agent because they can stimulate and modulate the adaptive immune system by inducing cytokine secretion and antigen presentation to T cells [30,31]. The adaptive immune response is complimentary to the innate immune response and these two processes can simultaneously eliminate pathogens. In most cases, monocytes initiate and enhance

the immune response. However, LPS activation of monocytes has been shown to suppress the T cell immune response and induce the expression of FOXP3 regulatory T cell function modulators in resting CD4 + CD25 T cells via a PGE2-dependent mechanism [32].

LPS also plays an immunosuppressive role in autoimmunity [22]. For example, repeated exposure to LPS causes a state of endotoxin tolerance that, in part, contributes to the well-recognized state of immunosuppression seen in sepsis [33,34]. This effect is particularly important in antigen presenting cells such as monocytes [35] and dendritic cells [27,36,37].

Furthermore, exposure of bone marrow-derived dendritic cells (BMDC) to high doses of pure lipopolysaccharide for 24 h (LPS-primed BMDC) increases their potency in the prevention of inter-photoreceptor retinoid binding protein in Freund's adjuvant-induced experimental autoimmune uveoretinitis (EAU) [38].

The concept that exposure to LPS is important for interacting with the immune system to prevent allergic and autoimmune diseases has a long history. Strachan proposed the hygiene hypothesis in 1989, and since then there have been many studies indicating differences in endotoxin levels in different habitats. These studies showed an association between LPS in house dust and the incidence of asthma. Children in rural areas have significantly fewer autoimmune diseases, such as type 1 diabetes, asthma, allergies, and generalized atopy, compared to children in urban environments, but these observations are largely descriptive [39]. Children who grew up on farms had lower rates of allergies and asthma, and dust-contaminated bedding and mattresses in their homes contained higher levels of LPS [39], a result suggesting that chronic environmental LPS exposure can promote immunotolerance to environmental antigens.

Early studies in animal models showed that the increased sensitivity of C3H/HeJ mice to food allergens was due to an inability to signal through TLR4 [40]. Neonatal administration of a cocktail of broad-spectrum antibiotics induced a food allergy response in TLR4-sufficient mice—similar to those seen in TLR4-deficient mice—which identifies the intestinal microbiota as a source of TLR4 ligand [40]. The authors of this new study confirm that several mouse model studies have shown that NOD mice that are sensitive to T1D are protected against the disease by oral or intraperitoneal administration of LPS [41]. Recent developments have revealed the mechanisms underlying adjuvant stimulated fusion protein vaccines such as the cholera toxin B subunit adjuvant linked to autoantigens like proinsulin (CTB-INS) for the protection against autoimmunity. It was shown that CTB-INS impedes human monocyte-derived DC (moDC) activation through stimulation of indoleamine 2,3 dioxygenase (IDO1) biosynthesis [42,43]. The resulting state of DC tolerance was enhanced by the residual presence of E. coli lipopolysaccharide (LPS) in partially purified CTB-INS preparations [37]. This adjuvant-like action for LPS is now recognized in vaccine development. However, the toxicity of LPS may limit its use [44,45]. Later in this review we examine in a detailed fashion, the role of LPS in the suppression of CTB-INS-induced DC activation in the context of autoimmunity.

2. Function of LPS

2.1. Virulence and Toxicity

Lipid A, which is the toxic component of LPS, and polysaccharide side chains, which are considered the non-toxic but immunogenic part of LPS, act as virulence determinants in Gram-negative bacteria [46–48]. O antigens have adhesive properties, phagocyte resistance, antigen protection, and antigen mutation properties [47,49]. Lipid A acts as an immunostimulant that induces biological responses to a specific organism [50–52].

2.2. Biological Activity of Lipopolysaccharide

An animal's biological immune responses can be analyzed using various parameters, such as an injection of live or killed Gram-negative cells or purified LPS in laboratory animals, which causes a broad spectrum of pathophysiological responses, such as fever, changes in blood counts, disseminated intravascular coagulation white blood cells, hypotension, and shock resulting in death. Injecting very small doses of endotoxin can cause

death in most mammals. The sequence of events follows a regular pattern: (1) latency period; (2) physiological stress (diarrhea, exhaustion, shock); and (3) death. The rate at which death occurs depends on the dose of the endotoxin, the route of administration of the toxin, and the animal species.

3. Lipopolysaccharide Signaling and Immune Activation Mechanisms in Higher Organisms

3.1. Lipopolysaccharide Detoxification Mechanisms in Higher Animals

The defense against infection in vertebrates is mediated by two interdependent arms of the immune system, known as innate and adaptive portions of the immune system. The innate immune system, consisting of antigen presenting cells, recognizes a diverse array of non-self-antigens and if overwhelmed, can signal and activate the adaptive immune system through well-established signaling pathways to stimulate an array of T-cells and B-cells to overcome the pathogen [53]. As LPS can have significant adverse effects on animals and humans, a process to detoxify LPS has been developed [54]. The detoxification mechanism of LPS occurs through enzymatic degradation or through complement-mediated detoxification, which leads to the breakdown of LPS.

