Arch. Immunol. Ther. Exp. (2012) 60:13–18
DOI 10.1007/s00005-011-0155-9

REVIEW

Molecular Mechanisms and Pathological Consequences of Endotoxin Tolerance and Priming

Matthew Morris · Liwu Li

Received: 23 June 2011 / Accepted: 27 September 2011 / Published online: 6 December 2011

Abstract Lipopolysaccharide (LPS), a component of Gram-negative bacteria, is a potent inflammatory stimulant, with high doses due to disseminated bacterial infection resulting in systemic inflammatory response syndrome and death. Lower doses can induce a state of tolerance to subsequent toxic doses of LPS, but extremely low doses have an opposite effect, priming the immune system for an even more violent response to subsequent challenge. A substantial body of research exists on the phenomenon of endotoxin tolerance, which appears to be a state of generalized dampening of inflammatory pathways. Comparatively little is known about the mechanisms or indeed the phenomenon of priming, particularly regarding the shift from a priming to a tolerizing response. Our aim is to review recent findings in the field of the inflammatory response to endotoxin, with a focus on highlighting the gaps in current understanding and attempting to reconcile the competing tolerance and priming phenomena.

Keywords Endotoxin · Tolerance · Priming · Sepsis · Inflammatory diseases

Introduction

Lipopolysaccharide (LPS) is a major component of the cell walls of Gram-negative bacteria. When introduced into an organism, it acts through the Toll-like receptor 4 (TLR4) to set off a powerful immune reaction (Cavaillon et al. 2003). This response is tightly regulated, but can be sufficiently perturbed to spiral out of control. The unbalanced response, as often seen in systemic inflammatory response syndrome (SIRS) and endotoxin shock where disseminated infection leads to elevated circulating endotoxin levels, is an increasingly common cause of death in the USA, having increased almost threefold from a 1993 level of 70,000 annually (Henricson et al. 1993; Hotchkiss et al. 2002). Minor systemic inflammation leads to fever, but more pronounced inflammation manifests itself in a cryogenic response which can result in dangerous hypothermia (Steiner and Romanovsky 2007). In healthy humans, an LPS dose of 1 ng/kg is sufficient to induce symptoms including fever and nausea (Sivapalaratnam et al. 2011). Due to the significant health concern posed by SIRS, extensive studies have been undertaken that depict a highly complex and dynamic system of host responses to LPS. These responses are difficult to study, as they can vary widely between species, with humans in particular being some 100,000 times more sensitive than mice to LPS (Munford 2010). This difference in sensitivity has been attributed to different forms of the CD14 LPS-binding protein between species and more recently to different serum factors (Ferrero et al. 1993; Munford 2010). Other species-specific cellular receptors and intracellular signaling molecules may also contribute to the observed differences and cannot be excluded.

The immune response to LPS can take a number of different forms, depending on the dose. Low doses have been shown in vivo and in vitro to induce a state of tolerance, in which the immune response to subsequent LPS challenge is altered (Biswas and Lopez-Collazo 2009; Yoza and McCall 2011). This alteration is complex, involving both the suppression of pro-inflammatory actors and the activation of anti-inflammatory actors, leading some authors to suggest

M. Morris · L. Li (✉)
Department of Biological Sciences,
Inflammation Biology and Immunobiology,
Center for Inflammation, Virginia Tech,
Blacksburg, VA 24061-0910, USA
e-mail: lwli@vt.edu

that "reprogramming" might be a more accurate descriptor than "tolerance" (Yoza and McCall 2011). The duration of exposure has also been implicated in different immune responses (Vaknin et al. 2008). Repeated exposure to endotoxin was first discovered to result in a diminution of the immune response in 1946, and a large body of research on its mechanisms and operating constraints has since arisen (Cavaillon et al. 2003). A recent study showed that chronic exposure to LPS can protect against the development of allergies and asthma and in some cases even mitigate pre-existing allergies (Arora et al. 2011). For the purposes of this review, "low dose" will be used in reference to doses of LPS in the 1–100 ng/mL range.

