Review paper

Immunonutrition and lipopolysaccharide – induced Toll-like receptor signaling

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Abstract

Septic infections in malnourished surgical patients show the highest morbidity and mortality rate. The attempt to correct the postoperative immune and nutritional disorders by introducing immunomodulating nutrition is a promising way of improving outcome, but as yet little is known about the mechanisms of correcting postoperative extensive inflammatory response (SIRS) to a massive infection using this type of nutrition. A significant role in innate antibacterial and inflammatory response play Toll-like receptors that recognize PAMPs-pathogen-associated molecular patterns. In this paper special emphasis was put on clinical trials and the research result for TLR-dependent immune response, anti-bacterial/anti-inflammatory response applying immunonutrition with increased concentrations of glutamine and unsaturated fatty acids.

Key words: *immunonutrition, toll-like receptors, sepsis.*

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Malnutrition is a major global public health problem and can be defined as a state of nutrition in which a deficiency of energy, protein and other nutrients like arginine, glutamine, fatty acids, vitamins and trace elements causes measurable effects on body and tissue function and clinical outcome. Surgical trauma increases immune system suppression and deepens disease related malnutrition. The immune disorders and malnutrition worsen in the early postoperative period, considerably affecting the process of wound healing, intestinal barrier function and the number of post-operative infections. Infections in malnourished surgical patients increase morbidity and mortality rate. Despite advances in treatment, there is still no therapy available to efficiently reduce the excessive inflammatory response, which can increase the risk of multiple organ failure (MOF) [1]. The promising results of experimental studies on treating severe infections with LPS inhibitors, TNF-α, IL-1, PAF, NO, arachidonic acid metabolites, complement component inhibitors or free radicals did not considerably reduce the mortality rate in septic patients [2]. Other strategies for the treatment of sepsis in surgical patients based on the attempts to block LPS-binding receptors and on blocking signaling pathway proteins for antibacterial response (e.g. blockade of TLR4, caspases, Fasl-Fas or NF-κB activity and blocking of HMGB1- high mobility group box1 pathway) and on attempting to regulate the neutrophil and lymphocyte apoptosis (e.g. by over expression of anti-apoptotic proteins such as Bcl-2) are still subject of experimental research [2-6]. The aim of this study is to efficiently reduce the excessive inflammatory response, above all reducing the activation of nuclear factor κB (NF-κB), the production of post-inflammatory cytokines (TNF, IL-1, IL-6), chemokines and adhesive molecules.

More efficient therapy consists influences the mechanisms of inflammatory response to a massive infection. After a major surgery complicated by severe infection special attention should be paid to modulation of the expression of signaling pathway proteins in cells that take part in early (innate) immune response to infection by applying immunonutrition. It is well known that neutrophils and monocytes/macrophages that take part in innate immune response to trauma and infection play a significant role in the elimination of microorganisms and in local and systemic inflammatory response regulation (SIRS – systemic inflammatory response syndrome) that increases the risk of MOF [7]. 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 (CARS- compensatory anti-inflammatory response), which

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intensifies post-operative immunosuppression and may result in immunity breakdown [8]. These issues opens the discussion if the re-programming of signal transduction pathways in intestinal mucosa and innate immunity cells of septic patients after immunonutrition contribute to the attenuation of local and systemic hyperinflammatory response in massive bacterial load?

The immunomodulatory action of unsaturated fatty acids affects the decrease in activity of neutrophils, monocytes, lymphocytes, and the production of cytokines [9-12]. Immunostimulatory action of amino acids increases the phagocytal activity of leukocytes, enhances immunity to infections and accelerates wound healing [13-19]. In randomized studies it has been found that enteral immunonutrition improves the clinical course, decreases the frequency of severe infections, shortens hospital stays, reduces treatment costs and significantly decreases mortality in severe ill patients with MOF [20-25]. These benefits were found to be most impressive in surgical patients. In patients with severe trauma and infection receiving immunonutrition significant decrease in the duration of SIRS and in the frequency of MOF have been found [20, 23, 24, 26]. In the clinical setting immunonutrition (with arginine, nucleic acids and n-3 fatty acids) reduced infections complications in critically ill patients after trauma and cancer surgery [22, 23, 25, 27, 28]. The studies have been performed in various populations patients, which makes it difficult to compare their results. The most frequently included patients treated in intensive care units. In the majority of those studies, the changes in nutritional and immunity status in the course of immunonutrition and infection have not been monitored. Despite the advantage of the positive effects of immunonutrition on the treatment of surgical patients, the impact of this nutrition on the immune system still remains unclear. A better knowledge of advantages of immunomodulating nutrition in treating surgical infections requires studying the changes in the expression of signaling cascade proteins associated with their stimulation account not only for pathological inflammatory response to trauma or infection, but they can also have a protective action (e.g. increasing the apoptosis of selected cells, stimulation of signaling pathway inhibitors).

