Research Progress on the Mechanisms of Coagulation Dysfunction and Immune Inflammatory Response Related to Sepsis

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Abstract: Thrombocytopenia and Disseminated Intravascular Coagulation (DIC) are clinical pathological syndromes characterized by an imbalance between clotting and fibrinolysis activation as the primary pathogenic mechanism. DIC is a fatal complication of sepsis, which significantly increases the patient's mortality rate. Inflammation and coagulation act as the first line of defence against infection, with inflammation activation leading to the upregulation of clotting function, resulting in DIC. Thrombus formation due to the inflammatory response is a sacrifice of tissue circulation in order to prevent the systemic spread of pathogens, but it can be detrimental to the host itself. There is a close link between the inflammatory response and sepsis-related coagulopathy. Studies of coagulopathy mechanisms from immunologic and inflammatory aspects provide new approaches for early diagnosis and prognostic evaluation of DIC. This paper aims to summarize the research results in terms of immunoinflammatory and review the mechanism of sepsis-related coagulopathy.

Introduction

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection. It is a complex clinical syndrome with a high incidence rate, increasing by 8.7% annually over the past 20 years[1]. Coagulation activation and inflammatory response are the basic defense measures of the host during sepsis, including immune thrombosis, platelet involvement in coagulation, immune and inflammatory responses, damage-associated molecular patterns, activation of neutrophils and neutrophil extracellular traps, and vascular endothelial glycocalyx damage.

Tissue factor participates in sepsis-related coagulation dysfunction

TF is a transmembrane glycoprotein expressed by endothelial cells, including pericytes and fibroblasts, as well as blood-derived immune cells. Toll-like receptor 4 detects pathogen-associated molecular patterns, such as lipopolysaccharides, and rapidly induces TF expression at the messenger ribonucleic acid level, promoting the formation of coagulation factors and ultimately resulting in immune thrombosis[2]. The activation of TF is closely related to cell pyroptosis, which can be achieved through the nucleotide-binding oligomerization domain-containing protein 3 signaling pathway, containing NOD-, LRR-, and pyrin domains, or through a non-classical pathway activated by caspase-11, to reach the target area of TF. After activation, TF is highly expressed in the circulating outer membrane vesicles, forming a cell surface complex with coagulation factor VII/activated coagulation factor VII (FVII/VIIa) and activating factor IX to IXa and factor X to Xa through proteolysis. However, a study using a preclinical model of sepsis showed that the deletion of TF in endothelial cells did not decrease the production of α-thrombin or the mortality rate.

Thrombin is involved in sepsis-related coagulation dysfunction

Thrombin is generated through the cleavage of prothrombin, which is secreted by liver cells. Alpha-thrombin is generated in the extrinsic pathway through exposure to negatively charged molecules, such as inorganic polyphosphate secreted by platelets, RNA/DNA released by damaged or apoptotic cells, or the negatively charged surface of bacterial cell walls[3]. Thrombin plays a critical role in linking coagulation and inflammation, as it can cleave multiple substrates and regulate thrombus formation and inflammatory responses mainly through interaction with G protein-coupled receptors called protease-activated receptors (PARs). Four PARs have been identified: PAR1, PAR3, and PAR4 are activated by thrombin and tissue factor protease, while PAR2 can be activated by trypsin-like proteases, pancreatic enzymes, FVIIa and FXa. Upon cleavage of PARs by alpha-thrombin on platelets, a large amount of pro-inflammatory molecules are released, including chemokines, growth factors (such as platelet-derived growth factor), serotonin, P-selectin, adenosine diphosphate, CD40 ligand, thromboxane A2, and thrombin itself. This release triggers platelet procoagulant activity.

