CD14/TLR4 in sepsis pathogenesis and therapy.

Angelos Pazidis, Apostolos Champipis, Ioannis Gkougkourelas, Panagiota Boura

Clinical Immunology Unit, 2nd Internal Medicine Clinic, Aristotle University of Thessaloniki, Hippokratio General Hospital, Greece

ABSTRACT: Sepsis still remains one of the leading causes of death in critical care units all over the world. It seems that one of the major pathophysiological events in sepsis is the extreme activation of the immune system, which leads to massive production of several cytokines and other mediators of inflammation. Pattern Recognition Receptors (PRRs) are responsible for the recognition of the pathogens by the innate immunity cells and for the consequent cytokine production. This fact shows that PRRs could possibly play an important role in sepsis pathogenesis. Among all PRRs, TLR4 (Toll Like Receptor 4) and CD14 are primarily responsible for the recognition of Gram(-) bacteria, which are responsible for the majority of sepsis cases. It seems that the expression of TLR4 and CD14 present alterations during sepsis. Some of these alterations could be used as prognostic factors in septic patients, as they have been correlated with better or worse outcome. Finally, TLR4 and CD14 represent possible targets in sepsis treatment. Many attempts have been done to block these two receptors at many levels, using monoclonal antibodies, soluble analogues and especially antagonists. Results, in some cases encouraging in others disappointing, are still being tested.

Key Words: Immunology, Sepsis, TLR4/CD14, Pathogenesis, Therapy.

INTRODUCTION

The innate immune system consists of cells and molecules which represent the first line of defence against microorganisms after invasion into the body. Although the innate immune system is not able to launch a specific attack against the pathogens, it has the ability to discriminate self from non-self. Special receptors on the surface or into the cells of innate immunity are bound for this task. Innate immunity receptors are well preserved molecules, at innate immune cell surface, presenting few differences, at least structurally, among various species. They are called PRRs (Pattern Recognition Receptors). There are also soluble PRRs in the plasma. PRRs recognise certain, highly conserved components of the pathogens, referred to as PAMPs (Pathogen Associated Molecular Patterns). These molecules are crucial to invaders’ survival and since they are present only in pathogens, their recognition by PRRs offers a mechanism of discrimination between self and non-self at the level of innate immunity. PAMPs include LPS (Lipopolysaccharide) of Gram(-) bacteria, teichoic acids of Gram(+) bacteria, ds RNA of retroviruses, mannans of yeast cells and other molecules. PRR activation by PAMPs leads to the production of proinflammatory cytokines and other mediators and thus they trigger an inflammatory response.

Typically, cellular PRRs can be found on macrophages, dendritic cells, endothelial cells, epithelial cells of the mucosae, B cells and certain types of T lymphocytes. PRR family includes mannose receptors, scavenger receptors, opsonin receptors, N-formyl methionine receptors, TLRs (Toll Like Receptors), RLRs (RIG-I [Retinoid-inducible gene I] Like Receptors) and NLRs (NOD [Nucleotide Oligomerisation Domain] Like Receptors). Soluble PRRs include collectins (Mannose Binding Lectin), CRP, serum amyloid P, LBP (LPS Binding Protein) and other acute phase molecules.

Human organism responds to various harmful conditions with inflammation. Inflammation can be local,
affecting a certain part of the body, or systemic, affecting the whole organism. In general, this reaction is useful but it can become dangerous in overwhelming conditions. Systemic Inflammatory Response Syndrome (SIRS) is the term used to describe the systemic inflammation due to various reasons - such as trauma, burns, pancreatitis, infections and others. Two or more of the following criteria are necessary to diagnose Systemic Inflammatory Response Syndrome:

- Oral temperature >38°C or <36°C
- Tachypnoea (>24 breaths/min) or PaCO2 <32 mmHg
- Tachycardia (heart rate >90 beats/min)
- Leucocytosis (>12000/μL), leucopenia (<4000/μL) or >10% immature forms, in peripheral blood

When SIRS is caused by an infection then it is referred to as sepsis.