In regulating the mechanisms of local and systemic inflammatory response to a massive infection in surgical patients a significant role is played by Toll-like receptors (TLRs) expressioned in gut mucosa cells and the cells that take part in innate response to infection. Some studies performed show that trauma reduces, whereas severe infection increases the expression of TLRs recognizing bacterial antigens (e.g. LPS, peptidoglycan) [29-32]. As compared with healthy people, the expression of TLR4 in the monocytes of trauma patients was reduced [29]. In experimental studies the lack of TLRs increased the susceptibility to infections in mice [33] and caused disorders in inflammatory mediator secretion, disorders in phagocytosis and antigen presentation [34-36]. The experimental findings suggest that TLR4 plays a key role in regulating the expression of inflammatory cytokines in the lung during endotoxic shock [37]. 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.

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 can be the disorders of pathogen-associated molecular pattern (PAMPs) (e.g. LPS, peptidoglycan, teichoic acids, bacterial DNA) recognition by innate immunity cells. 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) 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 local inflammatory response and increase the release of cytokines into the blood.

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 [38-40]. Low plasma glutamine concentrations (<0.42 mM) at admission to intensive care units were associated with higher severity of illness and higher mortality rates [41]. The results of recent studies show the regulative glutamine impact on 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 [39, 42, 43]. Some most recent experimental studies show that the enteral administration of glutamine reduces the increased TLR4 expression, signal adaptor protein MyD88 (*myeloid differentiation factor 88*) and TRAF6mRNA (*TNF-α receptor-associated factor 6*) in intestinal mucosa as a response to LPS induced endotoxemia in rats (Fig. 1) [5]. In addition, the above-mentioned studies found a decreased injury to the mucous membrane of the small intestine. The effect of glutamine on intestinal TRL4 expression may be considered as a mechanism via which immunonutrition helps in the recovery of critically ill and septic patients. The mechanisms by which glutamine prevents the occurrence of infection are still unclear, but it is well known that in surgical or burn patients glutamine decreases the production of pro-inflammatory cytokines [44] and improves the bactericidal function of neutrophils [46].

The anti-inflammatory action of unsaturated fatty acids (mainly n-3 PUFAs) and their application in treating surgical infections and 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 [23, 47, 48]. Enhanced survival and reduced lung failure after enteral or parenteral usage of n-3 lipids was observed in experimental models of sepsis [49-51]. Interestingly, by incorporation into various membrane (phospho)-lipid pools, n-3 fatty acids may affect lipid-signaling events in different cell types [52, 53]. The omega-3 fatty acids have also an ability to selectively suppress the signaling cascade associated with innate antibacterial response (mainly leukocytes and macrophages), independently at sub-

