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Review

Histidine-rich Glycoprotein Modulates the Blood-vascular System in Septic Condition

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Histidine-rich glycoprotein (HRG) is a 75 kDa glycoprotein synthesized in the liver whose plasma concentration is 100-150 μg/ml. HRG has been shown to modulate sepsis-related biological reactions by binding to several substances and cells, including heparin, factor XII, fibrinogen, thrombospondin, plasminogen, C1q, IgG, heme, LPS, dead cells, bacteria, and fungi. Therefore, reduction of plasma HRG levels in sepsis leads to dysregulation of coagulation, fibrinolysis, and immune response, resulting in disseminated intravascular coagulation and multiple organ failure. This review summarizes the binding and functional properties of HRG in sepsis.

Key words: htidine-rich glycoprotein, septic pathogenesis, immunothrombosis

Histidine-rich glycoprotein (HRG), first isolated as histidine-rich 3.8S α2-glycoprotein in 1972 [1,2], is a 75 kDa plasma glycoprotein mainly produced by the liver at approximately 100-150 μg/ml in human blood [3,4]. It is composed of 4 domains: cystatin-like domain 1; cystatin-like domain 2; histidine-proline rich domain, which has a unique 12 GHHPH tandem repeat amino acid sequence; and a C-terminal domain [5,6]. HRG is present in the blood of vertebrates such as humans, rats, mice, rabbits, and chickens, and a few invertebrates [3,6,7]. HRG can bind a variety of ligands such as heparin, factor XII (FXII), fibrinogen, thrombospondin, plasminogen, C1q, IgG, heme, and lipopolysaccharide (LPS), and can interact with dead cells, bacteria, and fungi. These binding properties indicate that HRG modulates coagulation [8-14] and fibrinolysis [15-18], helps to scavenge toxic substances [19-25] and dead cells [26-28], and kills pathogens [29-32]. In addition, our recent studies have reported that the plasma concentration of HRG was strikingly reduced during severe systemic inflammatory and septic condition triggered by infection, leading to immunothrombosis and tissue damage, and subsequent disseminated intravascular coagulation (DIC) and multiple organ failure (MOF) (Fig. 1) [33-40]. These results suggest that HRG is involved in the regulation of coagulation and fibrinolysis and the immune system in septic condition. This review is focused on the function of HRG in these systems.

Functions of HRG in Coagulation and Fibrinolysis

Coagulation and fibrinolysis are rigorously regulated by several biological substances to prevent blood loss and unnecessary thrombus formation. HRG is reported to bind to coagulation and fibrinolysis-related molecules such as heparin, FXII, fibrinogen, thrombospondin, and plasminogen [8-18].

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Heparin. The anti-coagulant activity of anti-thrombin III (ATIII) is enhanced in the presence of heparin. HRG binds to heparin with high affinity, blocking the interaction between heparin and ATIII, and inhibiting its anti-coagulant activity [8-10].

FXII. HRG also modulates the intrinsic pathway through high-affinity binding to FXII, inhibiting FXII autoactivation and FXIIa-mediated activation of FXI [11].

Fibrinogen and thrombospondin. Although HRG interaction with fibrinogen, the platelet-bridging molecule, and subsequent incorporation into a fibrin clot does not induce the conversion of fibrinogen to fibrin within the clot, this interaction influences the structure of the fibrin gel [12]. HRG inhibits the interaction between GPIIb/IIIa and fibrinogen via its histidine-rich domain in a Zn^{2+}-dependent manner and inactivates the platelet-aggregation promoter thrombospondin on the surface of platelets, thereby interfering with platelet-platelet interactions [13, 14].

Plasminogen. HRG inhibits the interaction of plasminogen with fibrin/fibrinogen and retards fibrinolysis due to its binding to the plasminogen lysine-binding site competing with fibrin binding [15]. Contrarily, immobilized HRG on cell surface heparan sulfate results in 30-fold increase in the conversion of plasminogen to plasmin by the fibrinolysis promoter tPA [16-18].

Immunothrombosis. Immunothrombosis is a key phenomenon in the development of septic pathogenesis, which is triggered by activated-neutrophil adhesion to vascular endothelial cells, and subsequent platelet accumulation and fibrin polymer deposition on their surface. Immunothrombosis helps prevent the diffusion of pathogens to the systemic blood stream and their disposal in physiological conditions. However, impairment of this regulation in sepsis causes immunothrombus formation to lead to DIC and subsequent MOF [37-40]. Our recent study revealed that HRG inhibits immunothrombus formation by keeping circulating neutrophils quiescent (Fig. 1) [35, 36].