In contrast, even smaller doses of endotoxin (in the 0.05–0.5 ng/mL range; hereafter "super low") have been shown to have the opposite effect: the inflammatory response to subsequent endotoxin challenge is augmented, rather than reduced, in a phenomenon often referred to as the Shwartzman-like reaction (Heremans et al. 1990). The Shwartzman-like reaction has been well documented, but generally in vivo, with little molecular-level work having been done since the 1990s. Indeed, the phenomenon appears to have been largely overlooked, relegated to the status of a clinical curiosity useful only as a disease model for other conditions (Berg et al. 1995; Heremans et al. 1990; Motegi et al. 2006; Rocksén et al. 2004; Slofstra et al. 2006). The mechanisms governing the decision between a Shwartzman-like or tolerogenic response have been largely unexplored, with existing research on the subject having turned up a labyrinthine tangle of signaling cascades. Theoretical and systems approaches have been employed with some success, but suffer from a lack of data (Covert et al. 2005; Fan et al. 2010; Gilchrist et al. 2006; Jiang et al. 2006). It is the aim of this review to identify gaps in the current understanding of the innate immune response to LPS, with particular attention to the balance between the pro-inflammatory Shwartzman-like and the anti-inflammatory tolerogenic responses.

The Priming Effects of Super Low Dose LPS

Super low doses of endotoxin, in the 0.1 ng/mL range, have been associated with a spike in the production of pro-inflammatory cytokines upon subsequent endotoxin challenge, resulting in a significant increase in mortality in mice (Henricson et al. 1993; Heremans et al. 1990; Hirohashi and Morrison 1996; Li and Wei 2009). A 2002 study found that LPS was necessary for sensitization of humans to allergens in certain quantities, with low inhaled doses of about 100 ng inducing Th2 cells, while high, 100 μg doses induce a Th1 response (Eisenbarth et al. 2002). It is important to note that concentrations in the super low range described above were not examined in that study, leaving open the possibility for further induction of pro-inflammatory responses at that level. The increased inflammation can be augmented by co-stimulation of the pro-inflammatory cytokine interferon γ (IFN-γ), and was found to be ameliorated by an antibody against IFN-γ. In mice primed with higher doses of LPS, tumor necrosis factor α (TNF-α) levels upon secondary challenge were increased to a lesser degree. The dose necessary to induce priming appeared to be dependent on the injection site, with intravenous injections requiring lower levels of LPS while footpad injections elicited no response, leading the authors to suggest that it is the circulating levels of endotoxin which govern the immune response (Heremans et al. 1990). The discovery that higher initial doses can mitigate the TNF-α response to secondary challenge is suggestive of a dose-dependent mechanism governing the shift between priming and tolerance. Priming of lymphocytes with interleukin 12 (IL-12) has also been shown to result in increased TNF-α upon LPS exposure, acting through IFN-γ (Motegi et al. 2006). A 1996 experiment showed that pre-treatment of mouse macrophages with LPS at approximately 0.1 ng/mL resulted in a huge spike in IL-6 and TNF-α production upon secondary stimulation by a higher dose. Nitrite levels were found to be markedly reduced, which was taken as an indication of increased nitric oxide synthase activity, another sign of a heightened inflammatory state (Hirohashi and Morrison 1996). A 2009 in vivo study revealed that recruitment of pro-inflammatory (Gr1-high) monocytes to the lungs of mice was increased after an injection of super low priming doses of LPS. Of particular interest is the fact that this recruitment is slower, but more persistent than that induced by higher, more-toxic doses, indicating the involvement of different mechanisms (O'Dea et al. 2009). The connection between low-grade endotoxemia and chronic inflammation has been further buttressed by a study, which showed that levels of C-reactive protein, a marker of inflammation, were chronically elevated in human hemodialysis patients with circulating LPS levels in the 1–10 pg/mL range, so low that they have only recently become detectable (Terawaki et al. 2010).

We recently found evidence that this upregulation of inflammatory effectors acts through IL-1-receptor associated kinase (IRAK)1, selectively inducing CCAAT/enhancer-binding protein δ (C/EBPδ), while leaving nuclear factor κB (NFκB) unactivated. IRAK1 is critical for the removal of suppressive nuclear receptors from inflammatory genes in response to super low endotoxin in what appears to be a separate pathway from that engaged by higher doses (Maitra et al. 2011).

