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# Ulinastatin and Septic Cardiac Dysfunction

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## 1. Introduction

Sepsis is a common disease in the domain of Critical Care Medicine. It is a systemic inflammatory response syndrome (SIRS), which is response to infection. And severe sepsis may lead to septic shock and multiple organ dysfunction syndrome (MODS). The pathogenesis underlying cardiac dysfunction in sepsis is still incompletely understood and the mortality is high, although considerable effort has been applicable to understand the mechanism of inflammatory cascade response and multiple-system organ failure induced by sepsis (Wheeler and Bernard 1999). The research also found that the incidence rates of severe sepsis in the patients of hospitalization were annualized increase by 8.7 percent in the United States in the past decades years ago (Bernard et al. 1997; Martin et al. 2003; Melamed and Sorvillo 2009). However the mortality decreased in a certain, from 27.8 percent 1979 to 17.9 percent in 1995 (Martin et al. 2003; Melamed and Sorvillo 2009). But in the ICUs, incidence rate of severe sepsis occurs was still high which is up to 11% of the patients, and the mortality rates range from 18% to 55% in the developed country (Finfer et al. 2004; Karlsson et al. 2007).

## 2. Septic cardiac dysfunction

Defective cardiac function often occurs during sepsis, and it has been regarded as “cardiomyopathy of sepsis” (Niederbichler et al. 2006). The cardiac dysfunction greatly contributes to the the occurrence of sepsis shock and MODS in the sepsis patients. Decrease of the cardiac output can lead to hypoperfusion of the vital organs, the supply of oxygen and nutrition in tissue is reducing, the immunity is suppressed, and then the organs dysfunction happens (Kumar, Haery and Parrillo 2000).

## 3. The pathogenesis of septic cardiac dysfunction

Our understanding of septic cardiac dysfunction is ever more clear following the more and more studies on it. Early researches had revealed that myocardium intake 70%-75% oxygen from the coronary artery, and then saturation of blood oxygen in the coronary artery is only remains 25%-35%. In this situation when the need of the myocardium increase, ever more oxygen can't get from the blood of the coronary artery. Under this circumstances,

myocardium want to intake ever more oxygen only through increasing blood flow of the coronary artery (Messer and Neill 1962). Based on this theory, early researchers assumed that myocardial depression and myocardial ischemia are interrelated during the septic shock. However, 1986 Cunnion et al (Cunnion et al. 1986) discovered that the relation between myocardial depression and decrease of the blood flow in the coronary artery is not obvious. We review almost recently researches and found out septic cardiac dysfunction may refer to following factors.

### **3.1 Effect of circulating causative factors such as IL-1, TNF- $\alpha$ , HSP-70 in the progress of myocardial depression in sepsis**

Recently related review referred to the importance of pro-inflammatory cytokines and inflammatory protein in the septic cardiac dysfunction. These mediator are IL-1, TNF- $\alpha$ , C5a, CRP, HSP70, myocardial depressant factor (MDF), NO, epinephrine, endothelin and so on (Cohen 2002; Grocott-Mason and Shah 1998; Price et al. 1999; Sharma 2007; Tracey 2002). IL-1 and TNF- $\alpha$  are the most importance pro-inflammatory factors in the early stage of sepsis, and play a important in "cytokine storm" which the injury or endotoxin induces (Dinarello 1997; van der Poll and van Deventer 1999). Then the pleiotropic transcription factor NF- $\kappa$ B is activated and involves in the regulation of multiple biological phenomena, including stress response, cell growth, apoptosis, innate immunity, septic shock and so on (Brown and Jones 2004).

### **3.2 Cytopathic hypoxia and oxidative stress damage may be the causative factors of myocardial depression in sepsis**

Evidence indicates that mitochondria is the energy plant of the cell metabolism, it plays a critical role in oxygen utilization of cells and is responsible for supplying 90% ATP which the cell needed (Rolfe and Brown 1997). Redox-stimulated production of reactive oxygen species (ROS) may be one of the pathophysiologic mechanisms of sepsis. In that reactive oxygen may be through direct damage nucleotide of mitochondria then the DNA replication can be affected and the oxygen consumption can be reduced.

