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REVIEW

Innate Immunity Signaling Pathways: Links between Immunonutrition and Responses to Sepsis

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Abstract Septic infections in patients treated in intensive care units show the highest mortality rates. Despite advances in treatment methods, there is still no therapy available to efficiently reduce the excessive inflammatory response, which can increase the risk of multiple organ failure. One of the ways to discover new, more efficient treatment methods involves regulating the mechanisms of inflammatory response to a massive infection. Toll-like receptors (TLRs) that recognize pathogen-associated molecular patterns play a significant role in innate antibacterial and inflammatory responses. The regulatory impact of immunonutrition on TLR expression in septic patients seems to be a promising research direction. This paper presents the main mechanisms for the innate immune response to lipopolysaccharide, based on the research results for both TLR-dependent and independent signaling pathways. Special emphasis was put on the research results for the TLR-dependent immune response and the antibacterial/anti-inflammatory response after applying immunonutrition with increased concentrations of glutamine and unsaturated fatty acids.

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Introduction

In the group of patients treated in intensive care units (ICUs) the mortality rate caused by sepsis is the highest (25–60%) and still tends to increase, due to the lack of causal therapy methods necessary to efficiently reduce the excessive inflammatory response to massive infections (Alberti et al. 2003; Bernard et al. 2001; Hotchkiss and Karl 2003; Imahara and O'Keefe 2004; Linde-Zwirble and Angus 2004; Zieliński and Czarkowski 2004). The promising results of experimental studies on treating severe infections with lipopolysaccharide (LPS) inhibitors, tumor necrosis factor (TNF)-α, interleukin (IL)-1, platelet activating factor, nitric oxide (NO), arachidonic acid metabolites, complement component inhibitors or free radicals did not considerably reduce the mortality rate in septic patients (Riedemann et al. 2003). Other strategies for the treatment of sepsis based on attempts to block LPS-binding receptors and on blocking signaling pathway proteins for the antibacterial response e.g. blockade of Toll-like receptor (TLR)4, caspases, FasL-Fas or NF-κB activity and blocking the high mobility group box 1 (HMGB1) pathway as well as on attempting to regulate neutrophil and lymphocyte apoptosis (e.g. by overexpression of anti-apoptotic proteins such as Bcl-2) are still under experimental research. The aim of this study is to efficiently reduce the excessive inflammatory response, above all reducing the activation of nuclear factor (NF)-κB, the production of pro-inflammatory cytokines (TNF, IL-1, IL-6), chemokines and adhesion molecules.

In patients with severe infections special attention should be paid to attempts of modulating the expression of signaling pathway proteins in cells taking part in the early (innate) immune response to infection after administering immunonutrition. It is well known that neutrophils and monocytes/macrophages taking part in the innate immune response to trauma and infection play a significant role in the elimination of microorganisms as well as in local and systemic inflammatory response regulation systemic inflammatory response syndrome (SIRS) that increases the risk of multiple organ failure. It is suggested that the modulation of TLR expression found in the cells of intestinal mucous membrane, neutrophils, monocytes and dendritic cells (DCs) binding bacterial antigens and the modulation of expression of signaling pathway proteins of those cells by early administration of appropriate immunonutrition can help efficiently eliminate microorganisms and reduce the inflammatory response (production of cytokines, chemokines). The disorders of phagocytosis and microorganism elimination in the site of bacterial penetration (extensive surgical wound, catheter in a large vein) intensify the pro- and anti-inflammatory response (compensatory anti-inflammatory response syndrome), which intensifies postoperative immunosuppression and may result in immunity breakdown. The changes in TLR expression and in the expression of signaling cascade proteins associated with their stimulation not only account for the pathological inflammatory response to trauma or infection, but can also have a protective action (e.g. increasing the apoptosis of selected cells, stimulation of signaling pathway inhibitors). These issues make us ask the basic and still open question: can the re-programming of signal transduction pathways in intestinal mucosa and innate immunity cells of septic patients after administering immunonutrition contribute to attenuation of the local and systemic hyperinflammatory response in massive bacterial load?