Although NFκB is a potent transcription factor that can induce robust expression of pro-inflammatory mediators, it also induces compensatory negative regulators such as SOCS1, IκBα and MKP-1. As a consequence, high doses of

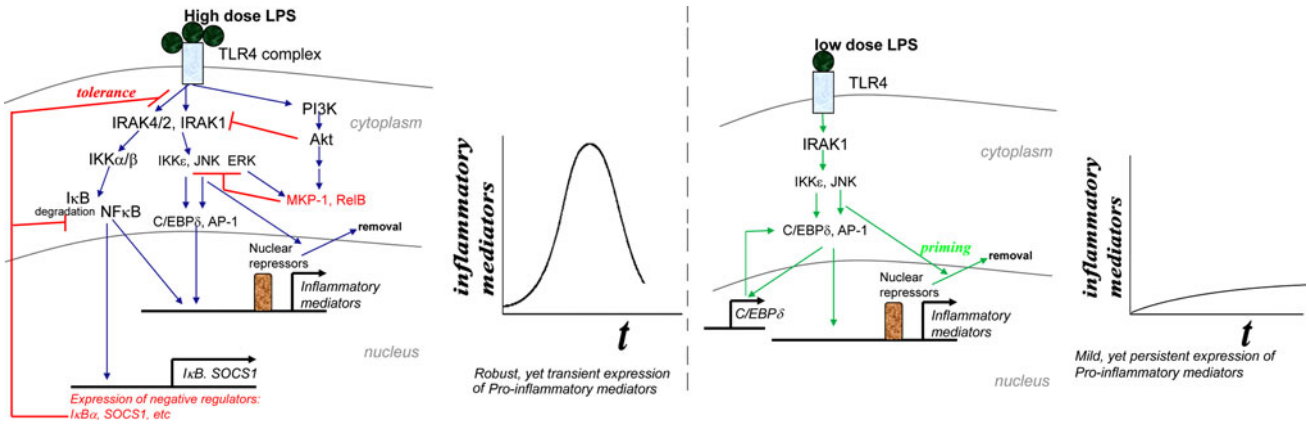

Fig. 1 A schematic illustration of potential mechanisms responsible for endotoxin priming and tolerance

LPS induce a robust yet transient expression of pro-inflammatory mediators (Fig. 1). In contrast, due to the lack of NFκB and related negative regulators, super low-dose LPS can induce mild and persistent expression of pro-inflammatory mediators, for example, the activation of C/EBPδ and removal of suppressive nuclear receptors (Fig. 1) (Maitra et al. 2011).

The anti-inflammatory cytokine IL-10 appears to play a crucial role in ameliorating the response of the immune system to LPS, as IL-10-deficient mice were shown to be far more susceptible than wild-type mice to endotoxic shock. This increased sensitivity translated to priming doses as well: IL-10-deficient mice exhibited the Shwartzman reaction after being primed with a dose of LPS 100 times less than that required to induce priming in wild-type mice. Importantly, injection of IL-10 established resistance to priming, and significantly decreased LPS susceptibility in both wild-type and IL-10-deficient mice (Berg et al. 1995). This observation has been further supported by an experiment showing a transient increase in IL-10 production in mice primed for a generalized Shwartzman reaction, along with the pro-inflammatory cytokines IL-1β, IL-6, and TNF-α (Slofstra et al. 2006). Taken together, those results suggest that IL-10 may be induced to counterbalance the potent pro-inflammatory mechanisms set in motion by LPS. In all, it appears that the response to LPS depends strongly on the inflammatory state of the immune system at the time of challenge. Even a small increase in the activity of pro-inflammatory cytokines tends to be associated with a violent immune response to subsequent LPS challenge. At the same time, exposure to super low doses of LPS seems to allow the upregulation of pro-inflammatory signals in an almost completely unchecked fashion, with the comparatively anemic attempts of the system to counterbalance the inflammatory response with anti-inflammatory mediators such as IL-10 appearing wholly inadequate.

