Sepsis and immune response

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Sepsis and secondary multi-organ failure are important causes of the death of critically ill patients. Despite a lot of work has been done recently, the exact mechanism of sepsis is not clear, and its mortality has not decreased significantly. At the European Conference on Critical Care Medicine held in Barcelona, Spain in 2002, the European Society of Intensive Care Medicine (ESICM), the American Society of Critical Care Medicine (SCCM), and the International "Sepsis" Foundation (ISF) signed the Barcelona Declaration, striving to a 25% reduction in the mortality of sepsis within 5 years. With the progress of the study, researchers gradually realized that sepsis is a dynamic, diverse syndrome due to the imbalance of the "inflammatory network".

SEPSIS AND IMMUNITY

Early studies of sepsis focused on infection, but clinical studies found that immune response in sepsis plays an important role, and hence sepsis is defined as a systemic inflammatory response syndrome (SIRS) after serious microbial infection. However, a simple anti-inflammatory therapy does not reduce the mortality of sepsis. Some sepsis patients die at early stage of inflammatory response, but most patients die in the late period of sepsis with a longer period of immune suppression. Thus researchers began to question whether the mortality of sepsis is only related to uncontrolled pro-inflammatory response. It was observed that immune paralysis and acquired immune system dysfunction both play important roles in the course of immunosuppression. [1] The immune pathogenesis of sepsis is very complex.

IMMUNE RESPONSE AND IMMUNE REGULATION IN SEPSIS

Immune response in sepsis

In the early state of sepsis, the excessive activation of the antigen recognition system and the release of pro-inflammatory mediators lead to serious multi-...
system dysfunction in the body. Immune cells express a series of receptors on membrane surface called pattern-recognition receptors (PRRs); these receptors can trigger the body's defense reaction rapidly after tissue injury or bacterial infection. Bacterial infection can be detected by pathogen-associated molecular patterns (PAMPs), and necrotic tissue immune recognition molecules are intracellular proteins or the media released by dying cells. PRRs subtypes or Toll-like receptors (TLRs) are important receptors which can recognize pathogens and induce the inflammatory response.

During sepsis, microbial infection or necrotic tissue released high levels of harmful substances, resulting in the activation of systemic immune response and excessive activation of immune cells. The excessive release of cytokines plays a destructive effect. TLR-4 interaction with the complement system, for example, complement C5a can negatively regulates TLR4-mediated inflammatory response. The high level of complement-activation product increases the expression of complement receptors C5AR and C3AR. A study found that the activation of platelet TLR4 can increase the bacterial adhesion to neutrophil cell surface, suggesting that there is a complex interaction between the coagulation system and the innate immune system. Since TLR4 plays an important role in the inflammatory response triggering, TLR4 may become a target for the treatment of sepsis.

**Immune regulation in sepsis**

T cells, especially TH1 and TH2 cells, play an important role in the regulation of inflammation. In the pathogenesis of sepsis, acquired immune response is transformed from the TH1 cell-mediated immune response (characterized by the production of IFN-γ and IL-12) into the TH2 cell-mediated immune response (characterized by the production of IL-4, IL-5, IL-10, IL-13), leading to further immune suppression. In addition, lymphocytes and dendritic cells (DC) apoptosis also play an important role in immune suppression. Apoptosis of macrophages and neutrophils is not significantly increased but decreased a little. Apoptosis of lymphocytes and DC leads to severe immune suppression so that it greatly increases the risk of nosocomial infection. The reduction of apoptosis of neutrophils and macrophages further promotes inflammation. Early T cell-mediated innate immune system suppression is reported to reduce the body damage and increase the body defense. There is evidence that sepsis not only affects the body's immune system but also acts on the body's coagulation system and the autonomic nervous system.

**EFFECTS OF INFAMMATORY MEDIATORS IN SEPSIS**

**Migration inhibitory factor (MIF)**

Migration inhibitory factor (MIF) was the first discovered cytokine, which plays an important role in the regulation of systemic and local inflammatory reaction. Bacterial endotoxin and exotoxin, a variety of pro-inflammatory media such as TNF, IFNγ and C5a are all strong inducers to stimulate neutrophils secretion of MIF.

MIF as a pro-inflammatory cytokine plays a role in the immune reaction, promoting innate and acquired immune response by activating macrophages and T cells. It is noteworthy that MIF pro-inflammatory activity depends on topoisomerase, which is a coding region containing a conserved active site. MIF not only regulates its own pro-inflammatory responses, but also induces or amplifies production of other pro-inflammatory cytokines, and up-regulates macrophage TLR4 expression. High concentrations of MIF prevent p53-dependent apoptosis of activated macrophages, thus leading to a sustained inflammatory response. But the exact effects of MIF on the inflammatory response are not clear.