Sepsis is a condition representing a systemic response to infection. It is obvious that sepsis consists of two essential elements: a microbial infection and the consequent systemic inflammation. When sepsis, as defined above, is accompanied by one or more signs of organ dysfunction, away from the site of the initial infection, then it is called severe sepsis. Organs and systems which may be affected are the cardiovascular system (arterial systolic blood pressure less than 90 mmHg), kidneys (urine output less than 0,5 mL/kg per hour despite sufficient intravenous liquid administration) and others (practically almost every system in the body). In severe sepsis hypotension responds to fluid resuscitation. When hypotension (defined as arterial systolic blood pressure less than 90 mmHg or 40 mmHg less than patient’s normal level) in a patient with severe sepsis cannot be controlled with adequate liquid administration and persists at least for 1 hour then it is considered septic shock. Sepsis is accompanied by high mortality despite the advances in diagnosis and therapy.

More than half a million patients are affected by severe sepsis every year in the USA. The incidence is approximately 3 patients in 1000 individuals in the USA and between 0,5-1,5 in 1000 individuals of population in Europe according to retrospective studies, while it is estimated that this number will be double by 2020. Mortality varies between 25% -30%, which may raise up to 50%-60% for patients with septic shock.

Sepsis is initiated by an overwhelming activation of innate immune system against the invader, resulting in an extreme cytokine production, usually referred to as cytokine storm. Since pathogens are firstly sensed by the immune system through a number of special receptors called PRRs, the interaction between the invaders and PRRs triggers the inflammatory response by inducing the production of proinflammatory and inflammatory cytokines, as already mentioned above. Thus, it seems that the first step towards sepsis is made at the level of these innate immunity receptors, PRRs.

**CD14 on mononuclear phagocytes**

CD14 is an important receptor that mostly recognises LPS of Gram(-) bacteria. CD14, a protein that is located on the surface of myeloid cells, binds the LPS causing cellular activation. This activation leads to the production of proinflammatory cytokines (TNF-α and IL-6) and chemokines (IL-8) and induces NO synthetase. The recognition and the signalling through the CD14 dependent pathways of monocyte activation demands three proteins: a) the protein that binds LPS (LBP), b) CD14 molecule and c) TLRs. LPS binding protein (LBP), a plasma protein that transfers lipids, acts on conglomerates of LPS or bacterial membranes and presents LPS monomers at the binding sites of CD14. It is significant that endothelium lacks membrane bound CD14 and this is why soluble CD14 is demanded to direct the recognition of LPS. LPS recognition mediated by CD14 is not enough for intracellular signalling. TLR-4, a receptor leading to the activation of the NF-κB pathway is needed for the activation of the intracellular signaling. This has been shown by the absence of activation of the pathway in mice that carry mutations in the intracellular region of TLR-4.

Experiments held on rabbits showed that anti-CD14mAbs administrations help to improve the haemodynamic status in septic shock, since they reduce significantly the concentrations of nitrite and nitrate in plasma. This indicates that improvement of the haemodynamic responses involve the blockage of NO production in vessels. So it seems that the systemic effects of CD14 blockade are beneficial, since they improve the haemodynamical status and reduce the demands for intracellular administration of fluids. On the contrary, at the point of inflammation this block-
age is catastrophic, e.g. it prevents the intrapulmonary bacterial clearance. Anti-CD14 treated rabbits had significantly worse hypoxaemia, delayed intrapulmonary bacterial clearance and a trend to higher levels of protein in BAL. The unfavourable results regarding the defective intrapulmonary bacterial clearance cannot be attributed to reduced attraction of neutrophils in the lungs or to the decreased levels of cytokines, since both appear to be normal. It is possible that the anti-CD14 mAbs affect the reactions between bacteria and leukocytes, given that phagocytosis of Gram(-) bacteria is facilitated by a CD14-dependent mechanism in vitro\textsuperscript{16,17}.

**TLR**

In general, TLRs form a family of transmembrane and intracellular receptors. Transmembrane TLRs consist of an extracellular rich in leucine repeats region, which comes in contact with a specific PAMP for each TLR and an intracellular TIR region (Toll/IL-1 Receptor region) which is common between TLRs and IL-1 receptor and is responsible for the induction of the intracellular signal\textsuperscript{12,18}. Each TLR shows a kind of specificity for certain pathogen molecules (PAMPs). TLR-1, -2, -4, -5 and -6 mostly recognise bacterial elements while TLR-3, -7 and -8 are specific for viral products. TLR-9 is thought to play a role in the recognition of bacteria and viruses as well (Table 1)\textsuperscript{12}.

