論 文 要 旨

HMGB1 Promotes the Development of Pulmonary Arterial Hypertension in Rats

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Rationale: Pulmonary arterial hypertension (PAH) is characterized by increased pulmonary vascular resistance leading to right ventricular failure and death. Recent studies have suggested that chronic inflammatory processes are involved in the pathogenesis of PAH. However, the molecular and cellular mechanisms driving inflammation have not been fully elucidated.

Objectives: To elucidate the roles of high mobility group box 1 protein (HMGB1), a ubiquitous DNA-binding protein with extracellular pro-inflammatory activity, in a rat model of PAH.

Methods: Male Sprague-Dawley rats were administered monocrotaline (MCT). Concentrations of HMGB1 in bronchoalveolar lavage fluid (BALF) and serum, and localization of HMGB1 in the lung were examined over time. The protective effects of anti-HMGB1 neutralizing antibody against MCT-induced PAH were tested.

Results: HMGB1 levels in BALF were elevated 1 week after MCT injection, and this elevation preceded increases of other proinflammatory cytokines, such as TNF-a, and the development of PAH. In contrast, serum HMGB1 levels were elevated 4 weeks after MCT injection, at which time the rats began to die. Immunohistochemical analyses indicated that HMGB1 was translocated to the extranuclear space in periarterial infiltrating cells, alveolar macrophages, and bronchial epithelial cells of MCT-injected rats. Anti-HMGB1 neutralizing antibody protected rats against MCT-induced lung inflammation, thickening of the pulmonary artery wall, and elevation of right ventricular systolic pressure, and significantly improved the survival of the MCT-induced PAH rats.

Conclusions: Our results identify extracellular HMGB1 as a promoting factor for MCT-induced PAH. The blockade of HMGB1 activity improved survival of MCT-induced PAH rats, and thus might be a promising therapy for the treatment of PAH.