Review paper

Toll-like receptor signaling pathway in sepsis

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Abstract

Despite advances in treatment methods, there is still no therapy available to efficiently reduce the excessive inflammatory response in sepsis, which can increase the risk of multiple organ failure (MOF). One of the ways of discovering new, more efficient treatment methods consists in regulating the mechanisms of inflammatory response to a massive infection. In septic patients a significant role in antibacterial and inflammatory response play Toll-like receptors. This paper presents main mechanisms for innate immune response to LPS, based on the research results for both TLR-dependent and independent signaling pathways.

Key words: *toll-like receptors, signaling pathway, sepsis.*

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Introduction

In the group of patients treated in intensive care units the mortality rate caused by sepsis is the highest (25-60%) and still tends to increase, due to the lack of causal therapy methods to efficiently reduce the excessive inflammatory response to massive infections [1-6]. Many aspects of the immunopathology of sepsis are still unclear. 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 [7]. One of the ways of discovering new, more efficient treatment methods consists in regulating the mechanisms of inflammatory response to a massive infection. Activation of the innate immune system by microbial pathogens and their products contribute to systemic inflammatory response (SIRS) and organ failure (MOF). A significant role in innate antibacterial and inflammatory response play Toll-like receptors that recognize PAMPs-pathogen-associated molecular patterns. The changes in TLR expression and in the expression of signaling cascade proteins associated with their stimulation account not only for pathological inflammatory response to infection, but they can also have a protective action (e.g. increasing the apoptosis of selected cells, stimulation of signaling pathway inhibitors). To better understand the main signaling pathways of innate antibacterial immune response in septic patients it is required to briefly discuss some selected mechanisms regulating the expression of 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 intensive care units and still the highest mortality rates in this group make that TLR4 binding Gram-positive LPS bacteria and their participation in the pathogenesis of sepsis and septic shock arise a lot of interest. The Toll-like receptors (TLRs) recognize a few highly conservative structures existing in prevailing microorganisms. It was found that about 13 receptors (including 11 in humans) and it was indicated that they had mainly affinity to bacteria (TLR1, 2, 4, 5, 6). Some of them (TLR3, 7, 8, 9) show also some affinity to viral RNA and DNA. The prevailing TLRs show an expression on the surface of cells (TLR1, 2, 4, 5, 6), but some of them can be also active inside cells and (TLR3, 7, 8, 9) occur on the surface of endosomes [8, 9]. However, it is still unknown how ligands for those receptors (e.g. exogenic ligands: LPS, peptidoglycan, bacterial DNA) penetrate into the cells. The endogenic ligands for TLRs include mainly some heat shock proteins (HSP60, 70) released from injured cells.