3.2. Host-Microbe Interactions (Lipopolysaccharide Activity) in Invertebrates—Insects

The innate immune system of insects plays an important role in the development of immunity [55]. In recent years, arthropods and insects have become the most useful models for describing the molecular regulation of the innate immune response [56]. Insects have highly effective defense mechanisms against invasive microorganisms, which include Gram-negative and Gram-positive molecules, LPS, and peptidoglycan [55–57].

These insect defense mechanisms include cellular and humoral responses. Cellular responses include phagocytosis and/or encapsulation of large parasites by bacterial nodules and blood cells [58]. In addition, the humoral response uses various antimicrobial peptides which are synthesized in the adipose body and some hemocytes after induction by septic lesions and which are then secreted into the hemolymph [59–61]. The insect defense system against LPS pathogens results in a transient increase in antimicrobial activity in the acellular hemolymph, including phagocytosis and encapsulation of invaders by blood cells and subsequent production of antimicrobial proteins (mainly in the insect's adipose tissue) [62]. Strong immunoreactivity was found in the interaction between *Galleria mellonella* (large wax moth) and LPS. The high tolerance of LPS to insects can be explained by an extremely effective detoxification mechanism involving the binding of LPS to hemolymph lipophorins [63]. This observation suggests that LPS has the potential to induce immune activation.

Activation of the proteolytic cascade and coagulation cascade using LPS triggers the limulus hemocyte to act as a signaling mechanism [64–66]. In addition, a blood cell membrane receptor for LPS has been isolated from Bombyx mori silkworm that can transmit an activation signal for the synthesis of the antibacterial peptide cecropin B [67–69].

3.3. Expression of Genes and Signaling Action Induced by Lipopolysaccharide in Vertebrates and Invertebrates

It is a general phenomenon that antibacterial protein gene expression culminates a few hours after bacterial infection and decreases over time in vertebrates. This reduction in antibacterial protein gene expression has been shown to correlate with LPS deprivation [70,71]. TLRs, a class of pattern recognition receptors (PRRs) found in vertebrates, play an important role not only in initiating innate immunity, but also in activating adaptive immunity (Figure 1).

