HMGB1: A potential therapeutic target for myocardial ischemia and reperfusion injury

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Myocardial ischemia and reperfusion (I/R) injury is well known in therapy for acute coronary syndrome and open heart surgery. Although reperfusion therapy (such as thrombolysis and percutaneous coronary intervention) is essential for the survival of ischemic tissue, reperfusion itself causes additional cellular injury. I/R could cause local myocardial inflammation, accompanying with apoptosis, which could result in myocardial cell damage [1]. High mobility group box 1 protein (HMGB1), a highly conserved nuclear protein, could regulate gene transcription and maintain the nucleosome structure. HMGB1 could be passively released from necrotic cell, apoptotic cell or actively secreted by innate immune cells (such as macrophages and monocytes) [2,3]. Recently, a present study shows that HMGB1 acts as a novel early mediator of inflammation and participates in the pathogenesis of myocardial I/R injury, and HMGB1 could promote the release of tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6), whereas HMGB1 A box peptide (a specific HMGB1 antagonist) could reduce myocardial ischemia and reperfusion injury and inhibit the release of TNF-α and IL-6 [4]. Meanwhile, lots of drugs have been found to reduce myocardial I/R injury by inhibiting HMGB1 expression, including asperosaponin X [5], minocycline [6], ethyl pyruvate, [7] etc. These suggested that HMGB1 may play an important role in myocardial I/R injury and inhibiting HMGB1 could reduce myocardial I/R injury.

There was a cross-talk between HMGB1 and other proinflammatory cytokines, such as TNF-α, IL-6 and C-reactive protein (CRP) [4,8,9]. Once released from necrotic cell, apoptotic cell or macrophages, HMGB1 functions as a proinflammatory stimulus that upregulates TNF-α, IL-6, CRP and macrophage inflammatory proteins (MIP-1α and MIP-1β) [8,9], indicating that this mechanism reinforced the inflammatory process. As inflammation plays a critical role in myocardial I/R injury [1]. Thus, inhibiting HMGB1 expression could suppress inflammation and reduce myocardial I/R injury. Jiang et al. [5] show that treatment of asperosaponin X could protect the rats from myocardial I/R injury and lower HMGB1 and other proinflammatory cytokines; meanwhile, asperosaponin X could attenuate hypoxia-induced cytotoxicity and block TNF-α-induced HMGB1 expression in vivo. These results further suggested that inhibiting HMGB1 expression by asperosaponin X could protect heart against myocardial I/R injury.

In conclusion, HMGB1 may be a critical mediator for myocardial I/R injury and a potential therapeutic target for myocardial I/R injury. Inhibiting HMGB1 expression may reduce myocardial I/R injury.

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References


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