In addition to the Shwartzman reaction, several studies have indicated that a phenomenon of cross-priming exists, in which low-level exposure to particular antigens can prime the immune system for a heightened response to an entirely different stimulus. As early as 1979, it was known that prior exposure to bacillus Calmette-Guerin, actinomycin or lead acetate markedly increased the susceptibility of various animals to endotoxic shock. An experiment was performed which showed that the hepatotoxic agent galactosamine increased LPS sensitivity several thousand times (Galanos et al. 1979). A cross-priming response to various antigens in neutrophils has been established since the 1980s, while more recent studies have shown that they can also be sensitized by LPS (McPhail et al. 1984; Pacquelet et al. 2007).

All of these observations show that the innate immune responses to a broad range of stimuli are interconnected and complex, with the identity and dose of an initial stimulus capable of inducing wildly different responses to a later challenge. Further characterization of these responses and the cross talk between them is imperative for the development of a fuller understanding of both endotoxic shock and runaway acute inflammation in general.

The Tolerance Effects of Elevated Levels of LPS

Low doses of endotoxin have been known since the 1940s to suppress the immune response to subsequent endotoxin challenge, in a phenomenon broadly characterized by suppression of pro-inflammatory cytokines and upregulation of anti-inflammatory actors (Biswas and Lopez-Collazo 2009; Cavaillon et al. 2003). Tolerance extends to the physiological level, with readily apparent effects on symptoms such as fever and ultimately survival of septic shock (Cavaillon et al. 2003). The molecular mechanisms responsible for endotoxin tolerance are multifactorial, and likely involve negative feedbacks at multiple levels. These include degradation of proximal signaling molecules such as IRAK-1 and induction of negative regulators including SOCS-1, IκBα, RelB,

IRAK-M and MKP-1 (Albrecht et al. 2008; Li et al. 2000; Jacinto et al. 2002; Nimah et al. 2005; Wiersinga et al. 2009; Xiong et al. 2011). Indeed, overexpression of RelB was shown to produce a phenotype similar to LPS tolerance, which suggests that RelB may play a crucial role in its establishment (Chen et al. 2009; Yoza et al. 2006). As an alternative to p65 sequestration, RelB has been recently implicated in the suppression of IL-1β through the formation of facultative heterochromatin (Chen et al. 2009).

RelB in turn seems to depend on abundant p50 to bind DNA, as it can only enter the nucleus in the form of the RelB/p50 heterodimer. RelB/p50 upregulates both RelB and p50, indicating that the system is biased toward dedicating to an anti-inflammatory response once established. When overexpressed, RelB/p50 enhances the antigen-presenting activity of dendritic cells (Gasparini et al. 2009). Interestingly, though antigen-presenting activity is a hallmark of classically activated macrophages, endotoxin tolerance strongly promotes the development of alternatively activated macrophages in a p50-dependent fashion (Porta et al. 2009). Additionally, p50-deficient mice are incapable of establishing endotoxin tolerance and become more susceptible to the violently inflammatory priming reaction described above (Porta et al. 2009).

Phosphatidylinositol-3-kinase (PI3K) is associated with signaling by TLR2 and TLR4, appearing to act as a negative regulator. Inhibition of PI3K in vitro in mouse bone marrow-derived macrophages has been shown to result in an upregulation of TNF-α and IL-6 in response to TLR2 signaling (Medina et al. 2010). Deficiency of phosphoinositide-dependent kinase 1, a downstream effector of PI3K, in myeloid cells has been shown to render mice more susceptible to TLR4-mediated septic shock (Chaurasia et al. 2010). In contrast, FoxO1, another molecule regulated by PI3K, upregulates the production of TLR4 in response to stimulation by TLR4 or TNF-α (Fan et al. 2010). The SH2-domain containing inositol phosphatase (SHIP) counteracts the effects of PI3K, and SHIP$^{-/-}$ mice have been shown to be unable to establish tolerance (Sly et al. 2004), suggesting a more complex role for PI3K than that of a simple, broadly anti-inflammatory pressure. More generalized anti-inflammatory effects have been associated with the activity of the Tyr3, Axl and Mer receptor tyrosine kinases (TAM). When challenged with LPS, neutrophils release ectosomes high in phosphatidylserine, a ligand for the TAM receptors (Eken et al. 2010). When activated, TAM receptors upregulate themselves along with inhibitory molecules such as the suppressor of cytokine signaling 1 (SOCS1), resulting in anti-inflammatory effects. Knockouts of the TAM receptors are also more susceptible to endotoxic shock (Rothlin et al. 2007).