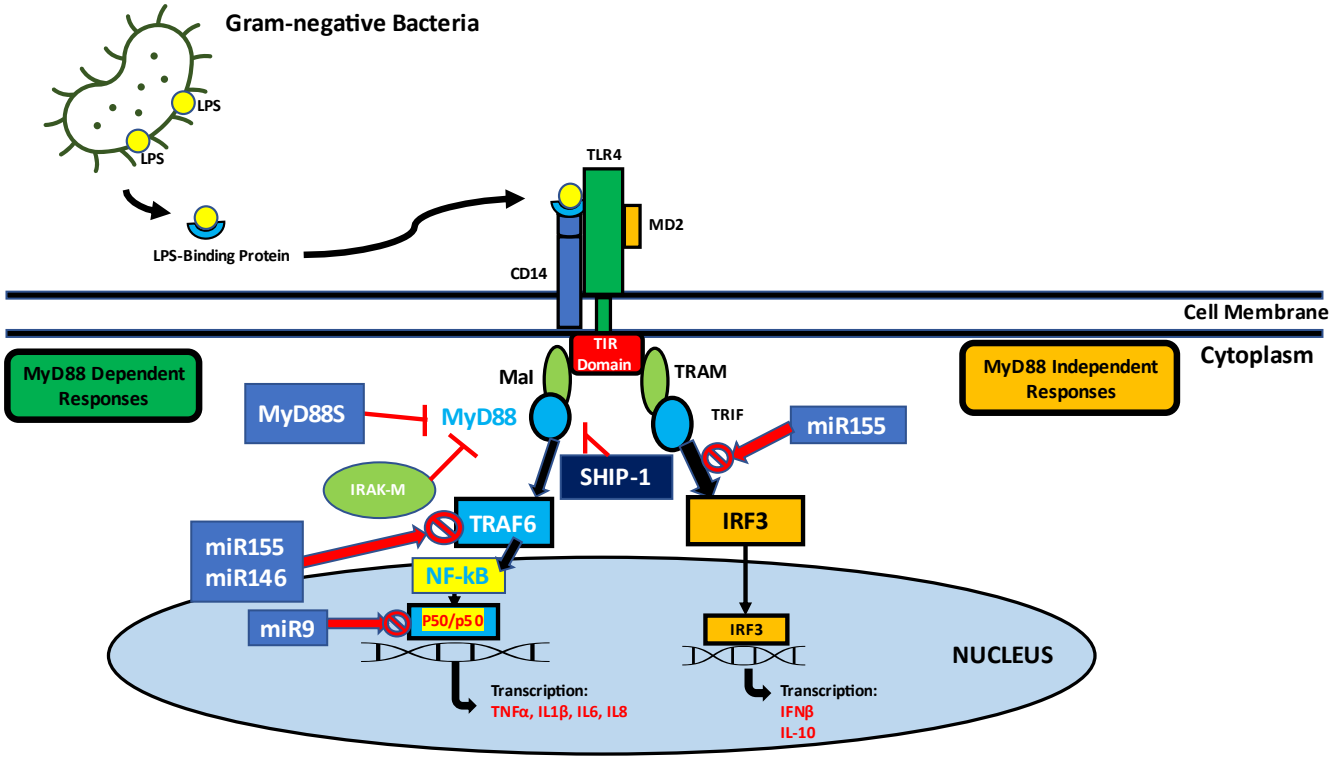

Figure 1. Endotoxin tolerance (ET) is defined as the reduced ability of cells to respond after exposure to endotoxin. The body becomes tolerant to subsequent attacks by lethal doses of endotoxin, and cytokine release and cell/tissue damage due to inflammatory responses are greatly reduced in endotoxin-resistant conditions. Key features of endotoxin tolerance are down-regulation of inflammatory mediators such as tumor necrosis factor (TNF-α) and interleukin-1β (IL-1β), upregulation of pro-inflammatory cytokines such as IL-10 and increased transforming growth factor (TGF-β). Alternative variants of MyD88S lacking an intermediate domain (ID) show a predominantly negative effect of suppressing the immune response by suppressing the MyD88 pathway. Tolerance mediators such as MyD88s, IRAK-M, and SHIP-1 are upregulated. In the endotoxin resistance phase, three LPS-inducible miRNAs (miR-155, miR-146α, and miR-9), were shown to mediate gene colocalization and transcription factor binding by blocking the binding of NF-kB p50 dimers and IRF3 as well as TRAF6-dependent NF-kB pathway, which contributes to the regulation of tolerance to endotoxins.

LPS non-specific recognition is well documented and reported in insects [72,73]. The signaling and triggering mechanism was identified in Bombyx mori [74,75]. LPS-increased levels of mRNAs were observed in A. gambiae mosquitoes containing Plasmodium berguei-infected abdomen contents [76,77]. LPS and β-1,3-glucan binding protein (LGBP) were isolated from Litopenaeus vannamei in which mRNA expression was induced by the challenge of the bacterium Vibrio alginolyticus [78,79].

Vertebrates have been shown to have acquired immunity with 'immunological memory', while invertebrates seem to lack this part of the adaptive immune system [80]. However, they have innate immunity, which is characterized by specific immune reactions against foreign antigens. Invertebrates are the most effective defense mechanisms of the cellular and humoral response against bacterial infections [57]. Mainly humoral reactions produce antimicrobial peptides to destroy pathogens [59,60] and this is followed by phagocytosis and nodule formation reactions as immediate defense responses to infection [81].

In addition, cellular defense reactions have been reported in invertebrates [82–84]. However, compared to cellular responses, humoral responses play an important role in immune defense. Insects do not appear to have an adaptive immune response that acts similarly to the well-documented antibody or the histocompatibility adaptive immune response of vertebrates [55]. In invertebrate immunity, LPS plays a role in the early stages

of signaling that activates acute phase protein genes. In particular, future research on immune surveillance and purification of pathogens in vertebrates and invertebrates could demonstrate the efficacy of innate immune systems based on bacterial endotoxins.

4. LPS in Inflammatory-Mediated Pathogenesis

4.1. Role of LPS from the Gut Microbiome in Inflammatory Conditions

The composition of the gut microbiome plays a critical role in maintaining local gut integrity, systemic homeostasis, and in regulating local and systemic immune responses. The microbiota can play a major role in immune regulation as well as the development of pathologies such as obesity, diabetes, fatty liver disease, carcinoma, and autoimmune diseases [85]. Incidences of esophageal adenocarcinoma have been increasing in recent years and it has been proposed to be linked to the resident local microbiota [86]. Recognition of the potential role of LPS was observed when mice fed a high-fat diet had higher blood LPS levels than normal chow-fed mice, resulting in inflammation of the liver and adipose tissue, which led to the development of insulin resistance, defining this condition as metabolic endotoxemia [87,88]. This low level of systemic LPS is related to an increased permeability or "leaky gut" phenomenon promoting inflammation in various tissue sites [89].

Subsequent studies on metabolic endotoxemia have been conducted for a variety of diseases. It has been reported that blood LPS levels are higher in humans with obesity [90,91]. The role of locally produced LPS has emerged as an important humoral factor that may have a key role in local and systemic inflammation and immune regulation [92].