Opinions regarding the effectiveness of immunonutrition in seriously ill patients are still controversial (Jones and Heyland 2008). The results of a meta-analysis of randomized studies have shown that in the group of seriously ill patients (SIRS, grave infections, ARDS: respiratory distress syndrome) immunomodulatory treatment with glutamine and fatty acids improves outcomes, which has not been confirmed after the enteral administration of arginine (Marik and Zaloga 2008). Another meta-analysis covering the perisurgical results of immunonutrition aimed at enhancing immunity in patients operated on for tumors of the digestive tract has shown a decrease in the number of postoperative complications, reducing the length of hospital stay and improving selected immune parameters such as: increase in the total number of lymphocytes, subpopulation of CD4 lymphocytes, and concentration of IgG, and decrease in the concentration of IL-6 (Zheng et al. 2007). Compared with the standard immunonutrition, the enteral administration of glutamine, arginine and/or fatty acids n-3 polyunsaturated fatty acids (n-3 PUFAs) in patients with acute pancreatitis shows no significant impact on decrease in the number of complications, the length of hospital stay and mortality rate (Petrov et al. 2008). Considering another review of study results the advantageous impact of enteral and parenteral administration of immunonutrition in patients with acute pancreatitis can be enhanced by administering inflammatory and immune response modulators (McClave et al. 2006). The bibliography-based data on the immunomodulatory effect of glutamine are unequivocal. In the group of patients after extensive surgical trauma, adding glutamine has always resulted in a decrease of post-surgical complications, reduction in the length of hospital stay and even a reduction of the mortality rate in seriously ill patients (Novak et al. 2002). Multi-center studies have shown that the administration of high doses of glutamine associated with antioxidants in seriously ill patients hospitalized in ICUs results in a significant increase in morbidity and mortality (Heyland et al. 2006). The majority of studies that have been carried out to date show that n-3 PUFAs have a significant regulative impact on the immune response and outcomes in patients after surgery with serious infections including ARDS (Mayer et al. 2006; Mayer and Seeger 2008). The enteral administration of unsaturated fatty acids in septic patients is still controversial due to the lack of prospective randomized studies. We still know very little about the mechanism of action of n-3 PUFAs that is among other things supposed to reduce the negative impact of n-6 PUFAs on the immune system (inflammatory response reduction). Considering the summary of the recent meta-analysis covering the outcomes of 3,013 patients treated mainly in ICUs, immunomodulating nutrition containing fish oils significantly improves the outcomes for those patients (Peterik et al. 2009). The authors of the meta-analysis emphasize that arginine-enriched diets with no glutamine or fish oil added do not improve outcomes as compared with standard immunonutrition.

In seriously ill patients following surgery treated with immunomodulatory agents, a new and not fully known method of evaluating this therapy may be immunity-based monitoring of alterations in the innate antibacterial response. To better understand the potential impact of immunonutrition on the main signaling pathways of the innate antibacterial immune response in septic patients it is necessary to briefly discuss some selected mechanisms regulating expression of the main proteins of TLR-dependent and independent pathways.

TLR-Dependent and -Independent Signaling in Sepsis

The rising frequency of septic infections in patients treated in ICUs and still the highest mortality rates in this group make TLR4 binding Gram-positive LPS bacteria and their participation in the pathogenesis of sepsis and septic shock an interesting problem. TLRs recognize a few highly conservative structures existing in prevailing microorganisms. Thirteen TLRs have been identified (including 11 in humans). Additionally, it was indicated that they showed mainly affinity to bacteria (TLR1, 2, 4, 5, 6). Some of them (TLR3, 7, 8, 9) also show some affinity to viral RNA and DNA. The prevailing TLRs show expression on the surface of cells (TLR1, 2, 4, 5, 6), but some of them can also be active inside cells and occur on the surface of endosomes (TLR3, 7, 8, 9) (Akira et al. 2006; Kaisho and Akira 2006). However, it is still unknown how ligands for those receptors (e.g. exogenous ligands: LPS, peptidoglycan, bacterial DNA) penetrate into the cells. The endogenous ligands for TLRs include mainly some heat shock proteins (HSP60, HSP70) released from injured cells.