Platelet-mediated immune response in sepsis-associated coagulopathy

In 2013, Engelmann and Massberg[4] proposed the concept of immune thrombosis, which is induced by the innate immune response triggered by thrombus formation within blood vessels. The function of innate immune cells that aggregate in the clot is regulated by the coagulation pathway and platelet release products. For instance, chemokine ligands such as CXCL1, CXCL4, CXCL5, CXCL7, and other mediators are released, promoting leukocyte bactericidal activity. At the same time, innate immune cells express PAR, which is activated by thrombin and factor Xa, and promotes pro-inflammatory signaling in dendritic cells. Platelet factor 4, stored in alpha granules, is a member of the CXC chemokine family, and is released during platelet activation. It can induce thrombus formation by activating and aggregating platelets through the immunoglobulin G of anti-PF4/heparin antibodies, which bind to Fc gamma receptor IIA on platelets. On the other hand, it has also been observed that integrin alpha IIb/beta 3 on platelets can bind to Mac-1 on monocytes and achieve fibrinogen binding. Furthermore, Mac-1 interacts with GPIb on platelets, causing white blood cells to adhere to the platelet surface and further enhancing platelet-von Willebrand factor interaction, which is also beneficial for the formation of stable clots.

Damage-associated molecular patterns (DAMPs) are involved in sepsis-associat ecoagulation disorders

Damage-associated molecular patterns (DAMPs) represent molecular patterns associated with danger or damage. These patterns are released passively after cell death or activated by inflammasomes. DAMPs from many different components or organelles have been identified, including histones, chromosomal DNA, mitochondrial DNA, high mobility group box 1 (HMGB1), heat shock proteins, S100 proteins, and adenosine triphosphate. HMGB1 is a protein that is widely present in the nucleus of cells and appears in almost all cell types. It is an important regulatory factor that plays a key role in innate immune responses and inflammation[5]. Initially, HMGB1 was described as a nuclear protein that binds to DNA. However, with further research, it was found that HMGB1 can also be secreted into the cytoplasm and extracellular space, becoming a cytokine. In standard models of systemic and local inflammation, HMGB1 can stimulate monocytes/macrophages to produce pro-inflammatory responses.

Endothelial cells participate in sepsis-related coagulation disorders

Endothelial cells are the primary targets of coagulation dysfunction and injury in sepsis. During coagulation dysfunction, activated polymorphonuclear neutrophils release NETs, reactive oxygen species, and other pro-inflammatory mediators. These immune and thrombotic reactions are very complex, producing not only procoagulant, proadhesive, and proinflammatory conditions but also causing glycan damage, upregulation of adhesion molecules, release of VWF, and vascular elastin damage, among other effects[6].One of the earliest and most crucial injury sites during sepsis is the endothelial glycocalyx. Plasma proteins regulate vascular permeability and ensure vascular health. The primary

physiological function of the glycocalyx is to inhibit leukocyte adhesion, thereby protecting the vessel and enhancing its self-repair ability. Once bacterial infection occurs, the glycocalyx may be targeted by inflammatory mediators such as histones and proteases, leading to its shedding and inducing leukocyte adhesion. At the same time, endothelial cells also express innate immune receptors[7], such as TLRs and PARs, which can interact with TLR agonists such as lipopolysaccharides, lipoteichoic acids, and peptide glycan, producing immune response effects such as regulating microvascular permeability and adhesion molecule expression.

Summary

Although sepsis-associated coagulopathy has been studied for decades, the understanding of the mechanisms underlying coagulopathy in sepsis is still limited. To date, no effective treatment for patients has been discovered, nor have new and safer anticoagulants been developed to target inflammasome activation and the mediators of the coagulation cascade. Therefore, interventions before the activation of the coagulation cascade and thrombin generation are necessary. Additionally, new approaches to improving endothelial function by addressing endothelial cell damage and repair mechanisms in sepsis can be effective strategies for addressing coagulopathy. Furthermore, the use of biomarker detection systems to identify and monitor coagulation abnormalities in sepsis patients can guide treatment.Sepsis is a complex disease that involves multiple systems and can lead to a wide range of complications, immune states, and susceptibility to infection. Therefore, a single treatment approach is unlikely to achieve good results in immune thrombosis.

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