Extracellular RNA in cardiac ischemia/reperfusion injury: prevention of heart failure and cell damage by RNase1

H A. Cabrera-Fuentes1; M. Ruiz-Meana2; S. Kostin3; S. Lecour4; D. Hausenloy5; D. Garcia-Dorado2; K. D. Schluter1; K. T. Preissner1

1Justus-Liebig University Giessen, Institute for Biochemistry, Giessen, Germany; 2Hospital Vall d’Hebron, Barcelona, Spain; 3Max Planck Institute for Heart and Lung Research, Bad Nauheim, Germany; 4University of Cape Town, Cape Town, South Africa; 5Hatter Cardiovascular Institute, London, United Kingdom

Despite optimal therapy, the morbidity and mortality of patients presenting with an acute myocardial infarction (MI) remain significant. Extracellular RNA (eRNA), exposed after cell damage, serves as co-factor for coagulation proteases and cytokines thereby promoting their procoagulant and proinflammatory functions in vivo. Following myocardial ischemia/reperfusion (I/R) in mice or I/R induced in the isolated Langendorff heart, increased eRNA levels were found together with cell injury markers. Likewise, eRNA was released from cardiomyocytes under hypoxia and subsequently induced tumor-necrosis-factor-α (TNF-α) liberation by activation of TNF-α converting enzyme (TACE) and provoked cardiomyocyte death. Conversely, TNF-α promoted eRNA release especially under hypoxia, feeding a vicious cell damaging cycle during I/R. Administration of RNase1 or TAPI (TACE-inhibitor) prevented cell death and myocardial infarction. Likewise, RNase1 significantly reduced I/R-mediated energy exhaustion, opening of mitochondrial permeability transition pores (mPTP) as well as oxidative damage in cardiomyocytes. Together, RNase1 as well as inhibition of TACE provide novel therapeutic regimens to interfere with the adverse eRNA-TNF-α interplay and significantly reduce or prevent the pathological outcome of ischemic heart injury.