The production of the LPS receptor complex (CD14, TLR4, MD-2) induces dimerization of TLR4 and initiates a signaling cascade which results in activation of phosphorylation kinases of NF-κB (IκB) transcription factor inhibitor. This process induces transcription of genes whose products take part in the inflammatory response (e.g. cytokines TNF-α, IL-1, IL-6, IL-12). Apart from extracellular TLRs' part in the signaling cascade of the antibacterial response there are also such "participants" as a cytoplasmic part referred to as the TIR domain (Toll-IL-1 receptor), adaptor protein myeloid differentiation factor 88 (MyD88), TIR-domain-containing adaptor protein (TIRAP) and TRIF-related adaptor molecule (TRAM), the protein Toll/IL-1-receptor domain-containing adaptor inducing interferon (TRIF), TNF-α receptor-associated factor 6 (TRAF6), kinases (IRAK1, IRAK4: IL-1 receptor-associated kinases; TAK: transforming growth factor (TGF)-β-activated kinases) and a kinase complex inhibitory κB kinase complex (IKK) (Akira and Takeda 2004; Kawai and Akira 2006; Takeda and Akira 2005). The MyD88, TRAF6, TRIF and TRAM proteins are key proteins of signaling pathways initiated by TLRs, which can be of significant importance in treating sepsis (Biswas and Tergaonkar 2007; Yamamoto et al. 2004). This process results in the activation of NF-κB and cytokine promoter genes. The production of inflammatory cytokines begins already after 60 min from the activation of macrophages by TLR4-binding LPS. In the case of MyD88-dependent transduction of the signal from TLR4, TLR2, the TRAF6 protein plays a significant role, while in the case of the MyD88-independent pathway the main participants include TRAM and TRIF proteins (Fig. 1). A deficiency of TRAM protein decreases the inflammatory response (cytokine production), whereas any deficiency of TRL4 or MyD88 protein delays bacterial phagocytosis. Attempts to block the signaling cascade in patients with severe infections attract the interest of many scientists. Especially interesting may be the use of negative regulation of signaling pathways associated with TLRs (e.g. RP 105/CD180 protein: TLR homolog, single immunoglobulin IL-1-receptor-related protein, signaling TIR family ligand, Toll-interacting protein; or Smad6), whose mechanism consists in suppressing the location of the bond between the ligand (LPS) and the receptor, proteolysis of TLR, blocking intracellular receptors binding antibacterial antigens, blocking the activity of kinases (suppression of phosphorylation process) and suppressing the activation of NF-κB (Brint et al. 2004; Burns et al. 2003; Choi et al. 2006; Divanovic et al. 2005; Qin et al. 2005; Zhang and Ghosh 2002). Numerous experimental studies indicate the possibility of conduction of signals from TLRs to the inside of cells after connecting with LPS, which may prevent the activation of NF-κB. Mice deprived of signaling pathway proteins associated with TLR4 (TIRAP, MyD88, TRIF) do not respond to LPS and are resistant to septic shock (Hoebe et al. 2003; Kawai et al. 1999; Yamamoto et al. 2002, 2003). On the other hand, mice deprived of TLR2 and the MyD88 adaptor protein are more susceptible to *Staphylococcus aureus* infections (Takeuchi et al. 2000). This indicates a protective action of some TLRs and adaptor proteins. In mice deprived of MyD88 protein, the systemic inflammatory response to LPS was significantly reduced but still present, which suggests cooperation of other routes of signal conduction in the antibacterial response (Weighardt et al. 2002). The above-mentioned fact at least partly shows that the effects of treatment are insufficient due to the blockage of signal conduction routes. For example, when there is a deficiency in MyD88 protein and there was no previous activation of NF-κB associated with stimulation of TRL4 by LPS, another adaptor protein called TRIF takes over the function of regulating the genes of the monocyte inflammatory response and increasing the production of particular chemokines (Feterowski et al. 2004; Weldon et al. 2007). It was found that the TRIF molecule, whose blockage could have reduced the production of cytokines in septic patients, could activate NF-κB through the pathway associated with TRAF6 protein, whereas trace amounts of TNF despite the lack of MyD88 protein can lead to late NF-κB activation (Covert et al. 2005). Research on the MyD88 protein-independent pathway of the antibacterial immune response in regulating the tolerance to endotoxins seems to be very interesting, because stimulation of the signal conduction route could be one of the mechanisms to protect patients against the development of SIRS. More detailed knowledge of the MyD88-independent pathway could be helpful for the therapies modulating the activity of