More specifically, TLR-4 interacts with the LPS of Gram(-) bacteria, while TLR-2 recognises mostly the peptidoglycan of Gram(+) bacteria\textsuperscript{19}. Moreover, TLRs can be activated by endogenous ligands, which act like danger signals (alarmins)\textsuperscript{12,20}. For instance it has been demonstrated that TLR-4 recognises oligosaccharides of hyaluronic acid, fibrinogen, polysaccharide fragments of heparin sulphate, oxidised LDL, neutrophil elastase, various heat shock proteins, defensin-2 and HMGB-1 (High Mobility Group Box-1)\textsuperscript{12,21}.

It was in 1985 when Christiane Nüsslein-Vohlard and her colleagues firstly described a receptor called Toll in Drosophila melanogaster. They showed that Toll receptor plays a role in the development of Drosophila embryos. In 1996 Drosophila’s Toll receptor was found to play another important role: Jules Hoffman and colleagues demonstrated that this receptor was associated with protection against fungal infections\textsuperscript{22}. Prior to that, Nomura and his co-workers, in

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<tr>
<th>Toll Like Receptors</th>
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<tr>
<td>TLR1\textsuperscript{(extracellular)}</td>
<td>Triacyl lipopeptide</td>
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<td>TLR2\textsuperscript{(extracellular)}</td>
<td>Peptidoglycan, Lipoteichoic acid</td>
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<td>TLR12**</td>
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<td>TLR13**</td>
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*not expressed in humans, **no orthologues in humans*\textsuperscript{29,3}.
an attempt to identify some of the unidentified genes of the human genome, discovered a gene similar to that of Drosophila’s Toll, named KIAA0012, later mapped to chromosome 4p14, which in 1998 proved to be identical with TLR123,24,25.

The first receptor to be identified in human as Toll Like Receptor was TLR4, as TLR1, although already known as a gene since 1994, it was classified as TLR by Rock and colleagues after the description of TLR4. TLR4 was firstly described by Charles Janeway, Ruslan Medzhitov and Paula Preston as hTLR (human TLR) in 199726. It was only a year later when Beutler and his colleagues showed that TLR4 recognises LPS27. Since then, many aspects of its function in the human immune system have been revealed and there are still even more to be discovered.

This review focuses on the role of TLR4, among other members of the TLR family, because of its participation in the recognition of Gram(-) bacteria. This is quite important, as Gram negative bacteria represent one of the most common causes of sepsis with a very high mortality rate. Actually, almost 40% of patients with severe sepsis are proven to be infected by a Gram negative bacterium, while Gram positive infection is responsible for 31% of severe sepsis cases.9 The role of TLR4 in sepsis has been tested by several experimental studies, all of which show that mice with certain mutations in TLR4 gene are highly resistant to LPS-induced sepsis but they also show dramatically high susceptibility to Gram negative infections28,29.

**Figure 1.** CD14-TLR4 activation and downstream signalling.

The role of LPS and TLR4 signalling cascade (Figure 1) LPS is the principal constituent of Gram(-) bacteria outer membrane. It consists of three parts, the lipid A, a core of oligosaccharide and the O-antigen polysaccharide. LPS causes the release of certain cytokines from the innate immunity cells, such as TNF-α, IL-6 and IL-1β. LPS is identified as the causative factor in many cases of sepsis and septic shock31.