The role that changes in the microbiome have on LPS production suggests that diet and the types of foods may both promote adverse immune–metabolic changes and can also serve as a remedy as demonstrated by the beneficial effects of green tea, a plant-based vegetarian diet [93], the Dietary Approaches to Stop Hypertension (DASH), and Mediterranean diets [94,95].

4.2. Bacterial LPS-Induced Lung Injury and Pathologies

As previously mentioned, inflammatory events can be regulated by NF-kB. TLR-4 activation by LPS can induce injury in areas where TLR-4 is activated [96]. Acute lung injury and acute respiratory distress syndrome are a result of strong inflammation that can potentially lead to extreme severe consequence including severe pulmonary edema and damage potentially triggering respiratory failure [96].

Non-typable Hemophilus influenzae (NTHi) causes lower respiratory tract infections, especially in patients with chronic obstructive pulmonary disease (COPD). Generally, NTHi infection is cleared by alveolar macrophages, but in patients with COPD it may not be readily cleared from the airway [97]. NTHi infections result in a TLR-dependent immune response in alveolar macrophages, eliciting the release of pro-inflammatory cytokines recruiting neutrophils to the lungs [98–101]. Proteins including Pellino-1 are E3 ubiquitin ligases that play a role in TLR-4 signaling in monocytes [102]. Expression levels of Pellino-1 are associated with persistent bacterial infections. Studies show that macrophages can up-regulate Pellino-1 in response to LPS and NTHi through TLR4 mechanisms [102,103]. In the Hughes et al. study, the absence of Pellino-1 gene in mice led to development of airway inflammation and resulted in recruitment of neutrophils. Another study shows that IL-5 expression in human peripheral blood mononuclear cells was induced by H. influenzae LPS. This increase in IL-5 expression is suggested to influence eosinophilic inflammation in patients with COPD [104].

4.3. LPS-induced Meningococcal Inflammatory Disorders

Neisseria meningitidis is a Gram-negative coccus that is implicated in meningitis and fulminant meningococcemia or meningococcal septicemia. The presence of *N. meningitidis* in the subarachnoid space can result in meningitis and while the organism continues to circulate and disseminate, it can lead to septicemia. *N. meningitidis* LPS cell activation requires an interaction with lipid A. Studies show that patients with fulminant septicemia

have high levels of LPS and CXCL10 while patients that manifest clinical symptoms of meningitis have low levels of LPS. Additional studies propose that meningococcal LPS leads to early expression of IFN-B through TLR-MyD88-independent pathway. It is suggested that IFN-B could activate the JAK/STAT signaling pathway [105].

4.4. LPS-induced Periodontal Inflammatory-Mediated Pathologies

Periodontitis is a chronic inflammation of the gum tissues that support the teeth. Gram-negative anaerobic and microaerophilic organisms including *Porhyromonas gingivalis*, *Treponema denticola*, *Tannerella forsythia*, and *Aggregatibacter actinomycetescomitans* are common etiological agents in periodontal disease. These bacteria are significant activators of inflammation in cells and tissues through increased secretion of inflammatory cytokines IL-B1, IL-6, and TNFα, among others. Studies report that hypoxia in the gingival region is commonly associated with inflammation [106]. The state of hypoxia can lead to activation of caspase-1 resulting in stimulating activation of IL-1B and IL-18 [106]. Gingival fibroblasts under hypoxia stimulated with *P. gingivalis* LPS resulted in the activation of caspase-1 and caspase 11 as well as IL-1B maturation [107]. Under normoxic conditions, in this study, there was a down-regulation of NLRP3, IL-1B precursor, and mature IL-1B resulting in a decrease in inflammation.

Autophagy is another important mechanism that stimulates inflammation. It has been shown that *P. gingivalis* LPS can stimulate reactive oxygen species-mediated autophagy. Further studies also showed that *P. gingivalis* LPS induced autophagy in human gingival fibroblasts [108]. Autophagy is generally down-regulated by the PI3K/Akt/mTOR pathway [108]. Suppression of these pathways are associated with autophagy. Human gingival fibroblast cells stimulated by *P. gingvalis* LPS showed suppression of PI3K/Akt/mTOR activity implicating autophagy [108].

In periodontal disease pathogenesis, LPS contributes to cellular senescence due to inflammation and remodeling of the extracellular matrix [109]. Studies show that exposure to Gram-negative bacteria components can facilitate cellular aging or senescence [110,111]. Further, prolonged exposure to LPS was shown to be proinflammatory and genotoxic on periodontal associated cells [112,113]. An example of such mechanisms can be seen in periodontitis, infection of gum tissues. Periodontitis is associated with alveolar bone loss. Studies show that bacterial LPS exposure in alveolar osteocytes can trigger premature alveolar osteocyte senescence leading to alveolar bone loss [109].