This suggests that the decision between priming and tolerization is governed by the induction of downstream effectors, with some critical point existing at which generally anti-inflammatory mediators such as p50, RelB and the TAM receptors are induced to a level sufficient to allow their positive feedback mechanisms to become self-sustaining. Theoretical methods could likely be employed here to a great effect.

At the cellular level, exposure to low concentrations of LPS induces suppressive cells related to, but distinct from, myeloid-derived suppressor cells, which appear to protect against allergy and asthma by suppressing Th2 cell activity. Doses of about 100 ng of LPS in humans (corresponding roughly to the subclinical level defined above) appear to increase the risk of asthma development along with all the attendant inflammatory symptoms, while low doses in the microgram range suppress inflammation (Arora et al. 2011). Inhalation of 100 ng of LPS has been shown slightly to ameliorate inflammation upon subsequent stimulation by ovalbumin, with LPS-stimulated mice showing slightly fewer immune cells in bronchoalveolar lavage fluid than a control group treated with phosphate-buffered saline (Eisenbarth et al. 2002). Low-dose LPS appears to owe its suppressive effects on allergy to the induction of nitric oxide synthase 2 (Rodríguez et al. 2003). This may indicate a tolerizing effect of inhaled LPS.

Cross-tolerance has been observed as well, in a fashion reminiscent of that seen in the priming response. Agonists of both TLR2 and TLR4, in particular, have been shown to induce refractory states toward the other's characteristic antigens, resulting in a downregulation of both (Zhong et al. 2008). It is worth noting that certain preparations of LPS may contain protein contamination that potentially signals through TLR2. Nevertheless, cross-tolerance has been documented with well-identified TLR2 and TLR4 agonists. This cross talk is likely mediated through the nuclear co-receptor NCoR, which is removed from inflammatory genes by both receptors, albeit through different mechanisms (Huang et al. 2009). The IL-1, TLR2 and TLR4 signaling pathways are known to be intimately connected, with IL-1β pretreatment diminishing the ability of both LPS and IL-1β to induce NFκB- and AP-1-dependent transcription (Medvedev et al. 2000). Here, it seems that a pre-established state of heightened immune excitement exerts a deadening influence upon the response to the otherwise potent inflammatory stimulus represented by LPS. On a related note, endotoxin tolerance has been associated with reduced mortality from conditions as diverse as ischemia/reperfusion injury and hemorrhagic shock (Cavaillon et al. 2003).

Out of these observations arises the question of fitness advantage: what benefit is conferred by the existence of so many mechanisms in place to dampen strongly the immune response to endotoxin?

The primary function of the TLRs in mammals is as a first line of defense against conserved pathogen-associated

molecular patterns such as LPS or peptidoglycan (González-Navajas et al. 2010). The receptors stimulate the innate immune system to action, promoting the production of pro-inflammatory mediators which can spiral out of control leading to endotoxin shock and SIRS if not carefully regulated (Foster et al. 2007). The induction of anti-inflammatory mediators in response to low doses of LPS could be a defense mechanism, put in place to ensure that the inflammatory response does not run out of control and damage the organism. Indeed, endotoxin tolerance seems to be a broad-based phenomenon, resulting in a generalized anti-inflammatory state. Such a mechanism is crucial for species which coexist with large numbers of commensal or symbiotic bacteria. While this does seem successful in reducing inflammation-associated damage, it also appears to render the individual more susceptible to infections (Cavaillon et al. 2003). Chronic stimulation of the innate immune system by LPS or other TLR ligands has been shown in particular to impair the antiviral activity of natural killer cells, leaving mice less resilient in the face of influenza infection (Vaknin et al. 2008). Tolerance itself, then, must also be kept under tight control, so as not to lower entirely the individual's immune defenses.