In the cecal ligation and puncture (CLP) animal models, through intraperitoneally administrating with or without polyethylene glycole-catalase: PEG-CAT ( $\text{H}_2\text{O}_2$  and  $\text{O}_2^-$  radical scavenger) 4 hours after CLP. Hirata discovered that the level of caspase-3, OGG1 in the former is significantly higher than the later, however, 8-Oxo-2'-deoxyguanosine (8-oxo-dG), Coenzyme (Co)Q1/CoQ1H2 and Cytochrome C are significantly lowered. Thus he realized oxidative stress may make the mitochondria DNA and the respiratory chain especially the complex II damaged. And it is the major causative factor of mitochondria dysfunction (Hirata 2009). In the other hand, Ritter et al (Ritter et al. 2003) found out the ratio of superoxide dismutase (SOD) to hydrogen peroxidase was increasing. As known that SOD mainly catalyze the production of  $\text{H}_2\text{O}_2$  and  $\text{O}_2^-$  and then make cell damaged. IL-1 $\beta$  and TNF- $\alpha$  may be the potential factors of the ratio imbalance (Schulze-Osthoff et al. 1992). All of these oxygen free radical can damage mitochondria and then damage the tissue and organs (Exline and Crouser 2008). Thus oxidative stress can damage mitochondria, decrease oxygen utilization of cell then lead to relative hypoxia.

### 3.3 The changes of expression of inflammation, energy metabolism and contractile related genes have been shown to be effective in the progress of septic cardiac dysfunction

In animal experiment, the differences in gene expression of cardiac tissue in septic rats was detected, which is under the CLP, by DNA microarrays. Y Liu et al (Y Liu et al. 2009) has found out Ace gene showed up-regulation may increase expression of Ang I, so that they elucidated Ace may play an important in pro-inflammatory reaction during sepsis. Available evidence suggests that Ace can activate renin-angiotensin system, increase the level of leucocyte and dose-dependently increased the poorer outcome of sepsis (Danser et al. 1995; Westendorp et al. 1997). A recent study demonstrated angiotensin II stimulation can increase the chemokine monocyte chemoattractant protein-1 (MCP-1) expression in vascular smooth muscle cells (SMCs) of rats so as to act as pro-inflammatory role (Hernandez-Presa et al. 1997). At the same time, another study verified this inference from the reverse side. The local concentrations of nitric oxide may be raised by the lower Ace enzyme activity with the II genotype, and then may make the efficiency of mitochondrial respiration better (Borutaite et al. 2001). Thus contractile function can be improved in both cardiac and skeletal muscle. In addition, angiotensin-converting enzyme inhibitor (ACEI) can reduce the level of MCP-1 induced by Angiotensin II, which in turn interfering with CD4<sup>+</sup> T cell proliferation and cytokine production mediated by MCP-1, so as to play anti-inflammatory effects (Hogaboam et al. 1998). Thus the pro-inflammatory effects of the Ace may be proved from the other side. What is more, our research team discovered that down regulation of intracellular corticosteroid receptor gene NR1D1 expression may be an important factor in septic cardiac dysfunction animal experiments. Overexpression of NF- $\kappa$ B induced by the pro-inflammatory cytokines such as IL-1b, Osmr, maybe the cause (Y Liu et al. 2009). Down regulation of NR1D1 expression makes the function of glucocorticoid receptor (GCR) changed, and the number decreased, so that it makes septic rats insensitive to the anti-inflammatory action of GCs (Rook et al. 2000). In addition, up-regulation of G-protein coupled receptor protein signaling transduction related gene (Gpr88) may be harmful to the heart. Because G-protein coupled receptor protein signaling pathway may along with the classic TPK signal transduction pathways to take part in signaling transduction of the heart tissue. Moreover up-regulation of transcription related gene (Cebpb) implies CCAAT/enhancer-binding protein beta (C/EBP $\beta$ ) may play an important part in sepsis (Y Liu et al. 2009). In 2010, through researching in nitric oxide synthase (NOS) gene  $-/-$  rats, Dos Santos C C et al (dos Santos et al. 2010) discovered that rats of NOS  $-/-$  group failed to down-regulate the level of bioenergy and metabolism related genes expression such as PEX11b, PEX19 and PEX3 and PGC-1 $\alpha$ -related genes. So they regarded inducible nitric oxide synthase may be the cause of sepsis-induced myocardial depression.

