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研究成果報告書

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予防医学的な健康状態把握のための方法確立

A proposal for monitoring physical states and contributing towards preventive medicine

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Abstract

High mobility group box-1 (HMGB1), a non-histone chromatin DNA-binding protein, is a unique molecule that is released by necrosis and injurious stress into extracellular space and exerts pro-inflammatory function. The applicant examined the HMGB1 dynamics, pathophysiological roles of HMGB1 and treatment in CNS and PNS diseases and noticed that elevation of plasma levels of HMGB1 reflected the severity of disease and the importance of vascular endothelial cells as responsible source of HMGB1 in blood. We newly identified histidine-rich glycoprotein (HRG) as a direct binding protein of HMGB1. “A man is as old as his arteries” is a well known phrase suggesting the importance of homeostatic regulation of blood vessels and its disorders leading to life-style-related diseases. In the present study, we analyzed the significance of HMGB1-HRG system in the maintenance of health focused on the regulation of interface between blood cells and endothelilal cells. Moreover, we assumed and searched for a novel signaling system triggered by reactive oxygen that might relate to HMGB1-HRG system. We also determined the plasma levels of HMGB1 and HRG to evaluate their significance as biomarkers in acute and chronic inflammatory diseases.

HRG was demonstrated to play many functional roles including maintenance of quiescence of neutrophils, inhibition of erythrocyte aggregation, neutralization of heme toxicity, inhibition of Fenton reaction, protection of vascular endothelial cells, inhibition of intrinsic and extrinsic coagulation cascades, and activation of NK activity. Sepsis was associated with rapid decrease in plasma HRG and was considered to be the catastrophic form of the homeostasis. Determination of plasma HRG provide an excellent biomarker of sepsis and supplementary therapy with HRG was proposed. The release of HMGB1 induced by LPS and TNF-α was strongly regulated by HRG which might be mediated by novel HRG receptor. HMGB1-HRG system was shown to play an important role in maintaining the multiple homeostatic reactions in the body. We characterized the HMGB1/HRG balance in ASO and diabetes. We also raised an interesting monoclonal antibody which may inhibit not only ROS-triggered processes but also HMGB1 translocation. As a whole, we propose that the determination of plasma HMGB1/HRG may provide a novel method for monitoring physical states and contributing towards preventive medicine.