LPS plays a major role in the recognition of Gram (-) bacteria. Firstly, LPS is transferred to the surface of the innate immunity cells by a plasma protein named LBP, where it binds to CD14. CD14 delivers LPS on MD2/TLR-4 complex. There, LPS binds to MD2 which is attached to TLR-4. Once the pair LPS-MD2/TLR4 is formed, a TLR4 dimerization occurs resulting in TLR-4 activation3,14,32. TLR-4 intracellular region (TIR: Toll/IL-1 Receptor) comes in contact with many signal transmitting molecules such as MyD88, TIRAP (TIR domain-containing Adaptor Protein), TRIF (TIR domain-containing adaptor inducing IFN-β) and TRAM (TRIF-Related Adaptor Molecule). The signal follows two different pathways into the cytoplasm until it eventually reaches the nucleus. The first pathway is TIRAP- MyD88 dependent (which is used by all TLRs except for TLR-3) and activates NF-κB and MAPKs (ERK-1/2, JNK, p38) causing the expression of several cytokines and other inflammatory molecules(e.g. IL-6, TNF-a IL-8, IL-12 and others), while the second one is MyD88 independent (it engages TRAM-TRIF molecules and is used by TLR-3,TLR-4, TLR-7 and TLR-9) and activates IRF-3 (IFN response factor 3) causing production of type I IFNs3,11. Recent studies show that Th2 cytokines, such as IL-4, are also produced as a result of TLR4 activation by LPS. IL-4 production though, is not so rapid as that of Th1 cytokines. It seems to require both MyD-88-dependent and -independent pathways at the same time, in contrast to Th1 cytokines which need only one of them so as to be produced33.

**Endogenous ligands of TLR4**

The idea of discrimination between self and non-self has always been fundamental in immunology, meaning that the immune system can only be activated by exogenous molecules while, on the other side, endogenous molecules are not able to trigger such an activation. This view though, could not fully explain
all immune responses and immune homeostasis under certain conditions. It was then hypothesised that certain endogenous molecule also interact with the immune system and, in fact, they are able to activate it. So, in 1994 Matzinger proposed the “danger model” in which the immune system is not triggered by “non-self” but actually by certain “danger signals”, introducing the term DAMP. DAMPs (Danger Associated Molecular Patterns) are signals able to activate the innate immune system. This group of molecules include alarmins, which are danger signals originating from damaged cells, and PAMPs which are the exogenous molecules that are recognised by the immune system.

Given that TLRs can be activated by endogenous DAMPs, it is quite possible that these molecules, among others, play a role in sepsis. HMGB-1 is an intracellular protein released in the extracellular environment after cell death or damage but not after apoptosis. Furthermore, this molecule is also released by immunocompetent cells. It has been shown that certain effects of HMGB-1 in injury, inflammatory conditions and sepsis are induced by its interaction with TLR-2, TLR-4 or both. Signalling through TLR-2 and -4 enhances the inflammatory response by inducing cytokine production and causes even more severe tissue injury. The potential role of HMGB-1 in sepsis pathogenesis is supported by studies showing that certain mutations in HMGB-1 gene are related with a reduced survival rate of septic patients. Although HMGB-1 is always present in sepsis, its levels in plasma do not always correlate with the outcome or with the survival. TLR-4 is part of a vicious cycle which enforces the inflammatory response through the recognition of certain DAMPs. MIP2 and neutrophil elastase are also components of the same cycle. In particular, during sepsis neutrophils are attracted to the lungs and liver by certain chemokines, where they excrete elastase. Neutrophil elastase causes tissue damage but besides that, it binds to TLR-4 and participates to downstream activation, leading to increased inflammation through chemokine production. Thus it closes the aforementioned cycle. This represents one of the possible mechanisms of tissue damage and MODS (MultiOrgan Dysfunction Syndrome) in sepsis. It seems that there is also an interaction between TLR-4 and complement system. Some of the cytokines produced through TLR activation upregulate the expression of C5aR and C3aR, while C5a component of complement system downregulates TLR-4-mediated responses.

Clinical Prospects

As TLR4 represents a very important component in the pathogenesis of Gram(-) sepsis, it is quite reasonable that it might be used as a measurable diagnostic and/or prognostic factor during sepsis. Unfortunately, studies up to date give conflicting data on this matter. There are some of these studies which show that TLR4 expression is upregulated in sepsis, while others claim that TLR4 expression makes no difference between healthy and septic patients. As far as CD14 expression, most studies agree that CD14 is upregulated in sepsis. Some studies though, show that only the soluble CD14 is upregulated, while on the contrary, membrane CD14 is downregulated.