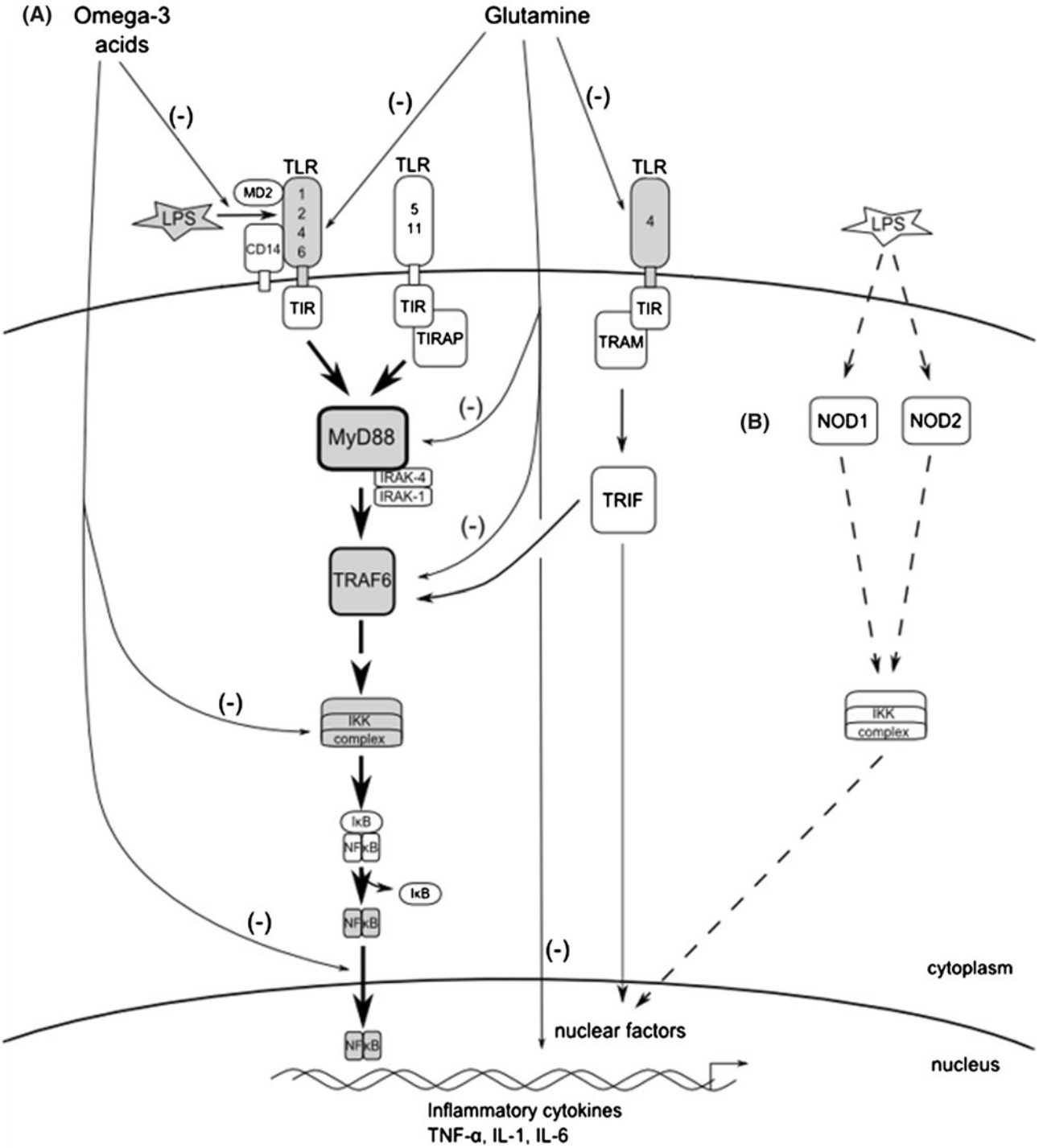

Fig. 1 Schematic diagram of TLR4, MyD88 and TRAF6 downregulation in rat intestinal mucosa following glutamine administration and LPS-induced endotoxemia **a** n-3 PUFA inhibition of TLR signaling pathway at the extracellular (DHA interferes with TLR4 receptor) and intracellular level: inhibition of phosphorylation and degradation of IκB, inhibition of NF-κB activation and inflammatory cytokines production in LPS-stimulated human leukocytes and macrophages **b** *LPS* lipopolysaccharide, TLR-independent signaling via the NODs cytoplasmic sensors of LPS does not require members of the MyD88 adaptor family (*interrupted lines*). *TLR* Toll-like receptor, *TIR* Toll-IL-1 receptor, *TIRAP* TIR-domain-containing adaptor protein, *TRAM* TRIF-related adaptor molecule, *TRIF* Toll/IL-1-receptor domain-containing adaptor inducing interferon, *MyD88* myeloid differentiation factor 88, *TRAF6* TNF-a receptor-associated factor 6, *IKK* inhibitory κB kinase complex, *NF-κB* nuclear factor κB, *NOD* nucleotide-binding oligomerization domain, *TNF-α* tumor necrosis factor-a, *IL-1* interleukin 1, *IL-6* interleukin 6

particular signaling proteins aimed at increasing the tolerance to LPS. It is well known that the pro-inflammatory cytokines (as a response to trauma and infections) produced locally by neutrophils and macrophages play a significant role in the development of SIRS. A significant increase in cytokine concentrations in peripheral blood was observed in septic patients. It was found that blocking the activity of cytokines and adhesive molecules reduced the susceptibility of animals to severe infections caused by LPS (Kamochi et al. 1999; Kumasaka et al. 1996; Raeburn et al. 2001). The priming by LPS exaggerates acute lung injury as a response to peptidoglycan, whereas death in mice is preceded by NF-κB-mediated upregulation of TLR2 (Matsuda et al. 2008). The transfection of NF-κB oligonucleotides in vivo strongly prevented the upregulation of TLR2 after LPS stimulation at pulmonary cellular and tissue levels.

Apart from TLRs, a significant role in recognizing pathogen-related molecular patterns and regulation of the innate antibacterial response is also played by other proteins belonging to pathogen-associated molecular pattern (PAMP) receptors, including peptidoglycan recognition proteins, cytosolic nucleotide-binding oligomerization domain (NOD) proteins and TREM1 receptor (triggering receptor expressed on myeloid cells-1) (Carneiro et al. 2004). They possess the ability to (e.g. NLRs—NOD-like receptors: NOD1, NOD2) connect with LPS and the bacterial peptidoglycan as well as to transfer a signal independently of TLRs, which also results in NF-κB activation and stimulates the expression of cytokine coding genes (for NOD1: TNF-α and IL-6, and for NOD2: TNF-α and IL-1β) and adhesive molecules (Sońdka et al. 2006). NOD1 recognizes the compounds of Gram-negative bacteria (meso-diaminopimelic acid with peptidoglycan) and some Gram-positive bacteria (Chamaillard et al. 2003), whereas the ligand for NOD2 is muramyl dipeptide coming from the wall of Gram-positive and Gram-negative bacteria (Girardin et al. 2003). The transduction of the signal by NLRs does not require any participation of the MyD88 protein. The highly conservative NOD2 receptors that mainly respond to peptidoglycan have the ability to regulate (suppress) the signals coming through TLR2. Any mutations in NOD2 located in monocytes, but also in intestinal mucosa, correlate with the occurrence of Crohn's disease (Hugot et al. 2001). TREM1 is a glycoprotein and occurs mainly in monocytes and macrophages. In infections caused by Gram-positive and Gram-negative bacteria its expression grows significantly, at the same time intensifying the inflammatory response. The blockade of TREM1 prevents the development of shock and sepsis (Colonna and Facchetti 2003). Scientists are trying to use the changes in the protein plasma concentration in diagnosing sepsis (Gibot et al. 2004).