4.5. LPS and Neuroinflammation

There is evidence correlating inflammation with dementia and nerve injury. LPS from Gram-negative bacteria modulate TLR 2 and 4 as well as cytokine expression [114]. Studies strongly correlate chronic periodontitis with dementia [115–117]. These inflammatory responses can lead to neuronal loss and apoptosis. Additional studies show that *P. gingivalis* and *Escherichia coli* LPS can induce inflammatory changes within the nervous system [115]. Behavioral studies indicated that *P. gingivalis* LPS can induce cognitive impairment. While LPS from both *P. gingivalis* and *E. coli* impaired spatial learning and memory, *P. gingivalis* LPS was shown to activate microglia and astrocyte immune cells in the cortex and hippocampus [115]. Expression analysis of mice cortex stimulated with *P. gingivalis* showed an upregulation in proinflammatory cytokines TNF-α, IL-1β, IL-6, and IL-8 [115,118]. Microglia can produce potent proinflammatory cytokines inducing neuroinflammation [119]. Inflammation normally precedes the production of amyloid plaque development in brain tissue. In addition, LPS activated TLR4 leading to stimulation of the NF-kB signaling pathway, resulting in upregulation of TLR4, CD14, IRAK1, and p-p65 [115].

4.6. LPS Aggravates Inherited Retinal Dystrophy

Activated microglia release inflammatory mediators contributing to neurodegenerative diseases including retinal neurodegenerative diseases. Studies have shown that systemic administration of LPS activate retinal microglia [120]. Experiments with Sprague

Dawley rats show there are no significant morphological changes that alter retinal function [121]. Using a retinal dystrophy rat model, P23H, studies show that LPS exposure increases the degeneration of the P23H retina in comparison with untreated retina [122]. To evaluate changes on a molecular level, mRNA analyses show that LPS injection in Sprague Dawley rats caused upregulation in retinal expression of apoptotic genes including caspase 8, Bad, Bax, and Bcl-2 among others [121]. There were no inflammation genes that were upregulated in response to LPS. In P23H rats, the retina did show upregulation of several inflammation genes including TNF-α and IL-1β cytokines. Genetic analysis of apoptosis in p23H rat retinas treated with LPS showed upregulation of pro-apoptotic factors including Bcl-2, Bax, Bad, and Apaf-1 [121].

4.7. LPS-Induced Perinatal Impact of Maternal Inflammation

Chronic inflammatory responses are implicated in pre-term births, perinatal morbidity, and mortality. Pregnant mice challenged with *E. coli* LPS were likely to go into preterm labor. Further LPS exposure was able to cause neutrophilic infiltrates in fetal renal and pulmonary tissues [123,124]. When LPS was injected mid-or full gestation into pregnant sheep, there were observable injuries to the fetal brain, particularly in the white matter [125–128]. Intracerebral LPS exposure showed increased pro-inflammatory markers and caused a loss of oligodendroglial precursors. Intracerebral LPS exposure was also implicated in loss of myelination and bilateral ventricular dilation [129–131]. In addition, Oskvig et al. showed that pregnant Sprague Dawley rats exposed or challenged with LPS showed an increase in maternal serum cytokines [132]. The amniotic fluid and fetal brains of LPS challenged rats also showed increases in pro-inflammatory cytokine levels. The marked increase in the maternal immune response was shown to dysregulate gene expression in the fetal brain.

5. The Function of LPS in Immune Suppression

5.1. Endotoxin Tolerance

Endotoxin tolerance (ET) is an important immune homeostatic response that prevents unnecessary overactivation of the inflammatory response. It impairs the response to repeated attacks against LPS, leading to decreased expression of anti-inflammatory modulators, antimicrobial up-regulation, and other mediators that contribute to the inhibition of inflammation. If the reaction is not controlled, endotoxic shock can occur, which can lead to death. Though the mechanisms associated with ET are still largely under investigation, several studies have given us some insight.

The aryl hydrocarbon receptor (AhR) participates in protection against LPS-mediated tissue damage through ET, as it plays a necessary role in restraining the proinflammatory action of IL-1β and TNF-α while fostering the expression of protective TGF-β [133]. TGF-β, in turn, promotes durable expression of the tolerogenic enzyme indoleamine 2,3-dioxygenase 1 (IDO1) [42]. In the same vein, it has been shown TLR4 ligation in LPS-primed DCs induced higher levels of IDO isoforms together with the transcription factor aryl-hydrocarbon receptor (AhR) compared to unprimed controls [134]. These data could potentially explain why Mbongue et al. observed higher levels of IDO1 in human monocyte-derived DCs co-cultured with CTB-INS fusion protein [42] later found to contain significant amounts of LPS [37].