### 4. The micro-characterization of septic heart tissue

As to the micro-characterization of septic heart tissue, inner and outer membranes of mitochondria was discovered patchily disrupted by electron microscopy (Suliman et al. 2004). In this experiments, electron-lucent matrix, distorted cristae and variable swelling were found in the rat heart (Suliman et al. 2004). Also, in the rats experiments, Tatsumi et al (Tatsumi et al. 2004) has the similar findings. Compare to the sham group, there was less electron density in the mitochondria of septic hearts (Watts et al. 2004). In addition, autophagy was presented in the hearts of CLP animals by examination of electron micrographs (Watts et al. 2004).

## 5. The research progress of effect of the Ulinastatin (UTI) on septic cardiac dysfunction

Recently years UTI as endogenous inhibitor has obvious effect on inhibiting various prolease. It maybe an effective therapeutic drug on sepsis cardiac dysfunction. From it was discovered to now, it has been commonly used in patients with inflammatory disorders including sepsis, surgery, disseminated intravascular coagulation, shock, pancreatitis and so on. As a reasonable and effective drug is mainly used in China, Japan, Korea. Research also suggests that UTI may suppress the expression of various inflammatory factors above mentioned.

Ulinastatin is a kind of serpin with 2 Kunitz-type domains, can inhibit the over expression of pro-inflammatory cytokines and then prevent subsequent organ failure induced by injuring or bacterial endotoxin. It was from human urine, as a urinary trypsin inhibitor, was described by Astrup T in 1964 (Astrup and Nissen 1964). It take part in regulating the physiological responses in the blood such as blood clotting response, complement activation, inflammation and so on to keep balance of internal environment. As for its protection role to septic cardiac depress maybe involve in the following aspects.