TLR4/CD14 function during sepsis proves to be particularly interesting, as some studies show that while TLR4/CD14 expression is upregulated in septic patients, the decrease of these molecules marks an unfavourable outcome. Indeed, the levels of gene expression for TLR receptors in monocytes show to be related with the state of sepsis. The lowest expression happens during septic shock, followed by severe sepsis. That means, TLR protein expression can be associated to sepsis severity. Thus, it seems that septic patients with lower TLR4/CD14 expression are more likely to die from sepsis. From all the above men-

Figure 2. The blockade of TLR4 by Eritoran and TAK242.
tioned, it is quite possible that TLR4/CD14 expression levels could play a prognostic and/or diagnostic role in sepsis, after their mechanistic effect on sepsis pathogenesis is elucidated.

THREATY

General

Sepsis must be viewed as an imbalance between pro-inflammatory and anti-inflammatory factors. Therapy cannot be the same for all patients, as sepsis is a quite complicated situation demanding a more personalised approach.13 Spleens from patients who died from sepsis show decreased numbers of B and CD4+ T lymphocytes. Most of the patients with sepsis die during CARS (Compensatory Anti-inflammatory Response Syndrome), a later stage of sepsis, following SIRS and characterised by Th2 inflammatory response and immunoparalysis8. Given that, an immunomodulating therapy in those patients could be hardly helpful.

Measurements of plasma cytokines in septic patients could be used to estimate the immune status of each patient. A patient in CARS may benefit from a strengthening of his/her immunity state, as shown by some studies in which IFN-γ administration seems to increase survival13,38. On the other side, when a Th1 response, which is responsible for further tissue damage and organ failure, predominates, the appropriate therapy might be an immunosuppressive one. These differences in the immunocompetence profile of each patient are not only due to different stage - SIRS or CARS - but also due to the genetic background. Thus, in some septic patients a severe proinflammatory response is predominant while in others an anti-inflammatory one is observed. This fact may explain differences in outcome of therapy in septic patients at the same disease stage who are treated the same way13.

PRR targeting therapies-Analogues

A possible therapeutic approach is to target and block LPS before it activates innate immune response. This could be achieved by LBP analogues which do not have the ability to present LPS to CD14 on the cell surface, ultimately preventing TLR4 activation and the consequent cytokine production. Another prospect is offered by a recombinant soluble CD14 molecule which seems to increase survival of septic mice. Also, since the reaction between CD14 and LPS leads to the intracellular signalling and the production of pro-inflammatory cytokines, its blockage at this early stage of the inflammation cascade could possibly be used as a therapy. In a model of causing septic shock in a primate using endotoxin, anti-CD14mAbs prevented hypotension, reduced levels of cytokines in the plasma and the permeability of the lung epithelium. Although it has been proven that the blockage of CD14 is beneficial, there is no data about its effects on the reaction between CD14 and bacteria. Furthermore, there are studies suggesting that HDL could act as a deposit for LPS which, as a result, cannot activate TLR 413.

There are many natural mechanisms which modify TLR expression in order to prevent an excessive activation which could possibly be detrimental. Such a mechanism engages RP105, a molecule presenting many structural similarities with TLRs, first detected on rodent B lymphocytes. Unlike TLRs though, RP105 does not have an intracellular region. Its extracellular region binds to TLR4, thus offering a natural inhibitor of this receptor. The complex formed by RP105 and MD1 interacts with TLR4 causing a reduced capacity of the latter to act as a binding site for LPS. This complex, among other possible mechanisms in humans, could be used to prevent one of the primary sepsis mechanisms, the excessive activation of TLR420. Soluble TLR4 molecules could also be helpful in septic conditions. A soluble TLR4 has been detected in mice, possibly acting as another natural protective mechanism from membrane bound TLR4 hyperactivation and consequently from the production of an excessive amount of proinflammatory cytokines, a dominant factor in sepsis.

PRR targeting therapies-Monoclonal antibodies

Another important approach is that of using antibodies against TLR4. The idea of blocking TLR4 with an antibody derives from the observation that TLR4 -/- mice are proven to be resistant to septic shock caused by E. Coli in terms of survival in comparison to wild-type mice. It is worth noting that according to some studies, anti-TLR4 mAbs could possibly be used for prophylaxis and for therapy of sepsis as well. Experiments show that in order to be effective as a therapy, mAbs must be administered from 1h upto 4h or even 13h after LPS injection, depending on the bacterial load.14 Anti-TLR4 mAbs may be useful in sepsis ther-
apy, as, in mice, they inhibit the response of innate immunity cells exposed to LPS in vitro and in vivo as well. These antibodies seem to protect mice exposed to live E. Coli\textsuperscript{20}. Another possibility is offered by mAbs against CD14 or against MD-2/TLR-4 complex as a whole, which though seem to be ineffective if administered after infection\textsuperscript{14,39}.