Upon binding to TLR4, LPS stimulates two signaling pathways—a gene-dependent pathway of the primary myeloid differentiation response 88 (My-D88) and a pathway independent of MyD88—both of which lead to NF-κB activation. ET is linked to overexpression of p50 NF-κB homodimers and decreased levels of the active p65/p50 NF-κB heterodimers [33,135]. Recent evidence has also shown RelB plays an important role in gene silencing in resistance. TLR4-induced RelB activation, together with G9a methyltransferase and histone H3 demethylation, induces a histone code switch from active transcription to attenuated transcription at the IL-1β promoter [136]. It is not surprising that Kim et al. have shown that a CTB-INS vaccine (later shown to have significant amount of endotoxin) [37] inoculated with moDCs showed by chromatin immunoprecipitation (ChIP) analysis that RelB bound to NF-κB consensus sequences in the IDO1 promoter and was crucial in its biosynthesis [43].

As Lopez-Collazo et al. expertly reviewed, extensive studies on the development of ET in genetically deficient mice have analyzed the participation of intracellular molecules in this process and established the roles of interleukin-1 receptor-associated kinase (IRAK) family (IRAK-M) and SRC-homology-2-domain-containing inositol-5-phosphatase (SHIP-1) occasionally observed in various models [34,137]. Since IRAK-M pseudokinase is one of the genes consistently induced in ET, it can be considered an important regulator of ET [138,139]. This was corroborated by a study conducted by Kobayashi and colleagues [140] that reported the first link between ET and IRAK-M when they described IRAK-M-deficient mice as unable to develop ET in vivo [34].

Cross-tolerance between TNF-α and LPS, as well as IL-1 and LPS, can also be induced in vivo and in vitro, although treatment with high doses of these cytokines is required [141]. Monocytes from patients with sepsis exhibit numerous characteristics of ET. For example, after an ex vivo challenge with LPS, it was shown that monocytes failed to produce proinflammatory cytokines, such as TNF-α, IL-12, IL-23, and IL-6 [142] in comparison with monocytes from healthy subjects. Down-regulation of major histocompatibility (MHC) class II, costimulatory factor CD86 has also been observed in circulating cells from patients with sepsis [34,143] which further decreases any T-cell interaction.

Based on studies showing that NF-κB activation is impaired in ET and that SHIP-1 inhibits the NF-κB pathway in bone marrow-derived mast cells stimulated with IgE plus antigen, SHIP has been identified as a potential target in understanding endotoxin tolerance. Further, SHIP-deficient mice have been shown to be more susceptible to LPS-induced toxicity than wild-type mice. SHIP-deficient mice produced significantly increased levels of pro-inflammatory cytokines and nitric oxide, suggesting that SHIP is a negative regulator of LPS-induced inflammatory mediator production. Unlike wild-type cells, bone marrow-derived monocytes and mast cells from SHIP-deficient mice showed no endotoxin tolerance [144,145]. In the latter study, TLR4 levels were similar for SHIP-deficient and SHIP-sufficient cells stimulated with a tolerizing dose of LPS. By contrast, SHIP protein expression was markedly upregulated after low-level stimulation with LPS in cells that were SHIP deficient. This suggests that the lack of induction of SHIP expression is the reason for the inability to generate endotoxin tolerance. Since microRNAs (miRNAs) can regulate gene expression at the transcriptional level, these factors have been studied in the field of ET. Several authors have described the activation of several miRNAs during ET, including miR-98, miR-221, miR-155, miR-125b, miR-579, let-7e, and miR-146a [146,147]. The expression of miR-146a involved in LPS-induced cross-tolerance acts as a negative regulatory feedback mechanism (or optimization mechanism) to prevent the destructive consequences of uncontrolled inflammatory responses caused by overactivation of TLR signaling [148]. Additionally, miR-98-mediated post-transcriptional control has been shown to be involved in fine tuning the critical level of IL-10 production in endotoxin tolerance [149]. miR-579, miR-221, and miR-125b were increased significantly in LPS-tolerized THP1 cells compared with naive cells and a second LPS stimulus in tolerized cells significantly increased their expression [150]. As Akt1$^{-/-}$ mice do not develop endotoxin tolerance in vivo, overexpression of let-7e and suppression of miR-155 in Akt1$^{-/-}$ APCs have been shown to restore LPS tolerance [151].

Gene-specific regulation in macrophages is mediated by modification of chromatin to silence a subset of TLR-inducible genes. Silencing is achieved by acquisition of non-permissive histone modifications and a block in nucleosome remodeling. This blocks the accessibility of gene loci to transcription factors [152,153]. For example, histone H3K4 trimethylation is induced in the promoter in response to LPS stimulation [154]. However, during resistance, H3K4 trimethylation is no longer induced at the promoter of a repressed gene, such as IL-6, but only at the promoter of a nonresistance gene [152]. In this study it was shown that treatment with the H3K4-demethylase-lysine-specific demethylase 1A inhibitor pargylin can restore the induction of H3K4 trimethylation at the IL-6 promoter and reduce IL-6 repression during resistance.