The general nature of tolerance also begs for closer examination. Endotoxin tolerance, rather than being a specific protective response against inflammation due to endotoxin, appears to be a protective mechanism against excessive inflammation, resulting in anti-inflammatory reprogramming of the immune system as a whole (Biswas and Lopez-Collazo 2009). The phenomenon of cross-tolerance discussed above is especially suggestive of this, along with data showing decreased TNF-α during surgical procedures in humans (Kawasaki et al. 2001). It is possible that the Shwartzman-like response to super low doses of endotoxin is due to the failure of the induced inflammation to reach a level sufficient to engage the protective tolerance mechanisms. Since the pro-inflammatory mediators have feedback loops of their own, this would result in a dampening of the anti-inflammatory mediators, stripping the inflammatory system of its brakes, as it were, and leaving no checks on the inflammatory response to a higher dose at a later point in time.

Unsolved Questions and Future Directions

By far, the most glaring gap in our understanding of the response to endotoxin is in the mechanisms of priming. While it has become almost axiomatic that low doses of endotoxin result in tolerance, doses even lower have been shown drastically to increase shock susceptibility upon subsequent stimulation with a higher dose (Heremans et al. 1990). Compared to the wealth of experiments and studies analyzing the mechanisms of tolerance, priming has been virtually ignored since the 1990s. Further study of the mechanisms governing priming is absolutely crucial if our understanding of endotoxin shock and SIRS is to proceed.

Once these have been further elucidated, the connections between priming and tolerance should become much clearer. If, as we suspect, the shift from one to the other is determined by a dedication to a pro- or anti-inflammatory response at the time of the subclinical dose, theoretical and systems approaches would be tremendously useful in locating the boundaries of the system: the precise doses and time points at which the response shifts between tolerance and priming.

The results of these experiments have implications reaching far beyond the boundaries of septic shock and the immune response to Gram-negative bacteria. An understanding is emerging of tolerance, not simply as a protective measure against endotoxin, but as a general defense against runaway inflammation. Discovering the mechanisms and rules governing this system and ultimately how to manipulate it could lead to new treatments and therapies for all manner of inflammatory conditions.

References

Albrecht V, Hofer TP, Foxwell B et al (2008) Tolerance induced via TLR2 and TLR4 in human dendritic cells: role of IRAK-1. BMC Immunol 9:69

Arora M, Poe SL, Ray A et al (2011) LPS-induced CD11b(+) Gr1(int)F4/80(+) regulatory myeloid cells suppress allergen-induced airway inflammation. Int Immunopharmacol 11:827–832

Berg DJ, Kühn R, Rajewsky K et al (1995) Interleukin-10 is a central regulator of the response to LPS in murine models of endotoxic shock and the Shwartzman reaction but not endotoxin tolerance. J Clin Invest 96:2339–2347

Biswas SK, Lopez-Collazo E (2009) Endotoxin tolerance: new mechanisms, molecules and clinical significance. Trends Immunol 30:475–487

Cavaillon J-M, Adrie C, Fitting C et al (2003) Endotoxin tolerance: is there a clinical relevance? J Endotoxin Res 9:101–107

Chaurasia B, Mauer J, Koch L et al (2010) Phosphoinositide-dependent kinase 1 provides negative feedback inhibition to Toll-like receptor-mediated NF-kappaB activation in macrophages. Mol Cell Biol 30:4354–4366

Chen X, Yoza BK, El Gazzar M et al (2009) RelB sustains IkappaBalpha expression during endotoxin tolerance. Clin Vaccine Immunol 16:104–110

Covert MW, Leung TH, Gaston JE et al (2005) Achieving stability of lipopolysaccharide-induced NF-kappaB activation. Science 309:1854–1857

Eisenbarth SC, Piggott Da, Huleatt JW et al (2002) Lipopolysaccharide-enhanced, toll-like receptor 4-dependent T helper cell type 2 responses to inhaled antigen. J Exp Med 196:1645–1651

Eken C, Martin PJ, Sadallah S et al (2010) Ectosomes released by polymorphonuclear neutrophils induce a MerTK-dependent anti-inflammatory pathway in macrophages. J Biol Chem 285:39914–39921

Fan W, Morinaga H, Kim JJ et al (2010) FoxO1 regulates Tlr4 inflammatory pathway signalling in macrophages. EMBO J 29:4223–4236

