

MicroRNA-155 as a Central Regulator of Sepsis-Associated Acute Cardiovascular Dysfunction

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Purpose: Sepsis-associated cardiovascular dysfunction (SACVD) remains a leading cause of death in critically ill patients. MicroRNA-155 targets important transcripts in inflammation and cardiovascular system. The present study assessed the role of miR-155 in SACVD.

Methods: Experimental sepsis was induced using endotoxin injection (LPS) or cecal ligation and puncture (CLP) models. Genetic loss (KO) and pharmacological inhibition (LNA-anti-miR; AM) of miR-155 were evaluated. SACVD was evaluated through echocardiography, vascular reactivity to AngII and vascular permeability; mortality analysis was also performed. Quantification of myocardial miR-155, pro-inflammatory cytokine mRNA profile, miR-155 targets, apoptosis and activation of pro-inflammatory intracellular signaling pathways were assessed. In another experiment, myocardial miR-155 expression, cellular localization and associations between its levels and other clinical variables were evaluated using post-mortem samples from septic shock patients. Vascular response to AngII, endothelial function and miR-155 expression were also analyzed in IM arteries from CABG patients after incubation with LPS.

Results: MiR-155 levels were increased in plasma and myocardium in experimental and human sepsis. This was accompanied by decreased ejection fraction (EF) and cardiac output (CO), aortic hyporreativity and increased vascular permeability. KO and AM-injected animals presented with preserved EF and CO, aortic reactivity and vascular permeability; this was accompanied by ~50% mortality reduction. Experimental sepsis induced downregulation of SOCS1, myocardial cytokine upregulation, increased apoptosis as well as pro-inflammatory kinase and transcription factor activation, all of which were attenuated in KO and AM. In human myocardium, miR-155 expression was positively associated with 24h antemortem period plasma troponin I levels. In human IMAs, LPS incubation induced miR-155 upregulation and AngII hyporreativity.

Conclusions: Mir-155 is upregulated in experimental and human septic shock. Loss or inhibition of miR-155 attenuated cardiovascular dysfunction, blunted proinflammatory activation and reduced mortality. This suggests miR-155 as a potential target in SACVD.