5.2. Role of LPS from the Gut Microbiome as an Anti-Inflammatory Agent

A group of LPS molecules mainly produced by certain microbiota bacteria such as Bacteroidetes show a decreased or even antagonistic activity in initiating pro-inflammatory responses (anti-inflammatory LPS, abbreviated as A-LPS and P-LPS standing for pro-inflammatory LPS) [155]. In a recent study, computational and experimental analyses of healthy human fecal samples on the TLR4 signaling capacity of the gut microbiota, revealed significant immunoinhibitory activity of LPS suggesting possible implications for prevention of autoimmunity. Comparative analysis of metagenomic data from the Human Microbiome Project and healthy-donor samples indicates that immune silencing via LPS is a microbe-intrinsic feature in all healthy adults [41,156,157]. Metagenomic sequencing delineated strain level contributions to the gut LPS pool and found that bacteria across the members of the order *Bacteroidales* produce forms of LPS (A-LPS), that drive immune silencing for the entire microbial community.

Chilton et al. established that the natural heterogeneity observed in the lipid A structure portion of LPS may produce differential modulatory effects on immune responses [45,155] and the immune silencing mechanism of A-LPS has been found to be closely related to lipid A acylation in contrast to P-LPS, where hypoacylation is frequently observed [157,158].

5.3. Role of LPS in CTB-INS-mediated Tolerance

5.3.1. CTB-INS Vaccines

Parenteral vaccination is widely considered to be the most effective treatment for the prevention of infectious diseases. Recently, combinatorial vaccination strategies have been developed to bind immunostimulatory molecules to antigens for mucosal vaccination and to increase vaccine efficacy. Important among the strategies to improve the immune system are bacterial toxins A and B, including subunits A (CTA) and B (CTB) of cholera toxin. Unlike the toxic CTA subunit, the non-toxic CTB subunit has transport and immunostimulatory properties [159,160]. When bound to a non-self-pathogen expressed antigen, CTB can confer immunostimulatory properties characteristic of the bound antigen. Vaccination strategies have been expanded to include "self" proteins used for immunological suppression of autoimmunity [159]. For example, in type 1 diabetes and many other tissue-specific autoimmune diseases, self-proteins are highly immunosuppressive. Interestingly, binding of CTBs to tumor-associated antigens can induce strong anti-inflammatory responses and is being developed for cancer immunotherapy.

To investigate this strategy, a type 1 diabetes vaccine was constructed linking CTB, a known mucosal immune adjuvant, to proinsulin as the autoantigen. The fusion protein uses a DNA sequence that codes for 258 bp of the human proinsulin gene (INS M12913.1) linked to the carboxy terminus of the DNA fragment (309 bp) that codes for the cholera toxin B subunit gene (CTB U25679.1) to create the CTB-INS fusion gene. Four GpGp sequences were inserted between the two genes to increase the flexibility of the molecule [42,161]. The CTB-INS fusion gene was then cloned into the *E. coli* PBR-322 expression vector and the amplified plasmid into the E. coli HB101 strain [162]. To obtain high levels of transgene expression, CTB-INS gene fusion was subcloned into the *E. coli* pRSET-A expression vector under the control of the T7 bacteriophage promoter. The resulting bacterial expression vector (pRSET-CTB-INS) contains oligonucleotides encoding six adjacent histidines immediately upstream of CTB-INS to allow isolation of recombinant fusion proteins on a nickel affinity column. The expression vector pRSET-CTB-INS was transformed with *E. coli*-producing strain BL21 (DE3) pLysS for the production and isolation of milligrams of CTB-INS protein [42,43,161–164]. The preparation of CTB-INS protein from *E. coli* was shown to lead to significant levels of endotoxin contamination largely responsible for the results obtained in vitro [37,42,43].

5.3.2. CTB-INS Vaccine Stimulation of Dendritic Cell Maturation

Tissue-specific autoimmune diseases with impaired metabolism, such as type 1 diabetes (T1D), are prone to serious medical conditions that shorten overall life expectancy [165,166].

Treatments that prevent or reverse the progression of T1D autoimmunity can have a significant impact on prolonging patients' rapidly increasing life expectancy. An important component of immune cells considered to be the key to autoimmune pathogenesis are dendritic cells (DC) [24].

Current immune strategies aim to inhibit DC induction of anti-inflammatory effector T cell differentiation by reducing inflammation that causes autoimmune diseases through functionally stable toxic resistance. The combination of proinsulin with the adjuvant of the B subunit of the cholera toxin expressed in plants (CTB-INS) has been shown to prevent insulitis and hyperglycemia in obese prediabetic mice (NODs) [167–169] and cell culture experiments have shown that DC stimulates autoimmunity in mice [36,170,171]. Conversely, induction of CTB-INS tolerance in mouse DCs was found to prevent T1D autoimmunity. Together, these experiments suggest that CTB-INS prevention of T1D is related to treatments that generate DC tolerance. Further studies suggest that CTB autoantigen fusion proteins induce tolerance by expanding Foxp3 (+) regulatory T-cell populations [172–174].

