論　文　要　旨

Recombinant Thrombomodulin Protects Mice against Histone-Induced Lethal Thromboembolism

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Abstract

Introduction: Recent studies have shown that histones, the chief protein component of chromatin, are released into the extracellular space during sepsis, trauma, and ischemia-reperfusion injury, and act as major mediators of the death of an organism. This study was designed to elucidate the cellular and molecular basis of histone-induced lethality and to assess the protective effects of recombinant thrombomodulin (rTM). rTM has been approved for the treatment of disseminated intravascular coagulation (DIC) in Japan, and is currently undergoing a phase III clinical trial in the United States.

Methods: Histone H3 levels in plasma of healthy volunteers and patients with sepsis and DIC were measured using enzyme-linked immunosorbent assay. Male C57BL/6 mice were injected intravenously with purified histones, and pathological examinations were performed. The protective effects of rTM against histone toxicity were analyzed both *in vitro* and in mice.

Results: Histone H3 was not detectable in plasma of healthy volunteers, but significant levels were observed in patients with sepsis and DIC. These levels were higher in non-survivors than in survivors. Extracellular histones triggered platelet aggregation, leading to thrombotic occlusion of pulmonary capillaries and subsequent right-sided heart failure in mice. These mice displayed symptoms of DIC, including thrombocytopenia, prolonged prothrombin time, decreased fibrinogen, fibrin deposition in capillaries, and bleeding. Platelet depletion protected mice from histone-induced death in the first 30 minutes, suggesting that vessel occlusion by platelet-rich thrombi might be responsible for death during the early phase. Furthermore, rTM bound to extracellular histones, suppressed histone- induced platelet aggregation, thrombotic occlusion of pulmonary capillaries, and dilatation of the right ventricle, and rescued mice from lethal thromboembolism.

Conclusions: Extracellular histones cause massive thromboembolism associated with consumptive coagulopathy, which is diagnostically indistinguishable from DIC. rTM binds to histones and neutralizes the prothrombotic action of histones. This may contribute to the effectiveness of rTM against DIC.