Ferrero E, Jiai D, Tsuberi BZ et al (1993) Transgenic mice expressing human CD14 are hypersensitive to lipopolysaccharide. Proc Natl Acad Sci USA 90:2380–2384

Foster SL, Hargreaves DC, Medzhitov R (2007) Gene-specific control of inflammation by TLR-induced chromatin modifications. Nature 447:972–978

Galanos C, Freudenberg MA, Reutter W (1979) Galactosamine-induced sensitization to the lethal effects of endotoxin. Proc Natl Acad Sci USA 76:5939–5943

Gasparini C, Foxwell BM, Feldmann M (2009) RelB/p50 regulates CCL19 production, but fails to promote human DC maturation. Eur J Immunol 39:2215–2223

Gilchrist M, Thorsson V, Li B et al (2006) Systems biology approaches identify ATF3 as a negative regulator of toll-like receptor 4. Nature 441:173–178

González-Navajas JM, Fine S, Law JE et al (2010) TLR4 signaling in effector CD4+ T cells regulates TCR activation and experimental colitis in mice. J Clin Invest 120:570–581

Henricson BE, Manthey CL, Perera PY et al (1993) Dissociation of lipopolysaccharide (LPS)-inducible gene expression in murine macrophages pretreated with smooth LPS versus monophosphoryl lipid A. Infect Immun 61:2325–2333

Heremans H, Van Damme J, Dillen C et al (1990) Interferon gamma, a mediator of lethal lipopolysaccharide-induced Shwartzman-like shock reactions in mice. J Exp Med 171:1853–1869

Hirohashi N, Morrison DC (1996) Low-dose lipopolysaccharide (LPS) pretreatment of mouse macrophages modulates LPS-dependent interleukin-6 production in vitro. Infect Immun 64:1011–1015

Hotchkiss RS, Tinsley KW, Swanson PE et al (2002) Depletion of dendritic cells, but not macrophages, in patients with sepsis. J Immunol 168:2493–2500

Huang W, Ghisletti S, Perissi V et al (2009) Transcriptional integration of TLR2 and TLR4 signaling at the NCoR derepression checkpoint. Mol Cell 35:48–57

Jacinto R, Hartung T, McCall C, Li L (2002) Lipopolysaccharide- and lipoteichoic acid-induced tolerance and cross-tolerance: distinct alterations in IL-1 receptor-associated kinase. J Immunol 168:6136–6141

Jiang Z, Georgel P, Li C et al (2006) Details of toll-like receptor: adapter interaction revealed by germ-line mutagenesis. Proc Natl Acad Sci USA 103:10961–10966

Kawasaki T, Ogata M, Kawasaki C et al (2001) Surgical stress induces endotoxin hyporesponsiveness and an early decrease of monocyte mCD14 and HLA-DR expression during surgery. Anesth Analg 92:1322–1326

Li Y, Wei H (2009) Lipopolysaccharide "two-hit" induced refractory hypoxemia acute respiratory distress model in rats. J Huazhong Univ Sci Technolog Med Sci 29:470–475

Li L, Cousart S, Hu J et al (2000) Characterization of interleukin-1 receptor-associated kinase in normal and endotoxin-tolerant cells. J Biol Chem 275:23340–23345

Maitra U, Gan L, Chang S et al (2011) Low-dose endotoxin induces inflammation by selectively removing nuclear receptors and activating CCAAT/enhancer-binding protein {delta}. J Immunol 186:4467–4473

McPhail LC, Clayton CC, Snyderman R (1984) The NADPH oxidase of human polymorphonuclear leukocytes. Evidence for regulation by multiple signals. J Biol Chem 259:5768–5775

Medina EA, Morris IR, Berton MT (2010) Phosphatidylinositol 3-kinase activation attenuates the TLR2-mediated macrophage proinflammatory cytokine response to *Francisella tularensis* live vaccine strain. J Immunol 185:7562–7572

Medvedev AE, Kopydlowski KM, Vogel SN (2000) Inhibition of lipopolysaccharide-induced signal transduction in endotoxin-tolerized mouse macrophages: dysregulation of cytokine, chemokine, and toll-like receptor 2 and 4 gene expression. J Immunol 164:5564–5574

