**THERAPEUTIC POTENTIAL OF TISSUE INHIBITOR OF METALLOPROTEINASES (TIMPS) FOLLOWING MYOCARDIAL INFARCTION**

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Objective: Investigate the therapeutic potential of TIMPs in cardiac recovery post-myocardial infarction (MI).

Background: Coronary artery disease is the leading cause of heart failure worldwide. Adverse remodeling of the cardiac extracellular matrix (ECM) is a common characteristic of failing heart. Integrity of the ECM network is maintained by matrix metalloproteinases (MMPs) and their endogenous inhibitors, tissue inhibitor of matrix metalloproteases (TIMPs). The four TIMPs (-1 to -4) are altered differently after MI in the heart.

Methods and Results: MI was induced in wild-type mice through LAD ligation. At 1-day post-MI, protein levels of TIMP1 and TIMP2 were elevated while TIMP3 and TIMP4 were markedly reduced in the infarct and peri-infarct regions. We used replication-deficient adenoviruses to over-express TIMP3 or TIMP4 in the peri-infarct myocardium (5x107 PFU/heart, 5 injections/heart, 4microL/injection) immediately after LAD ligation. Empty Ad-virus (Ad-Null) was injected as a parallel control. Echocardiography was performed at 1 week post-operation. Overexpression of TIMP3 improved LV dilation, systolic and diastolic function but did not improve the rate of LV rupture compared to Ad-Null-MI mice. TIMP4 overexpression, on the other hand, reduced the rate of LV rupture but did not improve the LV dilation or dysfunction. Overexpression of TIMP3 and TIMP4 together resulted in an additive effect of reduced rate of LV rupture and improved LV dilation and dysfunction.

Conclusions: The early reduction in TIMP3 and TIMP4 levels could be the driving factors in adverse remodeling of the heart post-MI, as TIMP3 and TIMP4 impact different aspects of cardiac remodeling in this process.