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The production of LPS complex – CD14 receptor- MD2 adaptor protein – TLR4 induces dimerization of TLR4 and initiates signaling cascade, which results in activation of phosphorylation kinases of NFκB (IκB) transcription factor inhibitor. This process induces a transcription of genes whose products take part in inflammatory response (e.g. cytokines TNF-α, IL-1, IL-6, IL-12). In the signaling cascade of antibacterial response apart from extracellular TLR part there are also such "participants" as cytoplasmic part referred to as the TIR domain (Toll-IL-1 receptor), adaptor protein MyD88 (myeloid differentiation factor 88), TIRAP (TIR-domain-containing adapter protein) and TRAM (TRIF-related adapter molecule), protein TRIF (Toll/IL-1-receptor domain-containing adapter inducing IFN), TRAF6 (TNF receptor-associated factor 6), kinases (IRAK1, IRAK4- IL-1 receptor-associated kinases, TAK – TGF-beta-activated kinases) and a kinase complex (IKK – inhibitory κB kinase complex) [10-12]. The proteins MyD88, TRAF6, TRIF or TRAM are key proteins of signaling pathways initiated by TRLs, which can be of signicant importance in treating sepsis [13, 14]. This process results in activation of NF-κB and cytokine promotor genes. The production of inflammatory cytokines begins already after 60 minutes from the activation of macrophages by TLR4-binding LPS. In the MyD88 – dependent transduction of signal from TLR4,2, TRAF6 protein plays a significant role, while in the MyD88 pathway – independent, the main participants are TRAM and TRIF proteins (Fig. 1). A deficiency of TRAM protein decreases the inflammatory response (cytokine production), whereas a 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 can be the use of negative regulation of signaling pathways associated with TLRs (e.g. RP 105/CD180 protein- TRL homolog, SIGIRR – single immunoglobulin IL-1-receptor-related protein, ST2L – signaling TIR family ligand, TOLLIP – Toll-interacting protein or Smad6), whose mechanism consists in suppressing the location of bond between the ligand (LPS) and the receptor, proteolysis of TLR, blocking intracellular receptors binding antibacterial antigens and blocking the activity of kinases (suppression of phosphorylation process) and suppressing the activation of NF-κB factor [15-20]. Numerous experimental studies indicate the possibility of conducting 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 [21-24]. On the other hand, mice deprived of TLR2 and adaptor protein MyD88 are more susceptible to *Staphylococcus aureus* infections [25]. It 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 suggested a cooperation of other routes of signal conduction in antibacterial response [26]. This fact partly explains that the effects of treatment are insufficient because of blocking the routes of signal conduction. For example, when there is a deficiency in MyD88 protein and there is no previous activation of NF-κB associated with stimulation of TRL4 by LPS, other adaptor protein called TRIF takes over its function regulating the genes of monocyte inflammatory response and increasing the production of particular chemokines [27, 28]. 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 the trace amounts of TNF despite the lack of MyD88 protein can lead to late NF-κB activation [29]. Research on the MyD88 protein-independent pathway of antibacterial immune response in regulating the tolerance to endotoxins arise a lot of interest, because stimulating the signal conduction route can be one of the mechanisms to protect patients against the development of systemic inflammatory response syndrome (SIRS). More detailed knowledge of MyD88-independent pathway could be helpful in the therapy modulating the activity of particular signaling proteins to increase the tolerance to LPS. It is well known that the locally produced pro-inflammatory cytokines (as a response to trauma and infections) by neutrophils and macrophages play a significant role in developing SIRS. A significant increase of cytokine concentration 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 [30-32]. The priming effect of LPS on peptidoglycan induced a lung injury, whereas death in mice is preceded by NF-κB-mediated up-regulation of TLR-2 [33]. *In vivo* the transfection of NF-κB oligonucleotides strongly prevented the up-regulation of TLR-2 after LPS stimulation at pulmonary cellular and tissue levels.

Apart from TLRs, a significant role in recognizing the pathogen-related molecular patterns and the regulation of innate antibacterial response play also other proteins belonging to PAMP receptors, including peptoglycan recognition proteins (PGRPs), cytosolic NOD (nucleotide-binding oligomerization domain) proteins and TREM1 receptor (triggering receptor expressed on myeloid cells-1) [34]. They possess the ability to (e.g. NLRs-*node-like receptors: NOD1, NOD2*) connect with LPS and bacterial peptidoglycan and transferring signal independently of TLRs, which also result 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 particles [35]. The NOD1 recognizes the compounds of Gram-negative bacteria (meso-diaminopimelic acid with peptidoglycan) and some Gram-positive [36], whereas the ligand for the NOD2 is muramylodipeptide (MDP) coming from the wall of Gram-positive and Gram-negative bacteria [37, 38]. The transduction of signal by NOD receptors does