### 5.1 Inhibit releasing of IL-1 to act as protective action

Interleukin (IL)-1, a fever inducing substance secreted by activated leukocytes which lies at the center of the inflammatory response, was originally reported in the 1940s (Atkins 1960). It has two sub unites that are IL-1 $\alpha$  and IL-1 $\beta$ . They have major roles in pro-inflammatory activities and host responses to not only exogenous but also endogenous noxious stimuli. Certainly these effects are contribute to the clearance of bacteria. However, in some cases these effects are detrimental, such as in serious septic shock and septic MODS (Miller et al. 2006). The mechanism of the pro-inflammatory response is as follows( Ninomiya-Tsuji et al. 1999). IL-1 binds to IL-1RI to form a complex protein associated with IL-1, then induces myeloid differentiation primary response gene 88 (MyD88) and the IL-1R-associated kinase (IRAK) recruitment to its receptor. And then IRAK dissociates from IRAK-receptor complex and interacts with tumour-necrosis factor receptor-associated factor 6 (TRAF6). Activated TRAF6 can make IL-1 signal transmit to the NF- $\kappa$ B-inducing kinase I $\kappa$ B  $\alpha$ /b ( NIK-IKK- $\alpha$ /b) kinase pathway (Cao, Henzel and Gao 1996; Cao et al. 1996; Wesche et al. 1997). Interestingly, TNF receptor associated factor 6 (TRAF6) may activate both Jun N-terminal kinase (JNK) and NF- $\kappa$ B pathway (Song et al. 1997). Of course, the mechanism is different. That is NIK is the key mediators of IL-1-mediated NF- $\kappa$ B activation (Karin and Delhase 1998; Song et al. 1997). TAK1 can activate JNK pathway (Moriguchi et al. 1996; Shirakabe et al. 1997; Yamaguchi et al. 1995). However, TAK1 can be activated by TAB1 protein(Ninomiya-Tsuji et al. 1999). At last NIK  $\pm$  IKK cascade storm happens under the regulation of IL-1 signal pathway. Moreover, evidence also showed that under administration of LPS, the level of the mRNA for leptin in adipose tissue can be increased by IL-1 or TNF- $\alpha$  (Grunfeld et al. 1996). It was known that leptin not only through decreasing food intake, but also increasing energy expenditure via activation of the autonomic nervous system to regulate energy balance (Pelleymounter et al. 1995). Thus IL-1 not only regulates inflammatory reaction but also energy metabolism. However protein levels of IL-1b in the liver is significantly greater in UTI -/- than in normal WT mice after LPS challenge under the administration of UTI (Takano et al. 2009). So UTI may play an important part in inhibiting the expression of IL-1.



## 5.2 Inhibit releasing of IL-6 to act as protective action

The level of IL-6 is a sensitive marker of tissue damage, and directly related to endotoxin production of the infectious diseases. It is commonly known that endotoxin is an important element of activated complement and cytokine which the inflammatory reaction related and may be an important factor of systemic inflammatory response syndrome (SIRS) (Pallua, Low and von Heimburg 2003). In addition, IL-6 as an endogenous pyrogen can stimulate body to generate neutrophil elastase and take part in pathophysiological process of sepsis and acute respiratory distress syndrome (ARDS) (Inoue et al. 2009). Pathan, N. et al (Pathan et al. 2004) found out the level of IL-6 was positively correlated to the degrees of cardiac suppression and plays a central role in cardiac suppression induced by bacterial infection. At the same time, in order to confirm this discovery, their research team verified this effect in the septic rat model with recombinant IL-6. However, Park, J. H. et al (Park et al. 2010a) found out UTI can reduce the level of stress reaction related cytokine such as IL-6 during gastrointestinal operation, also in the trauma patients with hemorrhagic shock has the similar discovery (Park et al. 2010b). This function was also verified by the septic rat model (Cao et al. 2010). Thus, UTI may regulate the level of IL-6 to act as anti-inflammatory role.

## 5.3 Inhibit releasing of IL-8 to act as protective action

It is well known that IL-8, a major mediator for neutrophil-mediated cell and tissue injury, is a member of C-X-C cytokine family. It is secreted by macrophages, epithelial cells and other cell types included. As a pro-inflammatory factor, it can through enhancing neutrophil infiltration, releasing of lysosomal enzyme and generating of superoxide anions, then induce tissue damage (Sekido et al. 1993). Kurt, A. N. et al (Kurt et al. 2007) found out the level of serum IL-8 in the patients with positive blood culture was found elevated significantly more than negative ones. It was also reported that UTI, as a broad-spectrum anti-inflammatory substance, may significantly down-regulate the production of IL-8 (Cao et al. 2010). Bae, H. B. et al (Bae et al. 2011) discovered the level of IL-8 in the UTI preconditioning sepsis rats is significantly lower than those in sepsis rats without treatment, and associated pathological section, they hold the opinion that UTI may through inhibiting IL-8 and so on mediators of inflammation in septic rats to act as a protective role in the septic process. Also there is evidence which shows that UTI can suppress the expression of IL-8 in vitro (Nakamura et al. 1997).