MIF is an important cytokine because it connects the immune system with the endocrine system together. Under stress, the hypothalamus, pituitary and adrenal all secrete MIF. Most importantly, MIF antagonizes anti-inflammatory effects of endogenous cortisol, and inhibits glucocorticoid via negative feedback. In the acute phase of sepsis, excessive production of MIF is harmful to the body, and the levels of serum MIF relate to the severity of sepsis. Neutralization of MIF or target inhibiting the activation of MIF topoisomerase can lower the inflammatory response and improve the survival of patients with sepsis. This treatment in the early period of inflammatory response also significantly increases the survival of patients with sepsis, indicating that MIF is an important therapeutic target.

**HIGH-MOBILITY GROUP BOX 1 PROTEIN**

High-mobility group box 1 protein (HMGB1) was initially thought to be a transcription factor. Being re-defined as pro-inflammatory media, HMGB1 has become...
the focus of many important researches. HMGB1 can be expressed by all types of nucleated cells, and in the inflammatory response its main sources are macrophages, monocytes, and neutrophils.\(^\text{14,15}\) HMGB1 can be released by immune cells and necrotic cells. In sepsis, the endocrine secretion mechanism of HMGB1 is not clear. HMGB1 released by the exocrine secretion pathway is not secreted by necrotic cells directly, but is released from macrophages activated by necrotic cells.\(^\text{16}\) Extracellular HMGB1 can bind to PRRs including TLR2 and TLR4, specifically. HMGB1-inducing signaling has many effects on the immune system, promoting inflammation and destructing the epithelial cell barrier. In addition to activation of PRRs, HMGB1 can also bind to inflammatory mediators to promote the activity of pro-inflammatory mediators such as IL-1β. These evidences show that HMGB1 may be more superior to pro-inflammatory media, but also a vector of inflammation.\(^\text{17,18}\) In the process of inflammation, there is a systemic release of HMGB1, but the plasma HMGB1 concentration and survival are not relevant. Different with other inflammatory media, the peak of HMGB1 release is usually seen in the late inflammatory response, and HMGB1 levels are not necessarily declined in rehabilitation patients. Pathogens and pro-inflammatory media (TNF, IL-1β and IFNγ) could induce the production of HMGB1 in inflammation. The interaction of C5a and other receptors can also promote the secretion of HMGB1 in the inflammatory response. HMGB1 secretion affected by the autonomic nervous system and the activation of the cholinergic anti-inflammatory pathway can inhibit HMGB1 secretion from macrophages, and improve the survival rate of sepsis patients.

Since HMGB1 plays multiple roles in inflammation, treatment targeting to HMGB1 may be a new therapeutic strategy for sepsis. In the experiment, direct HMGB1 blocking or inhibiting its glycosylated end receptor can increase the survival rate of patients with sepsis.\(^\text{16,19,20}\) Similar with MIF, neutralization of HMGB1 is capable of reducing the mortality of sepsis and reversing multiple organ failure. However, the complex mechanism of HMGB1 prevents the clinical application of HMGB1 blockade.

### IL-17A

Many members of the IL-17 family are found to be important mediators regulating the immune response. These findings lead to the improvement of understanding of the interaction between the innate and specific systems. As the first discovered member of the IL-17 family members, IL-17A is mainly produced by Th17 cells in response to pro-inflammatory cytokines.\(^\text{21}\) IL-17A is also generated by other immune cells such as CD8+ T cells and NK cells. It regulates pro-inflammatory response by triggering a number of other cytokines (IL-1β, IL-6 and TNF) and by connecting with lymphocytes and macrophages. A recent study\(^\text{22}\) found that IL-17A level and clinical prognosis of sepsis are negatively correlated. Neutralization of IL-17A can significantly improve the survival rate of patients with sepsis. As the generation of IL-17 is essential to some specific immune response, the blocking of IL-17A in some cases may be not beneficial. Anti-IL-17A treatment of sepsis awaits further study.

### THE ROLE OF THE COMPLEMENT SYSTEM IN SEPSIS

Plasma C3a, C4a and C5a concentrations and the survival rate of patients with sepsis are also negatively correlated.\(^\text{23}\) Interestingly, C3a has both pro-inflammatory and anti-inflammatory effects. C3aR deficient mice are more sensitive to septic shock, and their intracellular levels of pro-inflammatory media are significantly increased. C3a and C3aR in combination may promote the pituitary gland to secrete anti-inflammatory hormones, indicating the anti-inflammatory properties of C3a.