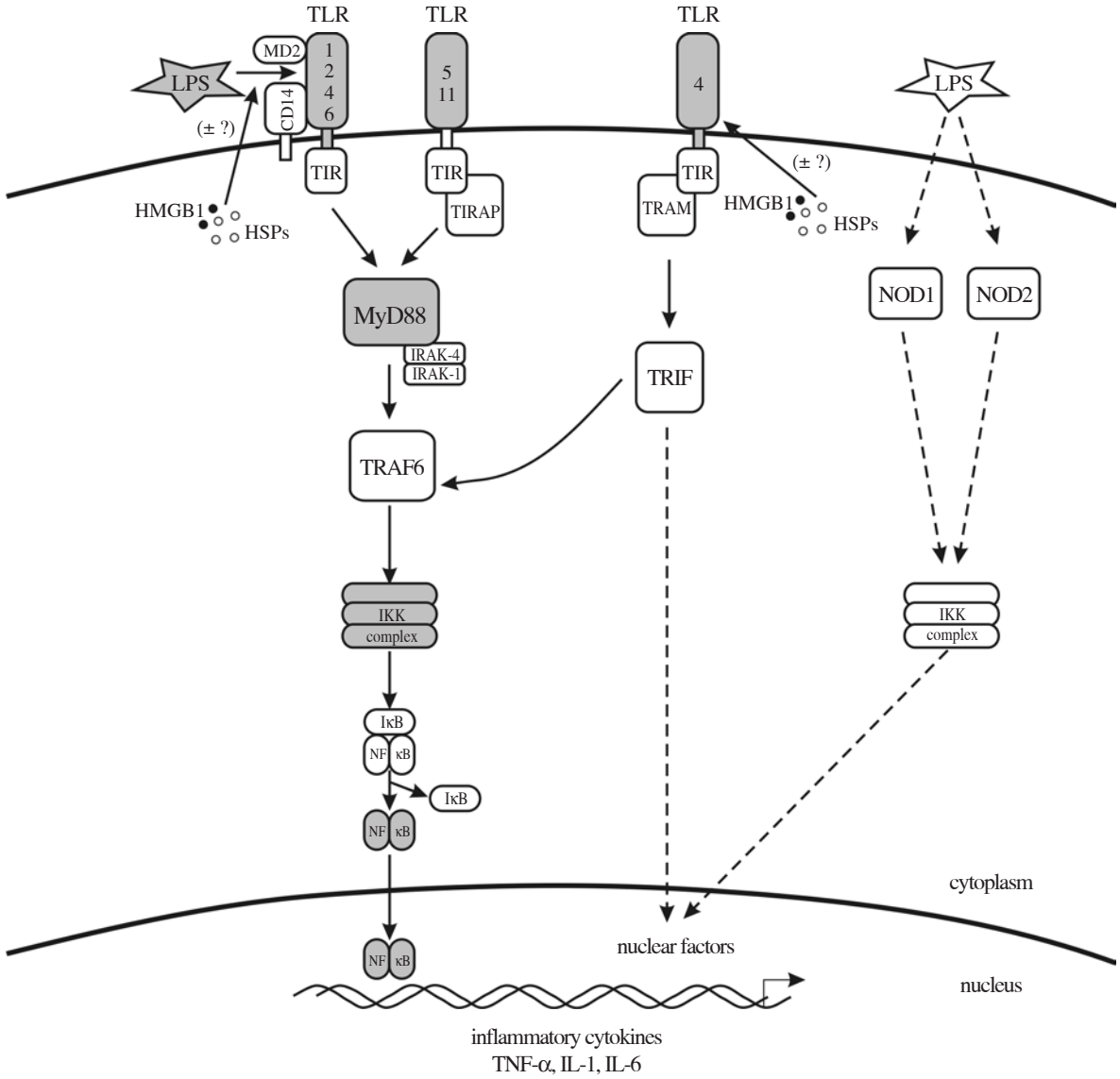

Fig. 1. Schematic diagram of TLR-dependent and -independent signaling after LPS binding. TLRs induce inflammatory reactions by the activation of signaling pathways mediated by the adapter proteins MyD88- myeloid differentiation factor 88 and TRIF – Toll/IL-1-receptor domain-containing adapter inducing IFN. MyD88 needs the bridging adapter MyD88-adapter-like/TIR-associated protein (Mal/TIRAP) for signaling induced by TLRs. MyD88 recruits IL-1 receptor-associated kinase (IRAK)-4 which phosphorylates IRAK-1. Activated IRAK-1 further recruits TNF-receptor-associated factor (TRAF)-6, which activates the transforming growth factor-b-activated kinase (TAK)-1/TAK1-binding protein (TAB)-2 complex as well as MAP-kinases and nuclear factor κB (NF-κB) and activator protein 1 (AP-1) transcription factors are activated resulting in the transcription of inflammatory genes. TLR-independent signaling via the NODs cytoplasmic sensors of LPS does not require members of the MyD88 adaptor family (interrupted lines). HSPs and HMGB1 protein can regulate TLRs functions. Abbreviations: TIR-Toll-IL-1 receptor, TIRAP-TIR-domain-containing adapter protein, TRAM – TRIF-related adapter molecule, IKK – inhibitory κB kinases complex, NOD- nucleotide-binding oligomerization domain, HSPs – heat-shock proteins, HMGB1 – high mobility group box1 protein

not require any participation of 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 [39]. 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 shock and sepsis [40]. Scientists try to use the changes in the protein plasma concentration in diagnosing sepsis [41].

An important group of proteins released as a result of tissue injury, damage to cells or infection includes endogenic molecules (heat-shock proteins HSP60, HSP70, fibronectin, β-defensin) and the ones having the ability to activate TLR4 and bind PAMPs, including high mobility group box1 protein (HMGB1) bound with DNA, stabilizing nucleosomes, and facilitating NF-κB activation and gene transcription [42, 43]. Like other inflammatory cytokines it is released from macrophages (within 24 hours) after LPS stimulation and plays an important role in regulating the release of nitric oxide (NO) by enterocytes and in activating neutrophils and macrophages that produce the increased amounts of cytokines and chemokines, but the scientists did not find a direct impact of HMGB1 on the process of releasing pro-inflammatory cytokines or chemokines. It is suggested that this action additionally needs LPS or inflammatory mediators to be involved (IL-1β) [44]. The last study demonstrates that HMGB1 modulates the inflammatory cascade in LPS-activated macrophages by inducing the 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 [45]. 