## 5.4 Inhibit releasing of TNF- $\alpha$ to act as protective action

Serum TNF- $\alpha$  is secreted by the activated macrophage. Its relative molecular weight is 17000. It can stimulate other inflammatory cytokine production and inflammatory cells into tissue (Cohen 2002). Also it acts as activator of the local and systemic inflammatory response, and its local accumulation can cause cardiovascular clinical symptoms, such as fever, swelling, pain and congestion. In vivo overall increase of the amount of TNF- $\alpha$  can decrease cardiac output, and then mediates tissue injury, such as formation of micro-thrombus and systemic capillary leak syndrome. As to regulating molecular pathway of the ischemia-reperfusion, TNF- $\alpha$  maybe one of the most significant factors (Niemann, Garner and Lewis 2004; Toledo-Pereyra et al. 2004). At the same time, TNF- $\alpha$  can also through activating other related cells secret cytokine such as IL-1, HMGB1, eicosanoids, NO, and reactive oxygen to enhance the role of inflammatory reaction and make this effect longer.

(Tracey 2002). Thus it makes the tissue damage severely. It was found that serum TNF- $\alpha$  significantly elevated during the septic systemic inflammatory response syndrome (SIRS) (Kurt et al. 2007). In all, TNF- $\alpha$  can promote occurrence and development of the sepsis, the level of TNF- $\alpha$  increasing can lead to cell death, apoptosis, and several organs dysfunction (Niemann, Garner and Lewis 2004). Thus it is very important to inhibit the release of TNF. In the recently years, study found out UTI may significantly reduce the level of TNF- $\alpha$  to protect the tissue and organ during sepsis (Cao et al. 2010). Also a Japanese research team verify above conclusion in the other side, they found out in the pathogenesis of post-resuscitation syndrome, insufficient production of UTI for norepinephrine (NE) releasing, accompanied by persistent high TNF- $\alpha$  levels (Hayakawa et al. 2008). More over in vitro UTI can inhibit the release of TNF- $\alpha$  (Aosasa et al. 1998). In addition, in the liver injured animal model experiment also found the UTI can protect against severe liver injury through the suppression of TNF- $\alpha$  production (Takano et al. 2009). What is more, other scholar hold the opinion that UTI may reduce the NF- $\kappa$ B activation and then subsequently inhibit the expression of TNF- $\alpha$ , CXC-chemokines and vascular endothelial cell adhesion molecules to protect hepatic cells against ischemia and reperfusion (I/R) injury (Wu et al. 2009).

### 5.5 To decrease the level of Nitric oxide(NO) expression

The iNOS has been shown to be induced by mediators associated with sepsis, that is IL-1b, IL-2, IL-6, TNF and so on the pro-inflammatory cytokines and interferon endotoxin, and then increases production of NO in vitro (Nathan and Xie 1994). Early in 1991, there was evidence showed that NO synthase may play an important in the pathogenesis of septic shock and suppressing activity of NO synthase may be a novel therapeutic option (Nathan 1992; Petros, Bennett and Vallance 1991). Recently, in several experimental models, research indicated that overproduction of NO under the regulation of cytokine-inducible NOS connects with the pathophysiology of microcirculatory failure and organs dysfunction during sepsis, and inhibiting NOS activity can prevent vessel from dilating and then hypotension happens were proved (Hollenberg et al. 2000; López et al. 2004; Avontuur et al. 1998; Evans et al. 1994; Nava, Palmer and Moncada 1992; Tracey, Tse and Carter 1995; Kilbourn et al. 1994; Laszlo, Whittle and Moncada 1994). However, several experimental studies also showed that inhibition of NO synthesis has no effect or might be harmful (Robertson et al. 1994). Recently years, scholars found that in a model of sepsis mice induced by CLP which is deficient in nNOS didn't get the desired effect, in that they found out such mice had impaired bacterial clearance. Certainly, the survival rate also decreased. Ever more in wild-type mice under the regulation of a selective nNOS inhibitor had similar outcome. This suggested that nNOS wasn't always harmful to sepsis, it may have a protective role (Cui et al. 2007). Moreover, mice with a cardiomyocyte-specific over expression of endothelial nitric oxide synthase (eNOS) was also partially protected against both endotoxemia and polymicrobial sepsis (Ichinose et al. 2006). Why does these phenomenon happen? Maybe a research team can give a reasonable answer. They found out NO at different concentration levels has different actions. Such diversity of cellular responses to NO as followings (Table 1) (Thomas et al. 2008).