An important group of proteins released as a result of tissue injury, damage to cells or infection consists of endogenous molecules (heat-shock proteins HSP60, HSP70, fibronectin, β-defensin) and those having the ability to activate TLR4 and bind PAMPs, including HMGB1 bound with DNA, stabilizing nucleosomes, and facilitating NF-κB activation and gene transcription (Bustin 1999; Wang et al. 2001). Like other inflammatory cytokines it is released by macrophages (within 24 h) after LPS stimulation and plays an important role in regulating the release of NO by enterocytes and in activating neutrophils and macrophages that produce increased amounts of cytokines and chemokines, but the researchers did not find any direct impact of HMGB1 on the process of releasing pro-inflammatory cytokines or chemokines. It is suggested that this action needs LPS or inflammatory mediators to be additionally involved (IL-1β) (Sha et al. 2008). The latter study demonstrated that HMGB1 modulates the inflammatory cascade in LPS-activated macrophages by inducing production of the pro-inflammatory cytokines TNF-α and IL-1β while attenuating the release of the anti-inflammatory mediators IL-10 and TGF-β1 (El Gazzar 2007). Trauma and concomitant infection increase the release of HMGB1. High concentrations of this protein were observed in patients with severe infections. In an experimental study the specific inhibition of HMGB1, using antibodies or recombinant box A, reduced lethality, even when started 24 h after induction of peritonitis (Wang et al. 1999; Yang et al. 2004). TLR2 and TLR4 receptors were identified to mediate the effects of HMGB1 in neutrophils and macrophages (Park et al. 2004). In contrast to monocytes/macrophages, any stimulation of neutrophils by HMGB1 results in TNF release within 60 min, whereas LPS induces a late TNF release peaking at 4 h (Park et al. 2003). Although both HMGB1 and LPS increased the nuclear translocation of NF-κB, the strength of this effect was greater in LPS-stimulated neutrophils from patients with sepsis-induced acute lung injury (Silva et al. 2007). As some studies have found, the blockade of HMGB1 after administering the lethal LPS dose protects mice against death. Nicotine, a selective cholinergic agonist, is more efficient than acetylcholine and inhibits HMGB1 release induced by either endotoxin or TNF-α (Matthay and Ware 2004). The results of studies suggest a potential use of nicotine in treating severe infections.

The intracellular equivalents of PAMPs also include the HSPs that protect the cell against injury. Increased concentrations of those proteins were noticed in patients after surgical trauma. Contrary to LPS, they do not induce release of TNF-α by antigen-presenting cells and they do not affect the ability of monocytes to bind LPS, but they can increase the expression of TLR4 in those cells (mainly HSP70). This may indicate the regulatory action of those proteins on the antibacterial response, where the TLRs act

as mediators. Interestingly, in vivo and in vitro HSP70 was found to induce those responses in both mice TLR-$2^{-/-}$ and TLR-$4^{-/-}$ (Blander and Medzhitov 2004). HSP70 can play indispensable roles in the effect of glutamine to protect against injuries caused by sepsis-induced endotoxin shock (Wischmeyer 2002; Wischmeyer et al. 1997, 2001). The results of those studies partly explain the beneficial impact of glutamine that increases the production of HSPs in septic patients. HSPs, like the HMGB1 protein, can be secreted outside cells and after binding TLRs can regulate their functions. One of the interesting examples of such actions is the allergizing impact of HMGB1 that intensifies the expression of TLR4 in DCs after trauma and tissue ischemia (Tsung et al. 2007).

The impact of immunonutrition on regulating the expression of NOD or HMGB1 proteins in septic patients still remains unknown. The results of recent studies on the impact of glutamine and fatty acids on signaling pathways associated with TLRs allow us to presume that modulating the activity of those receptors and related signaling pathways as well as changes in the expression of pathogen-binding proteins after the introduction of immunonutrition will have a significant impact on outcomes in patients with severe infections.

