Platelet-derived microRNAs play a pivotal role in cardiac remodeling after myocardial ischemia and reperfusion

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Background: Platelets can infiltrate ischemic myocardium and are increasingly recognized as critical regulators of inflammatory processes during myocardial ischemia and reperfusion (I/R). Platelets contain a broad repertoire of miRNAs, which, under certain conditions such as myocardial ischemia, may be transferred to surrounding cells or released into the microenvironment. Recent studies could demonstrate, that platelets contribute substantially to the circulating miRNA pool holding the potential for so far undiscovered regulatory functions.

Purpose: The present study aimed to determine the role of platelet-derived miRNAs in myocardial injury and repair following myocardial I/R.

Methods and Results: Combining an in vivo model of myocardial I/R, multimodal in vivo and ex vivo imaging approaches (LSFM, PET&MRI, speckle-tracking echocardiography), in vitro immune cell migration assays and Next-generation deep sequencing analysis of platelet miRNA expression pattern in mice with a MK/platelet-specific knockout of pre-miRNA processing ribonuclease Dicer, the present study discloses a key role of platelet-derived miRNAs in the tightly regulated cellular processes orchestrating LV remodeling after myocardial I/R following transient LCA ligation. Disruption of the miRNA processing machinery in platelets by deletion of Dicer resulted in increased myocardial inflammation, impaired angiogenesis, and accelerated development of cardiac fibrosis, culminating in an increased infarct size by d7 that persisted through d28 of myocardial ischemia and reperfusion. Worsened cardiac remodeling after myocardial infarction (MI) in mice with a platelet-specific Dicer deletion (Dicer Pf4Δ/Pf4Δ) resulted in an increased fibrotic scar formation and distinguishably increased perfusion defect of the apical and anterolateral wall at d28 post-MI. Altogether, these observations culminated in an impaired LV function and hampered long-term cardiac recovery after experimental MI and reperfusion therapy. Treatment with the P2Y12 antagonist ticagrelor completely reversed increased myocardial damage and adverse cardiac remodeling observed in Dicer Pf4Δ/Pf4Δ mice.

Conclusions: The present study discloses a critical role of platelet-derived miRNA in myocardial inflammation and structural remodeling processes following myocardial ischemia and reperfusion.