Generally, lower concentrations are good for cell survival and proliferation, and higher concentrations promote cell cycle arrest, senescence and apoptosis. As to the effects of UTI on NOS are still unknown. Chinese scholars discovered that UTI may through inhibiting the

activity of NF-κB to down-regulate the expression of iNOS mRNA within intestinal muscle to protect the intestinal motility in rats with bacterial peritonitis. However whether UTI can through regulating the activity of the NOS to act as protection on cardiac myocytes and if different dose of UTI has different effects are still poorly understood.

NO concentrations	Effects
1 to 30 nM	Physiological actions under the regulation of cyclic GMP-mediated processes predominate
30 to 100 nM	Tissue repair processes including AKT phosphorylation
100 to 300 nM	Hypoxia inducible factor-1 stabilization
>1 μM	Nitrosative stress

Table 1.

5.6 Inhibit releasing of sCD14 to act as protective action

Soluble CD14 (sCD14), an endotoxin-related signal molecule, can enhance sensitivity of macrophage activation to endotoxin stimulation. In 1990, CD14 was recognized as a receptor for bacterial endotoxin (LPS) and it was the firstly described pattern-recognition receptor (Wright 1995). When combining with the concepor TLR4, endotoxin-sCD14 complexes can lead to recruitment of IL-1-associated kinase under the endotoxin-induced, mediate nuclear factor (NF-κB) activation, then trigger the cytokine cascade. Evidence showed that sCD14 expression can be induced by interleukin (IL)-6 in liver cells and it was recognized as acute phase protein (Anas, van der Poll and De Vos 2010). It was also the key mechanism of the pathogenesis for multiple organ failure (Rahman et al. 2004). In the rat model of acute necrotic pancreatitis, the level of sCD14 in rats treatment with hyperbaric oxygen and UTI group significantly decreases compare to the ones hyperbaric oxygen only used. Combined with the level of IL-6, TNF-α and endotoxin, the author hold the opinion that UTI may decrease the level of sCD14 endotoxin related, and to function as inhibiting the pro-inflammatory reaction and then enhance the immunity function (Hou et al. 2010). Last year, Japanese scholars K Shirakawa. et al (K Shirakawa et al. 2010) hold the opinion that sCD14-ST may be the new sepsis marker. Thus UTI may through decreasing the level of sCD14 in blood to protect the heart tissue. But the reason is still unknown .

5.7 Enhance express of HSP-70 to act as protective action

Heat shock protein 70, which is conservative in organic evolution, was expressed constitutively in human erythroblasts that undergoes differentiation. It may suppress protein denaturation and keep the native conformation. It also acts as protective role in many physiological pathological and stress responses. Expression of HSP70 can be induced by fever, hypoxia, oxidative stress, endotoxin, cytokine, heavy metal ion and so on (Ribeil et al. 2007). Kustanova G. A. et al (Kustanova et al. 2006) found out the mortality of septic rat was decreased by supplying HSP-70 compare to control group. Another study suggested HSP-70 is closely associated with pulmonary biology, and has protective effects on lung injury, involves inhibition of NF-κB and pro-inflammatory gene expression. The mechanisms may concern that its anti-oxidation, anti-apoptosis, anti-inflammatory, stable transfection or molecular chaperone roles (Wheeler and Wong 2007). At the same time in animal experiments, Zhang, Z. et al (Zhang et al. 2010) found out the expression level of



HSP-70 in paraquat poisoning group under the treatment of UTI was higher than the control group. Then through associating the pathological section, they hold the opinion that UTI may regulate the expression of HSP-70 to increase the toxic tolerance and reduce lung injury. It was not reported that through up-regulation of HSP-70 in septic patients treated with UTI to increase the survival rate. However, based on the evidence above mentioned, we come out that UTI may has protective function of septic organs by up-regulating expression of HSP70.