Functions of HRG in Immunity and Inflammation

Insoluble immune complexes (IICs). Although immune complexes promote the clearance of pathogens and foreign substances, when IICs form and deposit in several organs, they lead to tissue injury and inflammation. C1q enhances IIC formation by directly binding and inducing the cross-linking of IgG molecules [19]. The N-terminal domain of HRG binds to C1q and the F(ab) region of IgG, inhibiting the formation of IICs composed of ovalbumin and the anti-ovalbumin antibody [20]. This domain binding also inhibits IIC formation by preventing Fc-Fc interactions by masking IgG epitopes recognized by rheumatoid factor. Furthermore, HRG promotes the solubilization and clearance of IICs [21].

Heme and LPS. Heme and LPS are damage-associated molecular pattern (DAMP)/pathogen-associated molecular pattern (PAMP) molecules, respectively, that promote tissue injury. HRG binds heme, neutralizing heme cytotoxicity and inhibiting hemolysis [22-24]. Synthetic peptides derived from the histidine-rich domain of HRG also bind and neutralize LPS, inhibiting LPS-stimulated IL-8 production of CD14-transfected THP-1 cells [25].

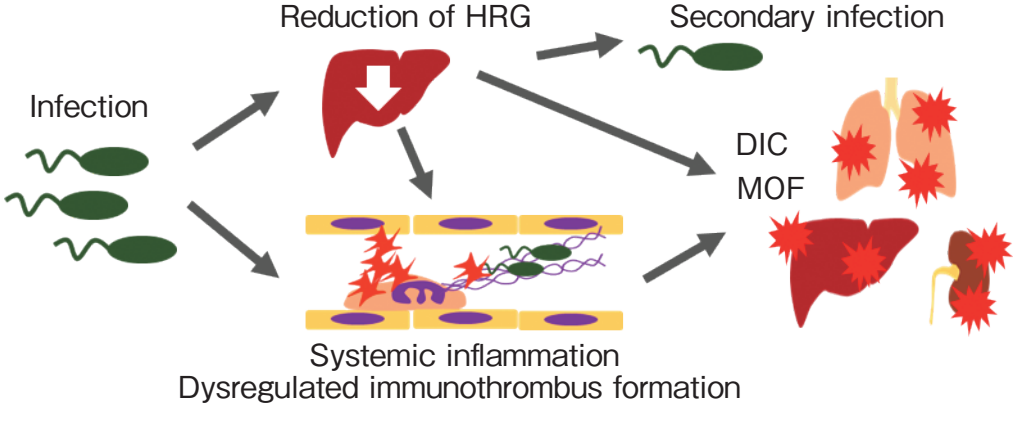

Fig. 1 Scheme of septic pathogenesis. DIC, disseminated intravascular coagulation; MOF, multiple organ failure.

Dying and dead cells. Rapid removal of apoptotic and necrotic cells from blood stream and tissue by phagocytes is necessary to maintain tissue homeostasis. Impairing clearance of these cells leads to the release of DAMP molecules, which induce inflammation and tissue damage. HRG can aid in the phagocytosis of apoptotic cells by macrophages, by acting as a bridge between FcγRI on macrophages and DNA on the surface of apoptotic cells [26]. Additionally, HRG recognizes intracellular phospholipids exposed in necrotic cells and aids in the recruitment of IgG, leading to the phagocytosis of necrotic cells via FcγRI and heparan sulfate on phagocytes [27, 28].

Antimicrobial activity. Moreover, HRG exerts antimicrobial activity by binding to the surface of the Gram-positive bacteria *Enterococcus faecalis* and *Streptococcus pyogenes*, the Gram-negative bacteria *Escherichia coli*, and the fungus *Candida albicans* under acidic conditions or in the presence of Zn^{2+} and inducing membrane destabilization [29-32].

Concluding Remarks

Septic pathogenesis can result from systemic coagulation, fibrinolysis, and inflammation. This review revealed that HRG can ameliorate septic condition by modulating these biological reactions through high-affinity binding to several key molecules and cells (Fig. 1). Thus, HRG has potential value as a therapeutic drug for the treatment of sepsis.

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