論 文 要 旨

Differential Regulation of Damage-Associated Molecular Pattern Release in a Mouse Model of Skeletal Muscle Ischemia/ Reperfusion Injury

（ マウス骨格筋虚血再灌流障害における ダメージ関連分子パターン放出の動向 ）

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Background: Skeletal muscle ischemia/reperfusion (I/R) injury is an important clinical issue that can cause remote organ injury. Although its pathogenesis has not been fully elucidated, recent studies have suggested that damage-associated molecular patterns (DAMPs) are mediators of remote organ injury in sterile inflammation. The purpose of this study was to investigate the possible involvement of DAMPs, including the nuclear proteins high-mobility group box 1 (HMGB1) and histone H3, in the pathogenesis of skeletal muscle I/R injury in mice.

Methods: Hindlimb ischemia was induced in mice through bilateral ligation of inguinal regions using rubber grommets. Reperfusion was induced by cutting the rubber grommets after 2–12 h of ischemic period. Survival rates, localization of HMGB1 and histone H3 in the gastrocnemius muscle, and circulating HMGB1 and histone H3 levels were analyzed. The effect of anti-HMGB1 and anti-histone H3 antibodies on survival was analyzed in mice with I/R injury.

Results: All mice with hindlimb ischemia survived for at least 36 h, while all mice died within 24 h if the hindlimbs were reperfused after ischemia for 4–12 h. Immunohistochemical analysis revealed that HMGB1 translocated from the nucleus to the cytoplasm in the ischemic gastrocnemius muscle, while histone H3 was confined to the nucleus. Accordingly, serum HMGB1 levels were significantly elevated in mice with hindlimb I/R compared with normal mice or mice with hindlimb ischemia ($P < 0.05$). Serum histone H3 levels were not elevated after I/R. Treatment with anti-HMGB1 antibodies significantly improved survival of mice with hindlimb I/R injury compared with control antibodies ($P < 0.05$).

Conclusions: HMGB1, but not histone H3, translocated to the cytoplasm during skeletal muscle ischemia, and was released into the systemic circulation after reperfusion in mice with

I/R injury. Treatment with anti-HMGB1 antibodies partially improved survival.

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