MyD88 also represents a possible therapeutic target. Actually, a heptapeptide called ST2825 has been designed to block MyD88 dimerisation and thus to prevent the activation of downstream molecules of the cascade towards the nucleus. TLR4 signalling pathway could be possibly blocked at various points\textsuperscript{40}.

**TLR4 antagonists**

The most promising therapy includes TLR4 antagonists such as Eritoran and TAK242\textsuperscript{20}. Despite the possibly favourable effect of TLR4 antagonists though, some recent studies express the paradox that, at least in some cases of sepsis, TLR4 agonists could be more efficient\textsuperscript{41}.

Eritoran (E5564) is a synthetic LPS antagonist binding to MD-2/TLR4 complex and it is an analogue of the lipid A of Rhodobacter capsulatus. Eritoran (E5564) and E5531 (another A lipid analogue with similar function to that of Eritoran) bind to TLR-4 thus preventing its activation by LPS (Figure 2). Eritoran lacks any agonistic activity on TLR4. Several studies have shown that the use of these analogues inhibits the production of all the cytokines for which TLR-4 activation by LPS is responsible\textsuperscript{40}. In particular, Eritoran seems to block cytokine production after in vitro challenge with LPS or with live Gram(-) bacteria in whole human blood. In animal models it has been shown that a minimal dose of 1mg/kg of body weight is sufficient to completely block LPS induced activation of TLR4, while in humans it is estimated that a dose of merely 100μg for a patient with 70kg of weight would have the same effect. Eritoran (E5564) is currently being tested in a phase III study\textsuperscript{31}.

TAK-242 is another molecule that has been designed to block TLR4-induced cytokine production. TAK-242 is a cyclohexene derivative which blocks the signal transduction via TLR-4 and thus it prevents lethality in experimental models of LPS septic shock or sepsis in rodents\textsuperscript{17}. In fact, TAK-242 is not an antagonist of TLR4 but an inhibitor binding to the intracellular domain of TLR4 and specifically to Cys747. After binding to this site it blocks the transduction of the signal of both MyD-88 dependent and independent pathways. TAK-242 is also proven to block TLR4 downstream signalling induced by endogenous ligands, such as HMGB1. TAK-242 has been tested in a phase III clinical trial, which proved no significant decrease in cytokine production compared with placebo therapy.

Despite any good results so far, it must be kept in mind that TLR blocking, at any stage, could be a double-edged sword, as an extreme blockade could result in an impaired immune defense against infections\textsuperscript{29,40}.

**CONCLUSION**

Sepsis is a critical situation accompanied by high mortality ranging from 25% up to more than 50% for patient in septic shock.

In sepsis, at least in the beginning, an extreme inflammatory response is observed.

PRR activation is responsible for the inflammatory cytokine production during infection as well as during sepsis through up regulation during sepsis usually occurs.

CD14/TLR4 complex plays a critical role in the pathogenesis of sepsis caused by Gram(-) bacteria.

Downregulation of PRR expression in septic patients might probably be associated with higher mortality.

PRR blockage (analogues, monoclonal antibodies, antagonists etc.) might be beneficial during sepsis treatment.

In some cases, blocking the PRR pathways might be detrimental rather than useful.

**Questions yet to be answered**

Do the PRRs have still unknown functions in sepsis pathogenesis, except for the expression of inflammatory mediators?

Can PRR expression measurements be efficiently used to predict sepsis outcome or even to foretell when an infected patient is heading towards sepsis?