TLRs in Signaling and Immunonutrition: Clinical Aspects

TLRs expressed in mucosal cells and in the cells that take part in the innate response to infections play a significant role in antibacterial response modulation in patients with severe infections. The TLRs recognize the structural components of microorganisms and occur both inside and outside cells (intra- and extracellular TLRs). Some studies show that trauma reduces, whereas a severe infection increases the expression of TLRs recognizing bacterial antigens (e.g. LPS, peptidoglycan) (Adib-Conquy et al. 2003, 2006; Brandl et al. 2005; Salgado et al. 2006). Compared with healthy people, the expression of TLR4 in the monocytes of trauma patients was reduced (Adib-Conquy et al. 2003). Therefore, it is tempting to postulate that increased expression of TLRs would have a beneficial effect in trauma patients. Polymorphism of TLRs was one of the factors that increased the susceptibility to infections caused by particular bacteria, but in patients with mixed severe infections did not show any significant effect on its course and outcome (Feterowski et al. 2003). In some experimental studies a lack of TLRs increased the susceptibility to infections in mice (Qureshi and Medzhitov 2003) and caused disorders in inflammatory mediator secretion as well as disorders in phagocytosis and antigen presentation (Akira 2003; Blander and Medzhitov 2004; Medzhitov and Janeway 2000). Intraperitoneal administration of living *Echerichia coli* bacteria or LPS TLR4 had a significant impact on the phagocytic activity of peritoneal macrophages. No TLR2, TLR4 in macrophages caused disorders in bacterial phagocytosis (*E. coli, S. aureus*). The experimental findings suggest that TLR4 plays a key role in regulating the expression of inflammatory cytokines in the lung during endotoxic shock. (Baumgarten et al. 2006). Six hours of LPS administration induced a significant increase in pulmonary TNF-α, IL-1β and IL-6 mRNA in control ($TLR4^{+}$) mice compared to TLR4-deficient mice (Baumgarten et al. 2006). Recent studies showed that apoptotic macrophages can have a protective action in septic shock caused by LPS administration in mice (Ren et al. 2008). This study for the first time demonstrated that the administration of apoptotic cells could protect mice against LPS-induced death, even when the apoptotic cells were administered 24 h after the LPS challenge. The beneficial effects of administration of apoptotic cells included the reduced circulation of pro-inflammatory cytokines (TNF-α), enhancement of IL-10 expression by LPS-activated macrophages, suppression of neutrophil infiltration in target organs, and decreased serum LPS levels. The apoptotic cells were an LPS carrier, which facilitated its phagocytosis and LPS elimination. This study showed that not TLR4, but CD14 is one of the receptors for LPS-coated apoptotic cell uptake. The experimental study suggests that the LPS-induced decrease of neutrophil apoptosis takes place mainly through TLR2, not through TLR4, but apoptosis-associated factors such as Bcl-XL or Bak do not play a major role in this process (Goshima et al. 2004). The regulation of this signaling pathway is crucial for decreased neutrophil apoptosis during sepsis, which may amplify and prolong any systemic inflammatory response.

After partially successful attempts to block LPS-binding receptors in septic patients and blocking the signaling pathway proteins associated with the antibacterial immune response (e.g. suppression of HMGB1), the attempts to modulate the response by immunonutrition seem to be a new and promising direction of studies. To date, several randomized clinical trials have evaluated the efficacy of arginine, glutamine, omega-3 fatty acids, nucleotides and trace elements with antioxidant properties in critically ill patients with trauma and/or infections, but the basic molecular mechanisms that can attenuate the overwhelming inflammatory response in sepsis are still unclear. In malnourished surgical patients with infections, the direct factor that intensifies the failure of local "first line" antibacterial defense may be disorders of PAMPs (e.g. LPS, peptidoglycan, teichoic acids, bacterial DNA) recognition by innate immunity cells. The increased activation of receptors taking part in PAMP recognition can develop severe infections. The hypothesis that one of the main

reasons for false recognition of bacterial antigens by immune system cells (mainly by phagocytic cells) is malnutrition is highly probable. The deficiency of immunoactive nourishing substances (e.g. glutamine, fatty acids or trace elements such as selenium and zinc) can intensify the disorders of expression of bacterial antigen binding extracellular receptors and intracellular proteins/receptors. The excessive accumulation of bacterial wall fragments and the microorganisms being proliferated in tissues intensify the inflammatory response and increase the release of cytokines into the blood.

Glutamine, the most abundant amino acid in the human body, performs multiple roles in the intestine and may even serve as a signaling molecule (Neu et al. 2002). Glutamine is an important energy source for lymphatic tissue and glutamine-enriched enteral nutrition has been found to reduce the incidence of sepsis in trauma patients, due to maintaining the integrity of intestinal mucosa (Foitzik 2001; Houdijk et al. 1998; Novak et al. 2002). Animal studies indicate that glutamine-supplemented total parenteral nutrition decreases bacterial translocation (Bruke et al. 1989). The experimental studies showed that adding glutamine to a culture of neutrophils taken from patients after surgical trauma increases their antibacterial activity (Furukawa et al. 2000). Low plasma glutamine concentrations (<0.42 mM) at admission to ICUs were associated with higher severity of illness and higher mortality rates (Oudemans-van Straaten et al. 2001). Glutamine deprivation can upregulate an important pro-inflammatory mediator (LPS-induced IL-8 production) via decrease of the inhibitor κB in both the immature and mature human intestine, showing the greatest response with the immature intestine (Liboni et al. 2005). The production of IL-8 by LPS-stimulated human blood monocytes in vitro was increased along with increasing glutamine concentration (Murphy and Newsholme 1999). The results of recent studies show the regulative impact of glutamine on the inflammatory response in severe infections and indicate that it is necessary to administer high doses (e.g. in parenteral administration 0.35 g/kg^{-1}/day^{-1}) to obtain a better therapeutic effect (Houdijk et al. 1998; Wischmeyer et al. 2001, 2003.