Motegi A, Kinoshita M, Sato K et al (2006) An in vitro Shwartzman reaction-like response is augmented age-dependently in human peripheral blood mononuclear cells. J Leukoc Biol 79:463–472

Munford RS (2010) Murine responses to endotoxin: another dirty little secret? J Infect Dis 201:175–177

Nimah M, Zhao B, Denenberg AG et al (2005) Contribution of MKP-1 regulation of p38 to endotoxin tolerance. Shock 23:80–87

O'Dea KP, Wilson MR, Dokpesi JO et al (2009) Mobilization and margination of bone marrow Gr-1 high monocytes during subclinical endotoxemia predisposes the lungs toward acute injury. J Immunol 182:1155–1166

Pacquelet S, Johnson JL, Ellis BA et al (2007) Cross-talk between IRAK-4 and the NADPH oxidase. Biochem J 403:451–461

Porta C, Rimoldi M, Raes G et al (2009) Tolerance and M2 (alternative) macrophage polarization are related processes orchestrated by p50 nuclear factor kappaB. Proc Natl Acad Sci USA 106:14978–14983

Rocksén D, Koch B, Sandström T et al (2004) Lung effects during a generalized Shwartzman reaction and therapeutic intervention with dexamethasone or vitamin E. Shock 22:482–490

Rodríguez D, Keller AC, Faquim-Mauro EL et al (2003) Bacterial lipopolysaccharide signaling through Toll-like receptor 4 suppresses asthma-like responses via nitric oxide synthase 2 activity. J Immunol 171:1001–1008

Rothlin CV, Ghosh S, Zuniga EI et al (2007) TAM receptors are pleiotropic inhibitors of the innate immune response. Cell 131:1124–1136

Sivapalaratnam S, Farrugia R, Nieuwdorp M et al (2011) Identification of candidate genes linking systemic inflammation to atherosclerosis; results of a human in vivo LPS infusion study. BMC Med Genomics 4:64

Slofstra SH, ten Cate H, Spek CA (2006) Low dose endotoxin priming is accountable for coagulation abnormalities and organ damage observed in the Shwartzman reaction. A comparison between a single-dose endotoxemia model and a double-hit endotoxin-induced Shwartzman reaction. Thromb J 4:13

Sly LM, Rauh MJ, Kalesnikoff J et al (2004) LPS-induced upregulation of SHIP is essential for endotoxin tolerance. Immunity 21:227–239

Steiner AA, Romanovsky AA (2007) Leptin: at the crossroads of energy balance and systemic inflammation. Prog Lipid Res 46:89–107

Terawaki H, Yokoyama K, Yamada Y et al (2010) Low-grade endotoxemia contributes to chronic inflammation in hemodialysis patients: examination with a novel lipopolysaccharide detection method. Ther Apher Dial 14:477–482

Vaknin I, Blinder L, Wang L et al (2008) A common pathway mediated through toll-like receptors leads to T- and natural killer-cell immunosuppression. Blood 111:1437–1447

Wiersinga WJ, van't Veer C, van den Pangaart PS et al (2009) Immunosuppression associated with interleukin-1R-associated-kinase-M upregulation predicts mortality in Gram-negative sepsis (melioidosis). Crit Care Med 37:569–576

Xiong Y, Qiu F, Piao W et al (2011) Endotoxin tolerance impairs IL-1 receptor-associated kinase (IRAK) 4 and TGF-beta-activated kinase 1 activation, K63-linked polyubiquitination and assembly of IRAK1, TNF receptor-associated factor 6, and IkappaB kinase gamma and increases A20 expression. J Biol Chem 286:7905–7916

Yoza BK, McCall CE (2011) Facultative heterochromatin formation at the IL-1 beta promoter in LPS tolerance and sepsis. Cytokine 53:145–152

Yoza BK, Hu JY, Cousart SL et al (2006) Induction of RelB participates in endotoxin tolerance. J Immunol 177:4080–4085

Zhong B, Ma HY, Yang Q et al (2008) Decrease in toll-like receptors 2 and 4 in the spleen of mouse with endotoxic tolerance. Inflamm Res 57:252–259