We found that the excessive generation of C5a would lead to the injury of the body. C5a is able to cause immune paralysis, multiple organ failure, apoptosis of thymus cells and adrenal cells, imbalance of the coagulation system, and septic myocardial injury.\(^\text{24}\) In sepsis patients, C5a plays an important role via different ways.\(^\text{25}\) In addition to C5aR, C5a can combine with C5L2 specifically. C5L2 was thought to be a competitive antagonist of C5aR, but recent studies found that C5L2 is a functional receptor.\(^\text{26}\) Reduction of C5L2 expression on the neutrophil surface is related to the occurrence of multiple organ failure, suggesting that C5L2 is involved in the pathogenesis of sepsis.\(^\text{27}\) Evidence shows that the synergic effects of C5aR and C5L2 increase the inflammatory response to sepsis although the two receptors have different functions.\(^\text{28}\) For example, C5a-induced MIF release depends on C5aR signaling, and C5L2 mediates the C5a-dependent release of HMGB1.\(^\text{28,29}\) Interestingly, blockade of one of C5a receptors can reduce the mortality of sepsis patients moderately, but the two receptors can play a protective role in severe sepsis if they are blocked. Current clinical trials have achieved satisfactory results by dual blocking of C5aR and C5L2 compared with a single blockade. As a result, C5a can be used as a new target for drug treatment of sepsis. And this treatment has the
advantage of non-intervention on the formation of membrane attack complex (MAC), which prevents from microbial invasion. However, complement activation happens in early sepsis, so a reliable, sensitive bedside monitoring system is necessary to monitor the degree of complement activation and helps to intervene the complement cascade.

**AUTONOMIC NERVOUS SYSTEM AND SEPSIS**

The autonomic nervous system and immune system are closely related in the inflammatory response. The main connecting pathway is the hypothalamus-pituitary-adrenergic axis and the autonomic nervous system. Immune cells can synthesize and secrete neurotransmitters which are considered as signals of the neuro-endocrine-immune network, and express as specific receptors. The autonomic nervous system is part of the peripheral nervous system, which consists of three parts: sympathetic, parasympathetic, enteric nervous systems. The autonomic nervous system controls heart rate, breathing, gastrointestinal peristalsis, sweating, body temperature and other physiological indicators to maintain a stable internal environment. Traditionally, the body is thought to be in stress by sympathetic nerve excitation and parasympathetic nerve excitation makes the body rest; whereas recent studies found that this pathway is complex. The receptor of the parasympathetic nerve is a cholinergic receptor, and the principal nerve is the vagus nerve. The sympathetic nerve system contains adrenergic receptor, a major neurotransmitter called dopamine; adrenergic receptor activation is based on a network of intracellular signaling completion.

Vagus nerve signaling in the inflammatory response is very important. Both vagus nerve stimulation and α 7-cholinergic receptor activation induced by agonist can reduce macrophage intracellular cytokine synthesis and lower the inflammatory response. A recent study has found that in sepsis the vagal branch domination of the spleen is essential in inhibiting cytokine synthesis. The spleen is an important source of TNF, and the levels of TNF in the serum and liver are significantly decreased after removal of the spleen in sepsis mice. It was reported that the survival rate of animals with sepsis significantly improved by activating cholinergic pathways, which inhibit the production of pro-inflammatory mediators.

The main neurotransmitters of the sympathetic nerve branch are catecholamines which combine with adrenergic receptors. In early sepsis, there are high concentrations of catecholamines in circulation; in late sepsis, synthesis and secretion of catecholamines are relatively insufficient because of apoptosis of adrenal medulla cells. In sepsis, catecholamines play a role in immune regulation through the α- and β-adrenergic receptors expressed by immune cells. The catecholamines stimulate these receptors and change lymphocytes transport, vascular perfusion, cell proliferation and apoptosis.

Sepsis can be caused by abdominal infection, and abdominal infection is usually due to intestinal barrier damage, intestinal bacteria breaking into the abdominal cavity. Bacteria shift not only is seen in the digestive tract, also enters the blood circulation. In sepsis the gut can produce a large amount of catecholamines to enter the intestinal blood circulation. Catecholamines enter into the liver through the portal vein; combined with adrenergic receptors of Kupffer cells, they promote the release of pro-inflammatory mediators and cause liver function failure.

There are no therapeutic approaches available for sepsis that target inflammatory response; the mortality of sepsis has not been significantly reduced. Sepsis is complex, and dynamic and it has a group of heterogeneous syndromes. Since different patients with sepsis have different etiology, susceptibility, and responses, treatment should be prescribed individually.

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