### **5.8 Inhibit expression of HMGB1 to act as protective action**

HMGB1, an intracellular protein, can translocate to the nucleus. It was originally described as a transcription factor which can bind DNA and regulate gene expression. HMGB1 is expressed by various cell types which contains a nucleus, such as macrophage, monocyte, neutrophil. The activating expression of HMGB1 may through non-transcriptional mechanisms and it is regulated by nuclear factor- $\kappa$ B (NF- $\kappa$ B) activation (Lotze and Tracey 2005). During inflammation, causative agent and pro-inflammatory mediator (such as TNF- $\alpha$ , IL-1b and IFN $\gamma$ ) can induce expression of HMGB1. Of course interaction of complement C5a and its acceptor C5L2 can also promote the expression of HMGB1 (Lotze and Tracey 2005). Signal transduction induced by HMGB1 is endowed with pleiotropic effects, that is pro-inflammatory and the role of potential damage to the endothelial barrier. Compare to other sepsis related cytokine, the peak level of HMGB1 occurs in the later stage and is regulated by autonomic nerves system(ANS) (Wang et al. 1999). Also a research found out that activation of the cholinergic anti-inflammatory pathway in sepsis can improve survival. The reason may be that this pathway can suppress macrophages secreting HMGB1 (Rittirsch, Flierl and Ward 2008). In the septic rat model experiment, HMGB1 is significantly decreasing in UTI treatment group than control group. In this experiment also found out UTI can suppress the generation of  $O_2^-$ , TNF- $\alpha$ , IL-6, and lactic acidosis. Thus the author hold the opinion that UTI may be helpful for sepsis through regulating expression of HMGB1 (Koga et al. 2010). As to whether UTI can decrease the level of HMGB1 express by activation of the cholinergic anti-inflammatory pathway is worth doing deep research.

### **5.9 Decrease the production of $O_2^-$ then reduce the activity of NF- $\kappa$ B to act on anti-inflammatory effect**

Activating of macrophage, neutrophils and reactive oxygen species (ROS) play an important in the pathophysiology of endotoxemia. Following activating of macrophage, neutrophils, NADPH oxidase is activated, leading to excessive ROS generation to kill the bacteria. Of course, one coin two sides, at the sometime ROS also injuries lung tissue and lead to breathlessness, and then enhance SIRS (Tanaka et al. 2010). Japanese scholars found out the level of  $O_2^-$ , HMGB1, TNF- $\alpha$ , IL-6 were lower in UTI treatment group than the control group (Tanaka et al. 2010). Previous studies had shown that the expression of HMGB1, TNF- $\alpha$ , IL-6 was regulated by NF- $\kappa$ B. However NF- $\kappa$ B as a oxidation-reduction related sensitive transcription factor was under the regulation of ROS (Pahl 1999; Bar-Shai et al. 2008). It was known that UTI may through suppress the expression of HMGB1 (Koga et al. 2010), TNF- $\alpha$  (Cao et al. 2010), IL-6 (Park et al. 2010a) to act as anti-inflammatory. Thus they come up with the idea that anti-inflammatory of UTI may through reducing the production of  $O_2^-$  to decrease the activity of NF- $\kappa$ B for the first time.

