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High-mobility group box 1 (HMGB1) protein was originally identified as a non-histone nuclear protein that stabilizes the nucleosome structure and regulates gene transcription. HMGB1 is highly conserved and ubiquitously expressed in the nucleus of almost all mammalian cells. In 1999, Wang et al. reported that HMGB1 is released from activated macrophages, and extracellular HMGB1 acts as a late and critical mediator of inflammatory responses in sepsis. This discovery has apparently stimulated further work on the inflammatory role of extracellular HMGB1 in the pathophysiology of various diseases. Therefore, it is currently accepted that HMGB1 is a danger signal (i.e., alarmin or damage/danger-associated molecular pattern molecule), serving as a link between cellular damage and inflammation. Furthermore, it has been shown that HMGB1 is not only passively released from damaged cells but also actively secreted from stimulated cells, and it stimulates the induction of inflammatory cytokines and chemokines by interacting with its receptors, such as Toll-like receptors (TLR) and receptor for advanced glycation end products (RAGE).

Increasing evidence indicates the importance of extracellular HMGB1 in the pathophysiology of myocardial infarction (MI). Previously, Kitahara et al. developed a transgenic mouse model with cardiac overexpression of HMGB1 under the control of the α-cardiac myosin heavy chain promoter (αMHC/HMGB1-Tg mice) and showed that the plasma HMGB1 levels after MI were higher and the infarct size was smaller in the αMHC/HMGB1-Tg mice than in the wild-type (WT) mice. In addition, the αMHC/HMGB1-Tg mice showed enhanced angiogenesis in the MI border zone. Consistent with this, Kohno et al. reported that HMGB1 inhibition by neutralizing antibody aggravated post-infarction healing process and remodeling in a rat model of MI. In addition, it was reported that HMGB1 could contribute to the pathophysiology of MI through another mechanism. Limana et al. demonstrated that when administered into the mouse heart, HMGB1 enhanced myocardial regeneration and differentiation of endogenous cardiac stem cells after MI, thereby resulting in improved cardiac dysfunction and remodeling. In the current issue of Journal of Atherosclerosis and Thrombosis, Nakamura et al., the same group of the study by Kitahara et al., studied the mechanism of how angiogenesis can be enhanced after MI in αMHC/HMGB1-Tg mice and found the contribution of bone marrow-derived endothelial progenitor cells (EPCs) in the enhanced angiogenesis. The authors used the αMHC/HMGB1-Tg mice whose bone marrow was replaced with that of green fluorescent protein (GFP) mice and showed that the number of circulating EPCs derived from bone marrow was significantly increased in the bone marrow-transplanted αMHC/HMGB1-Tg mice compared with the WT mice. In addition, the number of bone marrow-derived endothelial cells in the border zone of MI and the levels of cardiac vascular endothelial growth factor (VEGF) were also markedly increased in the αMHC/HMGB1-Tg mice. Based on these findings, the authors concluded that HMGB1 promotes angiogenesis and decreases the infarct size by enhancing the following EPC functions: the mobilization of EPCs from bone marrow, their migration into the ischemic myocardium, and their differentiation into mature endothelial cells. Supporting this, Chavakis et al. reported that HMGB1 activated integrin-dependent recruitment of EPCs and promoted angiogenesis in the ischemic tissue. The findings of the above mentioned studies, including that by Nakamura et al., suggest the beneficial role of HMGB1 in the pathophysiology of MI.

There have also been, however, several conflict-
ing reports regarding the role of HMGB1 in MI. Andrassy et al. showed that HMGB1 inhibition with a functional HMGB1 antagonist decreases myocardial ischemia-reperfusion injury, suggesting the detrimental role of HMGB1 in MI. Although the reason for this discrepancy is unclear, there are several possible explanations. First, the difference between these conflicting studies is MI models: models of permanent coronary artery ligation and ischemia-reperfusion. Since compared with the model of permanent ligation, the model of ischemia-reperfusion represents excessive release of reactive oxygen species and severe inflammatory responses; thus, the MI models may influence the role of HMGB1. Second, the protocol used for HMGB1 intervention is different. In this regard, it has been suggested that HMGB1 is beneficial at low doses but detrimental at high doses, indicating the dose-dependent effects of HMGB1. This is conceivable because inflammation acts as a double-edged sword: inflammation is important to protect from microbial infection and repair the damaged tissues, whereas excessive inflammation causes further tissue damage. Although the study by Nakamura et al. enhances our understanding concerning the role of HMGB1 in the pathophysiology of MI, further investigations are necessary to elucidate the precise role and therapeutic potential of HMGB1 in MI.

Conflict of Interest
None declared.

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