Some of the most recent experimental studies show that the enteral administration of glutamine reduces the increased expression of TLR4, signal adaptor protein MyD88 and TRAF6 mRNA in intestinal mucosa as a response to LPS-induced endotoxemia in rats (Fig. 1) (Kessel et al. 2008). In addition, the above-mentioned studies found a decreased injury to the mucous membrane of the small intestine. It is well known that TLR4 mRNA is present in mouse and human intestinal epithelial cell TLR4 lines (Cario et al. 2000) and the upregulation of expression of TLR4 and MyD88 after LPS leading to the induction of inflammatory cytokines such as TNF-α, IL-1 and IL-6 can explain the developed intestinal mucosal injury. Another study (Abreu et al. 2001) suggested that downregulation of TRL4 expression may be a mechanism used by intestinal epithelial cells to protect against dysregulated immune signaling in response to Gram-negative bacteria. In the case of critical care patients a recent study showed that parenteral nutrition supplemented with glutamine does not increase the expression of TLR2 or TLR4 in peripheral blood monocytes (Pérez-Bárcena et al. 2008). The mechanisms where glutamine prevents the occurrence of infection are still unclear, but it is well known that glutamine decreases the production of pro-inflammatory cytokines (Aosasa et al. 1999; O'Riordain et al. 1996) and improves the bactericidal function of neutrophils in the case of surgical or burn patients (Ogle et al. 1994). In cultured colonic biopsies from patients with active Crohn's disease, glutamine was found to decrease TNF-α and the main pro-inflammatory cytokines released by NF-κB (Lecleire et al. 2008). The impact of glutamine on TLR4 may suggest modulation of expression of other signaling proteins through omitting the main pathway with the MyD88 protein (e.g. by regulating the expression of TRIF protein).

The anti-inflammatory action of unsaturated fatty acids (including mainly n-3 PUFAs) and their use in treating early sepsis (in the first phase of sepsis syndrome) still seem to be very interesting. In traumatized and surgical patients an enteral diet containing n-3 fatty acids significantly reduced infectious complications and septic events (Braga et al. 1996; Kudsk et al. 1996; Senkal et al. 1997). Enhanced survival and reduced lung failure after enteral or parenteral administration of n-3 PUFAs was observed in experimental models of sepsis (Barton et al. 1991; Grimminger et al. 1997; Johnson et al. 1993). Interestingly, by incorporation into various membrane (phospho)-lipid pools, n-3 PUFAs may affect lipid-signaling events in different cell types (Chakrabarti et al. 1997; Diep et al. 2000). The omega-3 fatty acids also have an ability to selectively suppress the signaling cascade associated with the innate antibacterial response (mainly leukocytes and macrophages), independently at successive stages: (1) endotoxin interaction with TRL4, (2) activation of inhibitor phosphorylation kinases of the NF-κB (IκB) transcription factor and (3) translocation to the nucleus and connecting NF-κB to an appropriate DNA sequence (suppressing the transcription of inflammatory response mediator genes; Fig. 1) (Calder 2006; Li et al. 2005; Mishra et al. 2004; Moon et al. 2007; Novak et al. 2003; Weldon et al. 2007; Wendel et al. 2007; Zhao et al. 2004). The concept of free n-3 PUFAs as a TLR4 antagonist has not been demonstrated in vivo. Docosahexaenoic acid (DHA) can block the conduction of signals at the TRL4 level (Lee et al. 2001), which indicates the key role of the receptor in regulating

the response to increased concentrations of fatty acids in peripheral blood during sepsis. The interaction of those fatty acids with TRL4 intensifies the inflammatory response, and increases insulin resistance and tissue injury (Tsukumo et al. 2007). We can prevent it by administering appropriate nutrition mixtures. It has been demonstrated that the enteral administration of a diet enriched in unsaturated fatty acids (EPA) and glutamine in septic patients treated in ICUs reduced the inflammatory response and mortality rate caused by acute lung injury (ARDS) (Pontes-Arruda et al. 2006; Singer et al. 2006). The enteral administration of n-3 acids in septic patients modulated the functions of neutrophils, and changed the disadvantageous proportion of n-6 acids to n-3 in the direction of higher concentration of n-3 acids, which was associated with lower concentrations of pro-inflammatory cytokines (Mayer et al. 2003a, b). In mice, EPA- and DHA-enriched diets modulate the balance between pro- and anti-inflammatory cytokines, alter the early response of the host to *Pseudomonas aeruginosa* infection, and affect the early outcome of infection (Tiesset et al. 2009). Recent findings for the first time indicate that LPS administration causes the downregulation of TLR4 at the mRNA and protein level in pig adipose tissue and that dietary n-3 PUFA blocks this response (Gabler et al. 2008). In spleens from mice fed a fish oil diet, an increased proportion of macrophages secreting TNF-α and IL-10 and expressing the LPS receptor complex molecules CD14 and TLR4/MD-2 was observed (Petursdottir and Hardardottir 2007). The expression of TLR2 and TLR4 on peritoneal macrophages and DCs from mice treated with a combined diet (soybean isoflavones and green tea) was significantly decreased (Baeza et al. 2008).

