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Discussion on New Functional Aspects of Specific Plasma Proteins

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Description

In a recent review, I suggested the importance of the dynamics of specific plasma proteins, i.e., Histidine-Rich Glycoprotein (HRG) and Inter-Alpha Inhibitor Proteins (IAIPs), in cases of severe sepsis that include high pathogenic influenza and COVID-19 because these proteins (i) are dramatically decreased in severely septic patients and septic animal models, and (ii) appear to play crucial roles in maintaining the quiescence of circulating neutrophils and vascular endothelial cells to prevent and control the excessive activation of these cells [1-3]. Notably, the formation of Neutrophil Extracellular Traps (NETs) could be the trigger of the intravascular thrombosis in COVID-19 and the disseminated intravascular coagulation state and thus the regulation and control of neutrophils in the circulation would be very important.

The pharmacological profiling of HRG and IAIPs revealed that the actions of these proteins have similarity and overlap with regard to the actions exerted on leukocytes, vascular endothelial cells, and the coagulation cascade [1]. The rapid decrease in the plasma levels of these proteins (negative acute-phase proteins) in septic conditions could be expected to lead to the loss of constitutive and homeostasis-maintaining functions of these proteins. In other words, the magnitude of decreased levels of plasma HRG in septic patients in an ICU appears to be an excellent biomarker to estimate each patient's severity and prognosis [2]. In the review article, I noted that a representative DAMP, HMGB1, was released from vascular endothelial cells in culture by the infection with the highly pathogenic influenza A virus, and that HRG strongly regulated the mobilization and release of HMGB1 from vascular endothelial cells [4,5]. The relationship between viral infections such as SARS-Cov-2 and HMGB1 mobilization should be further pursued.

The outstanding feature of HRG is that it binds to a diverse range of factors including HMGB1, S100A8/A9, fibrinogen, plasminogen, thrombospondin, FXIIa, C1q, zinc, heme, Fe2+, heparin, glutathione peroxidase, DNA, and LPS [1]. Judging from the nature of these factors, it was strongly suggested that HRG is involved in the regulation of inflammation and coagulation/ fibrinolysis. Increasing evidence supports this notion [4]. When our group recognized the HRG's multifunctional roles, we hypothesized that there might be a specific receptor for HRG. To search for candidate HRG receptors we established a screening system in which HRG ligand was transfected and expressed at high levels in HEK293T cells together with the candidate receptor. After allowing a possible interaction, the HEK293T cells were solubilized, and immunoprecipitation was performed. A co-immunoprecipitated receptor candidate was detected by western blotting using anti-tag antibody. With this screening, we finally identified c-type lectin family 1A (CLEC1A) and confirmed the direct binding of HRG with the recombinant extracellular domain of CLEC1A [5].

Thus, plasma protein HRG binds to many factors but also has a specific membrane receptor, CLEC1A. It is probable that different modes of action of HRG [1] contribute to HRG's beneficial effects under septic conditions, especially in maintaining the homeostasis of blood cells, vascular endothelial cells and coagulation/fibrinolysis [1]. There are hundreds of plasma proteins in blood whose functions are obscure. The review strongly suggested that the case of a preceding protein HRG with multifunctional properties may open a new biological field regarding more plasma proteins with unknown functions and receptors [1].

Conflict of Interest

The author Masahiro Nishibori is an advisor of Japan Blood Products organization.

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