1550224

Systemic Administration of 5-Azacythidine Improves Cardiac Remodeling and Infarct Vascularization after Myocardial Infarction in Rat

Azab, M; Landa-Rouben, N; Holbova, R; Nagler, A; Leor, J
Sheba Medical Center, Tel-Aviv University, Tel-Hashomer 52621, Ramat Gan, Israel

BACKGROUND: Attempts have been made to induce transdifferentiation of fibroblasts to cardiomyocyte-like cells with 5-azacythidine (5-Aza). These attempts have been successful in some aspects in vitro. 5-Aza is a general demethylating agent, leading to unmasking of genes that are not expressed due to promoter hypermethylation. We tested the hypothesis that systemic administration of 5-Aza could convert infarct fibroblasts in situ and improve remodeling and function after myocardial infarction (MI) in rat.
METHODS & RESULTS: The optimal dose and safety of 5-Aza administration was determined in a pilot study in normal rats. Subsequently, 29 rats were subjected to permanent left anterior descending coronary artery occlusion and anterior MI. Seven days after MI rats were randomized to 7-day treatment with 5-Aza (50 mg/m2/d, n=15) or saline (n=14). Cardiac remodeling and function were assessed by echocardiography before and 30 days after initiation of treatment. Total RNA was extracted from the scar tissue and remote myocardium to determine spatial gene profile by DNA array analysis 30 days after MI. Serial echocardiography studies showed that systemic administration of 5-Aza attenuated left ventricular systolic and diastolic dilatation compared with controls ($p<0.05$). Moreover, 5-Aza treatment improved the number of vessels in the scar tissue ($p=0.008$). Immunostaining of scar tissue revealed positive staining for the myogenic transcriptional factor MyoD in 4 of the 11 animals treated with 5-Aza vs. 0 of 9 in control hearts ($p=0.09$). Gene expression analysis in the infarct and remote myocardium revealed upregulation of genes associated with regeneration and repair in 5-Aza treated animals.
CONCLUSIONS: Our study suggests, for the first time, that administration of 5-Aza after MI can improve left ventricular remodeling and infarct vascularization in rat. Our findings suggest a new strategy for infarct repair and regeneration by reprogramming fibroblasts in situ.