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 [46, 47]. TLR 2 and 4 receptors were identified to mediate the effects of HMGB1 in neutrophils and macrophages [48]. In contrast to monocytes/macrophages, any stimulation of neutrophils by HMGB1 results in TNF release within 60 minutes, whereas LPS induces a late TNF release peaking at 4 hrs [49]. 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 [50]. As some studies have found, the blockade of HMGB1 after administering the lethal dose LPS protects mice against death. In experimental studies it is nicotine that shows a suppressing action for this protein [51].

The intracellular equivalents of PAMPs include also the heat shock proteins (HSPs) that protect the cell against injury. Increased concentrations of those proteins were noticed in patients after surgical trauma. In contrary to LPS, they do not induce a release of TNF-α by antigen-presenting cells (APCs), they do not affect the ability to bind LPS by monocytes, but they can increase the expression of TLR4 in those cells (mainly HSP70). It may indicate the regulative action of those proteins to antibacterial response, where the TLRs act as mediators. Interestingly, HSP70 was found to induce *in vivo* and *in vitro* the responses in both TLR-2$^{-/-}$ and TLR-4$^{-/-}$ mice [52]. The heat shock protein 70 (HSP70) can play indispensable roles in the protective effects of glutamine from injuries caused by sepsis-induced endotoxin shock [53-55]. The results of those studies explain partly the beneficial glutamine impact that increases the production of HSP in septic patients. The heat shock proteins like HMGB1 protein can be secreted outside of cells and after binding TLRs can regulate their functions. One of the interesting examples of such action can be the allergizing impact of HMGB1 protein that intensifies the expression of TLR4 in dendritic cells after trauma and tissue ischemia [56].

The above-presented results of the studies are promising and suggest that modulating the activity of TLRs and related signaling pathways as well as a change in the expression of pathogen-binding proteins may reduce the life-threatening effects of massive infection, including mainly the increased inflammatory response and will have a significant impact on outcomes in patients with severe infections.

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