### 5.10 As to regulating gene express of septic heart tissue under the UTI to act as protection

Certainly in gene level, UTI treatment in sepsis was also make progress. An research team led by Inoue, K (Inoue et al. 2005) found out that the lung and kidney damage are serious in UTI<sup>-/-</sup> sepsis rats than control group. At the sometime IL-1 $\beta$ , macrophage inflammatory protein (MIP)-1 $\alpha$ , MIP-2 and monocyte chemotactic protein (MCP)-1 are also higher than the control group. At last they come out that UTI may has important protection on sepsis. In additional, our previous study suggest UTI may regulate exaggerated or expression of inflammatory response related gene (Agt, Ace, IL6r) to protect the function of septic heart and kidney (Y Lin et al. 2011; Y Liu et al. 2010).

### 5.11 At last UTI may also take important part in the energy metabolism during sepsis

Evidence showed that the activation of Na<sup>+</sup>-K<sup>+</sup>-ATP enzyme is associated with balance of electrolyte. It was known that well activation of Na<sup>+</sup>-K<sup>+</sup>-ATP enzyme is very important in absorption of edema fluid. Thus protection of Na<sup>+</sup>-K<sup>+</sup>-ATP enzyme can reduce cellular edema and play an important part in keeping the stability of cell membrane. Researching found out activation of Na<sup>+</sup>-K<sup>+</sup>-ATP enzyme remarkable decrease in ischemia tissue, while it was not obvious in UTI pretreatment ones (Xiaoqiao et al. 2004). Moreover, Na<sup>+</sup>-K<sup>+</sup>-ATP -ATPase and Ca<sup>2+</sup>-ATP-ATPase activity in UTI donor-pretreatment on liver graft group were higher than control group (Mao et al. 2011). In addition, a Japanese research team hold the opinion that UTI may maintain utilization of energy in the electron transfer system throughout the hypovolemic period and reperfusion and contributed to a rapid recovery of cardiac function after reperfusion, through reducing the damage of oxidative phosphorylation in mitochondria, even during hemorrhagic shock (Masuda et al. 2003). Those all suggest UTI may act as a protective role in organs of septic patients through maintaining the organs energy metabolism.

## 6. Concluding remarks

UTI may regulate the secretion of mediators of inflammation, related stress protein and related gene expression to release the inflammatory reaction, at the same time it can keep the activity of Na<sup>+</sup>-K<sup>+</sup>-ATP -ATPase to maintain the organs energy metabolism. It is derived from urine, as a endogenous anti-inflammatory drug, so it has little side effect and widely used in treatment of sepsis, acute pancreatitis, toxic shock, chronic pancreatitis. However, it's as a immunomodulators may along with other drug to treat sepsis in order to improve the survival rate.

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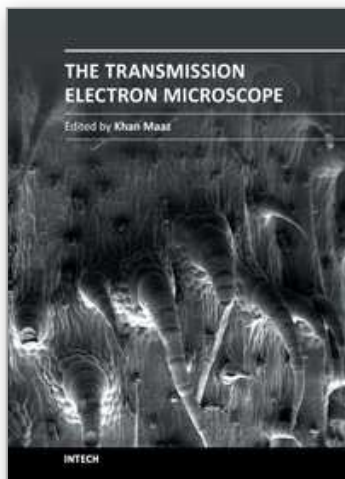
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Edited by Dr. Khan Maaz

ISBN 978-953-51-0450-6

Hard cover, 392 pages

**Publisher** InTech

**Published online** 04, April, 2012

**Published in print edition** April, 2012

The book "The Transmission Electron Microscope" contains a collection of research articles submitted by engineers and scientists to present an overview of different aspects of TEM from the basic mechanisms and diagnosis to the latest advancements in the field. The book presents descriptions of electron microscopy, models for improved sample sizing and handling, new methods of image projection, and experimental methodologies for nanomaterials studies. The selection of chapters focuses on transmission electron microscopy used in material characterization, with special emphasis on both the theoretical and experimental aspect of modern electron microscopy techniques. I believe that a broad range of readers, such as students, scientists and engineers will benefit from this book.

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