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敗血症での NETs に対するリコンビナントヒトトロンボモジュリンの効果

(Influence of the recombinat thrombomodulin to NETs on sepsis)

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Abstract

In patients with septic shock, both coagulation and fibrinolysis are activated, and disseminated intravascular coagulation (DIC) is induced. During DIC, activated neutrophils release the web-like structures of DNA (neutrophil extracellular traps, NETs). NETs contain nuclear and granule proteins as well as DNA, and can trap and kill microbes at the inflammatory and infection sites. However, the excessive and systemic release of pro-inflammatory molecules such as nuclear HMGB1 associated with NETs, causes the exacerbation of septic shock.

Recombinant human thrombomodulin (rTM) has recently been used for treating septic DIC to reduce coagulation disorders by inhibiting thrombin. However, it is unclear whether rTM modulates the NETs formation in septic shock. The purpose of this study is to evaluate the effect of rTM on the NETs formation in LPS-induced septic model mice.

C57BL/6 mice (8 weeks of age, male) were intraperitoneally administrated with LPS (15 mg/kg) with or without the intravenous injection of rTM (3mg/kg). The survival rates were evaluated, and serum and ascites levels of TNF-α, HMGB1 and nucleosome (as a marker of NETs) were analyzed by ELISA.

The survival rates were significantly improved by the administration of rTM. In addition, the administration of rTM suppressed the increase of serum and ascites levels of TNF-α in the septic model. The release of HMGB1 was suppressed at 12 h after LPS-injection, and the release of nucleosome was suppressed at 9 h after LPS-injection in the rTM post-treated group.

The present study revealed that the administration of rTM significantly improved the survival rate, and suppressed the circulating levels of TNF-α, HMGB1, and nucleosome in the LPS-induced septic shock model. Thus, rTM may exert the protective action on sepsis possibly by preventing the cytokine production and NETs formation during systemic inflammation.