

Sepsis and Intestinal Microvascular Endothelial Dysfunction

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Sepsis is a major life-threatening health-care problem. According to statistics, there are 20–30 million new cases of sepsis worldwide annually, which causes equivalent deaths from acute myocardial infarction and kills more people than breast cancer, stroke, and AIDS combined. About 41% of cases of sepsis progress to multiple organ dysfunction syndrome (MODS), resulting in mortality as high as 30–50%.^[1] We believe that excessive inflammation leads to a series of changes of endothelium-associated proteins and molecules, which eventually results in coagulation disorder, overactivation of inflammatory response, and vascular leakage.

VASCULAR ENDOTHELIAL CELL DYSFUNCTION INDUCED BY SEPSIS

Vascular endothelial cells (VECs) are continuous single-layered squamous epithelium lining the inner surface of blood vessels. Acting as a vascular barrier, VECs are in direct contacts with various cells in the blood. In sepsis settings, activation or injury of VECs may have the following characteristics. (1) Overactivation of inflammatory response: endothelium releases cytokines, such as interleukins, tumor necrosis factor- α , and increases expression of endothelial cell surface adhesion molecules, thus mediates firm adhesion of leukocytes and monocytes, further aggravates endothelium inflammation. (2) Coagulation disorder: endothelium up-regulates the expression of tissue factor (TF), activates the exogenous coagulation pathway, and increases the release of von Willebrand factor from endothelial cells. Meanwhile, secretion of anticoagulants, such as thrombomodulin, protein S, from endothelial cells is reduced, eventually resulting in coagulation dysfunction. (3) Depletion of the endothelial surface layer (ESL): endothelial glycocalyx forms a dynamic molecules layer with functions of anti-inflammation and mechanotransduction on the inner

surface of blood vessels, termed ESL. Within 30 min after onset of sepsis, amount of ESL is depleted, resulting in adhesion and exudation of neutrophils, as well as massive exudation of fluid and albumin. (4) Increased permeability: in intact vasculature, endothelial cells act as a continuous and semi-permeable barrier. Increased permeability and loss of the barrier function are two core characteristics of endothelial cells during sepsis, which are mainly attributed to morphological changes of endothelial cells, such as unbonding and protuberance of cell membrane, abnormal arrangement and obscured boundaries of endothelium, all above cause endothelium falling off from basal membrane, further translocation of circulatory substract, subendothelial edema, and systemic capillary leak syndrome, the latter results in plasma shifting from the blood vessel to interstitial spaces, decrease of central venous pressure and mean arterial pressure, and then hypoperfusion of organs, secondary systemic tissue injury and edema, and even MODS in severe cases. Therefore, the structure and function of VECs play a key role in the development of sepsis.

ACUTE GASTROINTESTINAL DYSFUNCTION CAUSED BY MICROVASCULAR ENDOTHELIAL INJURY

Microvascular endothelium injury and dysfunction can cause tissue edema, ischemia, and hypoxia, finally resulting in organ function failure. It is reported that gastroenteric system is the first target in such circumstance. The small intestine is about 5–7 m long, and the colon is about 1.5 meters long. The intestinal tract contains the plicae circulares and villi that increase its mucosa surface area by 20–30 folds. When

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spread out, surface area of intestinal tract reaches to 200 m², which is comparable to a standard volleyball court. The total blood flow of the intestinal tract accounts for 20% of the cardiac output. Superior mesenteric artery angiography shows that the blood flow in a normal adult is about 700 ml/min. Therefore, the massive intestinal microvascular endothelia are vulnerable to excessive inflammatory and ischemia-reperfusion injury during sepsis or septic shock. Meanwhile, a large number of opportunistic pathogens and endotoxins can translocate to the circulation through the injured VECs, leading to distant organ infection, systemic inflammation response and multiple organs dysfunction. Therefore, the intestinal tract plays a centric role in initiation and development of systemic stress response and multiple organs dysfunction during sepsis.

PROTECTIVE ROLE OF DAHUANG ON GUT BARRIER AND INTESTINAL VASCULAR ENDOTHELIUM

Sepsis-induced endothelial cell injury and microcirculation dysfunction are the important pathological basis of intestinal mucosal barrier compromise and intestinal dysfunction. There is no ideal treatment in Western medicine by far. The author's preliminary study suggested that Dahuang (*rheum officinale*) had a good protective effect on rat intestinal mucosal barrier in burns, hemorrhagic and LPS-induced shock by increasing blood perfusion of the gastrointestinal mucosa, scavenging free oxygen radicals (reactive oxygen species) in tissues and preventing translocation of intestinal bacteria and endotoxins. By observing the effects of broad-spectrum antibiotics and Dahuang on gastrointestinal flora translocation in rats with burns and sepsis, we found that both burns and broad-spectrum antibiotics enabled intestinal flora to translocate to the liver, lung, mesenteric lymph nodes, and blood, with *E. coli*. predominating. In addition, the use of antibiotics would aggravate the above pathological process. Dahuang could inhibit such bacteria translocation originating from burns, "two hits" from endotoxins, as well as the application of broad-spectrum antibiotics.^[2] In our subsequent experiments, we aimed to explore the feasibility and potential mechanism of Dahuang to improve the intestinal mucosal microcirculation in mice by observing changes in small intestinal mucosa, intestinal wall blood flow, and intestinal tissue oxygenation. The results showed that Dahuang was able to improve blood perfusion and oxygen supply of the intestinal mucosa in sepsis settings by dilating capillaries of the intestinal mucosa, reducing the formation of microthrombus, protecting endothelial cells of the intestinal mucosal capillaries, and increasing the number of functional intestinal mucosal capillaries.^[3]

However, all the above studies focused on the pharmacodynamics and pharmacology of crude Dahuang, and the potential mechanism remains undefined. On the basis of the previous studies, our research team further used the extraction technique to roughly extract Dahuang first; then isolated and purified it by repeated silica gel column

chromatography, sephadex column chromatography, ODS C18 reversed phase silica gel column chromatography and MCI column chromatography; and finally identified it by ¹H-NMR, ¹³C-NMR, and DEPT nuclear magnetic resonance spectroscopy. As a result, we obtained 21 Dahuang monomers. With these extracted monomers, we further explored the effect of Dahuang monomers on increased permeability of monolayer endothelial cells induced by matrix metalloproteinase-9.^[4] It was found that five Dahuang monomers had protective effects on VECs injured by inflammatory factors by reducing the permeability of monolayer VECs and preventing capillary leakage. The pharmacological mechanism may be associated with expression of gene and protein of VEC junction, and phosphorylation of light chain of myosin. The details of this pharmacological mechanism and signaling pathways will be elucidated in our subsequent articles.

Endothelial injury is the main pathological basis of microcirculation dysfunction. Microvascular endothelial injury of the gastrointestinal mucosa will directly lead to acute gastrointestinal injury, further triggering systemic inflammatory response and multiple organ dysfunction. What needs more attention is the heterogeneity of VECs among different tissues, which leads to difference of physiological characteristics and function, especially in the gastrointestinal mucosa. Current researches of sepsis-induced endothelial dysfunction are mainly in the lung, brain, and kidney, and there are few studies focusing on VEC function of the gastrointestinal tract. The underlying mechanism of sepsis-induced endothelial injury needs to be further investigated. Furthermore, there is a scarcity of drugs specific to sepsis-induced endothelial injury. In view of the above issues, it would be meaningful to seek new effective therapeutic strategies to reverse endothelial dysfunction and improve the prognosis of sepsis.

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