The investigation of Lee et al. revealed that saturated and unsaturated fatty acids circulating in the blood can modulate TLR4 signaling by acting as agonists or antagonists (Lee and Hwang 2006). For instance, lauric acid (C12:0, a component of *E. coli* lipid A) was a potent NF-κB activator. The activation of NF-κB and COX-2 expression was attenuated by DHA, probably in the mechanisms of TLR4/NF-κB pathway blocking at the receptor level (Lee et al. 2001). This stimulatory effect is not limited to immune cells. In adipocytes and endothelial cells saturated fatty acid (i.e. C18:0, palmitic acid) stimulated IKK and induced IL-6 and TNF-α expression also in a TLR4-dependent pathway (Shi et al. 2006; Kim et al. 2007). The divergent TLR response to saturated and unsaturated fatty acids suggests some clinical implications of immunonutrition. Parenteral nutrition with fish oil increased free EPA and DHA levels and modulated cytokine response in patients with sepsis (Mayer et al. 2003b). An experimental study revealed that diets enriched with fish oil/DHA might reduce inflammation after tissue damage (Gonzalez-Periz et al. 2006). Resolvin D1 and protectin D1, DHA-derived lipid mediators, are involved in these mechanisms. In a model of peritonitis in mice, intraperitoneal administration of protectin D1 preceding zymosan A reduced the number of neutrophils and the levels of pro-inflammatory cytokines and chemokines (Bannenberg et al. 2005). This means that the administration of n-3 PUFAs modulates the profile of lipid mediators not only by their impact on TLR-dependent signaling. Moreover, leukotrienes, thromboxane, and prostaglandins formed from EPA are considered to have less of a pro-inflammatory impact on the immune response (Calder 2003). We believe that parenteral n-3 PUFA administration during a hyperinflammatory reaction may have positive effects on the outcomes of critically ill patients.

Recently there has been evidence that TLRs may mediate immunomodulatory activity of probiotics via ligation with certain probiotic antigens and/or nucleic acids (Christensen et al. 2002; Mills and McGuirk 2004). TLRs' interactions with bacterial ligands support intestinal barrier function and communication to immune cells (e.g. DCs) that play important roles in regulating intestinal homeostasis in the healthy intestine and in the dysregulated response seen in the inflammatory bowel diseases (Rakoff-Nahoum et al. 2004; Stagg et al. 2004). In experimental colitis (hapten-induced colitis in BALB/c mice, and the IL-10 knockout mice model) the DNA of bacterial origin that binds to TLR9 has been shown to reduce inflammation (Rachmilewitz et al. 2002). The immunomodulatory function of probiotic bacterial DNA has also been demonstrated in a study of peripheral blood mononuclear cells taken from healthy donors where *Bifidobacterium* genomic DNA caused the induction of secretion of the anti-inflammatory IL-10 (Lammers et al. 2003). In addition, probiotics have been shown to reduce NF-κB activation in intestinal inflammation (Petrof et al. 2004). A possible mechanism by which probiotics interfere with the NF-κB pathway is based on the fact that a mixture of probiotic bacteria elicits immunosuppressive activity by stabilizing IκB levels and inhibiting both NF-κB activation and IL-8 secretion (Jijon et al. 2004). These inhibitory effects on the proinflammatory NF-κB pathway may be an important mechanism used by probiotics to regulate intestinal inflammation and response to infection. There are insufficient data to recommend the use of probiotics in critically ill patients during enteral nutrition. In the Besselink study, there was a significantly higher need for surgical intervention, organ failures and bowel ischemia associated with the use of pre/probiotics in acute pancreatitis (Besselink et al. 2008). It was noted that their use after multiple trauma might be associated with a reduction in diarrhea in critically ill patients (Kotzampassi et al. 2006). There is also emerging evidence for the use of probiotics in treating

gastrointestinal infections, to prevent postoperative bacterial translocation, irritable bowel syndrome, in ulcerative colitis and Crohn's disease (Harish and Varghese 2006).

Conclusion

The above-presented results show that improving outcomes in the group of patients with severe infections requires more attention to be paid to explaining the molecular mechanisms regulating the innate antibacterial response. One of the preconditions necessary to achieve progress in treating the most severely ill patients is to find out more about the impact of nutrition, severe infections and immunonutrition on the expression of selected signaling pathway proteins of innate antibacterial response cells. Attempts to modulate the innate antibacterial immune response by administering immunonutrition are promising and indicate that in the future it may be a valuable way of assisting the basic therapy by blocking selected signaling pathways aimed at reducing the life-threatening effects of massive infection, including the increased inflammatory response.

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