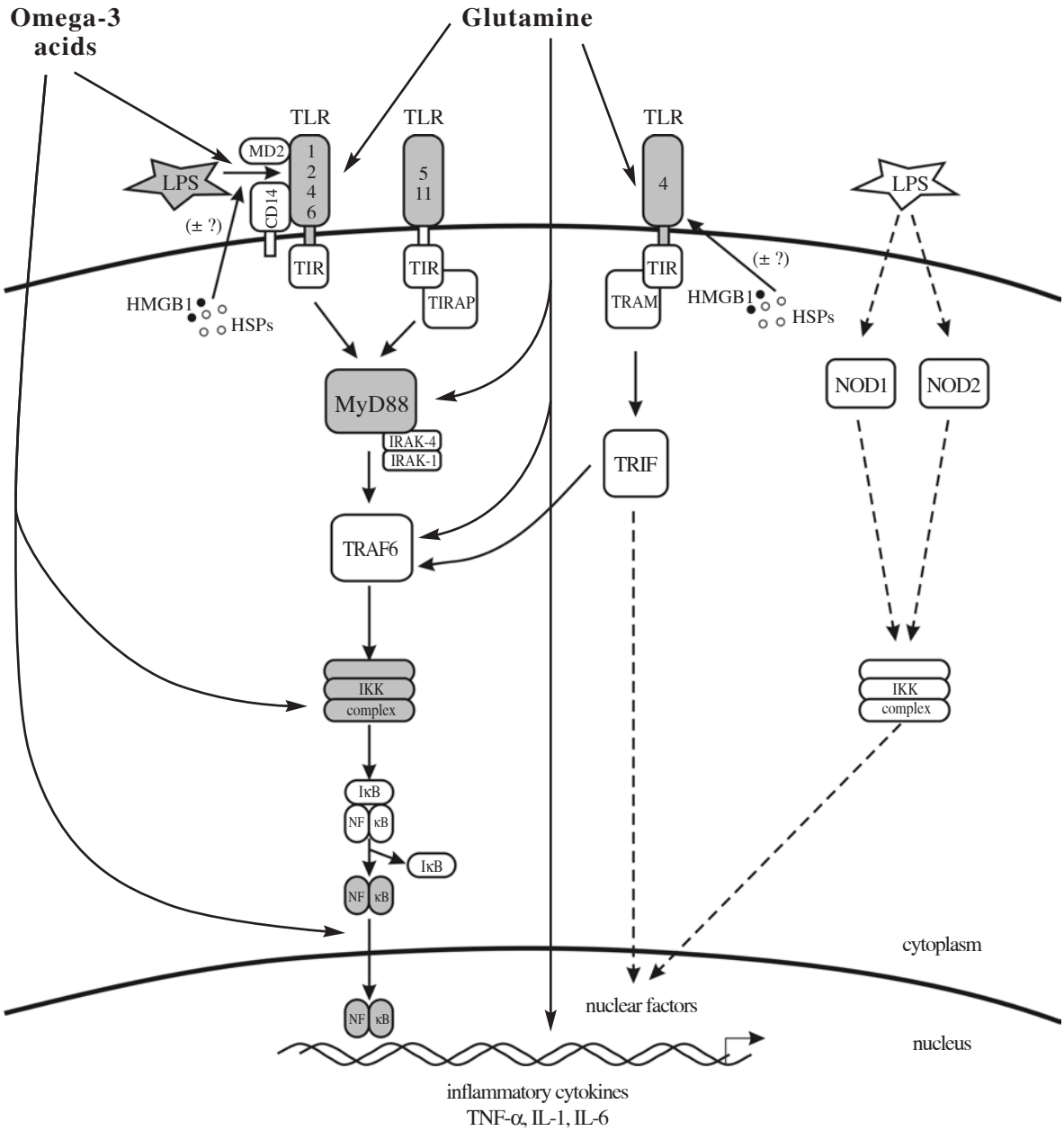

Fig. 1. Schematic diagram of TLR4, MyD88 and TRAF6 down-regulation in rats intestinal mucosa following glutamine administration and LPS-induced endotoxemia (A). N-3 omega acids inhibition of TLR signaling pathway at the extracellular (DHA interfere with TLR4 receptor) and intracellular level: inhibition of the phosphorylation and degradation of the IκB, inhibition of the NF-κB activation and inflammatory cytokines production in LPS-stimulated human leukocytes and macrophages (B). TLR-independent signaling via the NODs cytoplasmic sensors of LPS does not require members of the MyD88 adaptor family (interrupted lines)

sequent stages: a) endotoxin interaction with TRL4, b) activation of inhibitor phosphorylation kinases of the NF-κB (IκB) transcription factor and c) translocation to nucleus and connecting NFκB to an appropriate DNA sequence (suppressing the transcription of inflammatory response mediator genes) (Fig. 1) [54-61].

It was indicated that the enteral administration of diet enriched in unsaturated fatty acids (EPA) and glutamine in septic patients treated in intensive care units reduced the inflammatory response and mortality rate caused by acute lung injury (acute respiratory distress syndrome – ARDS) [62, 63]. The enteral administration of n-3 acids in septic patients modulated the functions of neutrophils, 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 [64, 65]. These findings indicate that immunomodulating nutrition may be an effective means of influencing the inflammatory response, particularly for those pathways affected by TLR4 signaling.

Our previous study has clearly indicated that the anti-inflammatory mechanisms are activated early in malnourished patients after pancreaticoduodenectomy receiving enteral immunonutrition [66]. Early enteral immunonutrition (with glutamine, arginine and n-3 fatty acids) in comparison to standard nutrition has an immunomodulative effect on the changes in the immune response after extensive surgical trauma. These consist in selective stimulation of IL-6, IL-8, IL-10 and IL-1ra production and down-regulation of IL-1 beta and TNF-α production. The temporary increase in IL-1ra concentration between post-operative days 7-14 obtained as a result of enteral immunonutrition decreases the inflammatory response to extensive surgical trauma and shortens its duration; this accelerates the wound healing process/tissue regeneration and may help avoid late complications (fistulas, abscesses).

The above-presented results show that to improve outcomes in the group of malnourished surgical patients suffering from severe infections more attention should be devoted to explaining the molecular mechanisms regulating the innate antibacterial response. One of the preconditions to provide progress in treating the most severely ill patients is to find out more about the impact of the state 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 applying immunonutrition are promising and indicate that in the future it can be a valuable supplement of the therapy using a blockade of selected signaling pathways to reduce the life-threatening effects of massive infection, including mainly the increased inflammatory response.

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