**Abbreviations**

PRRs (Pattern Recognition Receptors), PAMPs (Pathogen Associated Molecular Patterns), LPS
ΠΕΡΙΛΗΨΗ: Η σήψη παραμένει μια από τις κύριες αιτίες θανάτου στις μονάδες εντατικής θεραπείας παγκόσμως. Φαίνεται ότι ένα από τα κυρίωτερα παθοφυσιολογικά γεγονότα στη σήψη είναι η έντονη ενεργοποίηση του ανοσιακού συσήματος, η οποία οδηγεί σε υπερέκκριση συγκεκριμένων μεσολαβητών της φλεγμονής. Οι υποδοχές αναγνώρισης προτύπων δομών (Pattern Recognition Receptors-PRRs) είναι υπεύθυνοι για την αναγνώριση παθογόνων μέσω των κυττάρων της φυσικής ανοσίας και τη διαρκή παραγωγή κυτταροκινών και άλλων μεσολαβητών της φλεγμονής.. Αυτό σημαίνει ότι οι PRRs θα μπορούσαν να παίξουν σημαντικό ρόλο στην παθογένεση της σήψης. Από τους PRRs, ο TLR4 και ο CD14 είναι κυρίως υπεύθυνοι για την αναγνώριση των Gram(-) βακτηρίων, τα οποία ευθύνονται για τη σήψη στην πλειονότητα των ασθενών. Φαίνεται ότι η έκφραση των TLR4 και CD14 παρουσιάζει διακυμάνσεις στη σήψη. Αυτές οι διακυμάνσεις ίσως μπορούν να χρησιμοποιηθούν ως προγνωστικοί δείκτες στη σήψη. Αυτές οι διακυμάνσεις θα μπορούσαν να χρησιμοποιηθούν ως προγνωστικοί δείκτες στη σήψη. Αυτές οι διακυμάνσεις ίσως μπορούν να χρησιμοποιηθούν ως προγνωστικοί δείκτες στη σήψη. Αυτές οι διακυμάνσεις ίσως μπορούν να χρησιμοποιηθούν ως προγνωστικοί δείκτες στη σήψη. Αυτές οι διακυμάνσεις ίσως μπορούν να χρησιμοποιηθούν ως προγνωστικοί δείκτες στη σήψη. Αυτές οι διακυμάνσεις ίσως μπορούν να χρησιμοποιηθούν ως προγνωστικοί δείκτες στη σήψη. Αυτές οι διακυμάνσεις ίσως μπορούν να χρησιμοποιηθούν ως προγνωστικοί δείκτες στη σήψη. Αυτές οι διακυμάνσεις ίσως μπορούν να χρησιμοποιηθούν ως προγνωστικοί δείκτες στη σήψη. Αυτές οι διακυμάνσεις ίσως μπορούν να χρησιμοποιηθούν ως προγνωστικοί δείκτες στη σήψη. Αυτές οι διακυμάνσεις ίσως μπορούν να χρησιμοποιηθούν ως προγνωστικοί δείκτες στη σήψη. Αυτές οι διακυμάνσεις ίσως μπορούν να χρησιμοποιηθούν ως προγνωστικοί δείκτες στη σήψη. Αυτές οι διακυμάνσεις ίσως μπορούν να χρησιμοποιηθούν ως προγνωστικοί δείκτες στη σήψη. Αυτές οι διακυμάνσεις ίσως μπορούν να χρησιμοποιηθούν ως προγνωστικοί δείκτες στη σήψη. Αυτές οι διακυμάνσεις ίσως μπορούν να χρησιμοποιηθούν ως προγνωστικοί δείκτες στη σήψη. Αυτές οι διακυμάνσεις ίσως μπορούν να χρησιμοποιηθούν ως προγνωστικοί δείκτες στη σήψη. Αυτές οι διακυμάνσεις ίσως μπορούν να χρησιμοποιηθούν ως προγνωστικοί δείκτες στη σήψη. Αυτές οι διακυμάνσεις ίσως μπορούν να χρησιμοποιηθούν ως προγνωστικοί δείκτες στη σήψη. Αυτές οι διακυμάνσεις ίσως μπορούν να χρησιμοποιηθούν ως προγνωστικοί δείκτες στη σήψη. Αυτές οι διακυμάνσεις ίσως μπορούν να χρησιμοποιηθούν ως προγνωστικοί δείκτες στη σήψη. Αυτές οι διακυμάνσεις ίσως μπορούν να χρησιμοποιηθούν ως προγνωστικοί δείκτες στη σήψη. Αυτές οι διακυμάνσεις ή άλλες απογοητευτικά αποτελέσματα.


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