Additionally, stimulation of human DCs with CTB-INS has been shown to increase the biosynthesis of indoleamine-2,3-dioxigenase (IDO1), a key regulatory enzyme in the tryptophan degradation pathway known to induce a functional tolerance state in DC [42]. Moreover, the upregulation of IDO1 in DC takes place by activating the non-canonical NF-kB signaling pathway, but the receptors involved in CTB-INS signaling are still unknown [37]. It has previously been shown that DCs isolated from the blood of healthy subjects when stimulated with CTB-INS positively regulate the anti-inflammatory cytokines TGF-β and IL-10, which antagonize proinflammatory T cells and promote immune tolerance [163,164,175]. DC-T cell co-culture experiments have shown that DCs treated with CTB-INS inhibit the proliferation of anti-inflammatory T cells [163,164]. Furthermore, it has been shown that upregulation of IDO1 and its tryptophan degradation product (kynurenine) can induce a functional state of DC resistance that promotes DC tolerance and further inhibits DC activation by recruiting Tregs [42,43].

In this study, monocyte-derived dendritic cells (MoDCs) were prepared from freshly collected human peripheral blood cells isolated from aphaeresis filter cones obtained from a local blood bank. In the protocol outlined in [42], we had cultured CD14 monocytes with GMCSF and IL-10 until their differentiation into CD11c + dendritic cells prior to treatment with CTB-INS in vitro. Monocyte-derived dendritic cells (Mo-DCs) are a distinct subset of DCs involved in inflammation and infection, they originate from monocytes during circulatory stimulation, and their activation and function may differ in autoimmune diseases [176,177]. It is in this specific DC subset that the immunosuppressive effect of CTB-INS was observed. The authors have not observed this effect in macrophages but have not tested it in other DC subsets such as plasmacytoid DCs (pDC) or conventional DCs (cDC).

5.3.3. The Role of LPS in CTB-INS-Mediated Tolerance

Recent studies have shown that LPS residues present in CTB-INS fusion proteins used to treat healthy human DCs increase the regulation of IDO1 by CTB-INS [37]. The presence of residual LPS in CTB-INS-treated DCs activated the CD80 and CD86 co-stimulating factors, but did not stimulate the up-regulation of CD83 maturation factor, which may leave CTB-INS-treated DCs semi-activated [37].

Salazar et al. showed that TLR4 ligation induced higher levels of IDO isoforms, such as aryl hydrocarbon receptor (AhR) transcription factor, in DCs primed with LPS compared to untreated controls. Moreover, LPS has been shown to induce an anti-inflammatory phenotype in DC, as evidenced by up-regulation of IL-10 and increased expression of the programmed death ligands PD-L1 and PD-L2, which are dependent on IDO1 [178]. In addition, it was demonstrated that the aryl hydrocarbon pathway (AhR-IDO) may be responsible for the preferential activation of the LPS-regulated non-canonical NF-kB pathway in DC [134]. Taken together, these data suggest that LPS stimulates CTB-INS-induced DC synthesis of the immuno-inhibitory enzyme IDO1, which stimulates the release of kynurenines, tryptophan degradation products that initiate a state of functional tolerance

in human moDCs. Application of this experimental strategy could lead to the cessation of DC-mediated pro-inflammatory T cell responses important in the development of T1D autoimmunity. Furthermore, our data suggest that the presence of LPS in the CTB-INS fusion protein could significantly increase DC-mediated tolerance: (1) by inhibiting iDC activation (maturation), (2) through enzymatically active IDO1 levels, (3) through the production of functional kynurenines, and (4) through the increased secretion of anti-inflammatory IL-10 by DCs [10,37,43].

6. Future Directions

New antibiotics, vaccines and anti-inflammatory drugs may be the result of a deeper understanding of LPS-protein interactions at the molecular level. The application of structural biology, bacterial genomics, and animal knockout models to LPS biology is still under development. These new strategies need to be combined with older approaches, such as enzymology, carbohydrate chemistry, and membrane biochemistry to gain more information about the effects of LPS on the immune response. In the discussion of LPS biosynthesis, a detailed mechanical understanding of the biosynthesis and function of the base regions and O-polysaccharides is behind the understanding of lipid A function. However, genomic and other sequence-based studies have shown that the common biosynthetic pathway of LPS in different bacterial strains is evolutionarily conserved.

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Institutional Review Board Statement: Experiments on monocyte-derived DCs were performed ex-vivo, with aphaeresis blood provided by the Life Stream Blood Bank (San Bernardino, CA, USA) with Loma Linda University IRB and blood donor consent. Blood donor information was anonymized and de-identified prior to the study.

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