Transdifferentiation between Fibroblasts, Myofibroblasts, and Smooth Muscle Cells in Infarcted Myocardium and the Clinical Implication (Cardiovascular Development, The 69th Annual Scientific Meeting of the Japanese Circulation Society) (Fulltext)
Chromatin Remodeling during Differentiation of ES Cells into Cardiac Myocytes

KojI Hasegawa
Koh Ono, Tsutsui Morimoto, Teruhisa Kawamura, Toru Kita
Division of Translational Research, Kyoto Medical Center, National Hospital Organization, Kyoto, Department of Cardiovascular Medicine, Kyoto University, Kyoto

An embryonic stem (ES) cell line is a possible source for cardiac myocytes to be transplanted in patients with end-staged heart failure. Differentiation of ES cells into cardiac myocytes requires activation of cardiac-specific gene programs. Histone acetyltransferases (HATs) and histone deacetylases (HDACs) govern the expression patterns by being recruited to target genes through association with specific transcription factors. One of HATs, p300 serves as a coactivator of cardiac-specific transcription factors such as GATA-4. HAT activity of p300 is required for acetylation and DNA binding of GATA-4 and its full transcriptional activity as well as for promotion of a transcriptionally active euchromatin configuration. However, the role of HATs and HDACs in post-translational modification of GATA-4 during the differentiation of ES cells into cardiac myocytes remains unknown. In an ES cell model of developing embryoid bodies, an acetylated form of GATA-4 and its DNA binding increased concomitant with the expression of p300 during differentiation of ES cells into cardiac myocytes. Treatment of ES cells with trichostatin A (TSA), a specific HDAC inhibitor, induced acetylation of histone H3/4 near GATA-4 sites within the atrial natriuretic factor promoter. In addition, TSA augmented increase in an acetylated form of GATA-4 and its DNA binding during the ES cell differentiation. Finally, TSA facilitated the expression of GFP controlled by the cardiac-specific Nkx2.5 promoter, and of endogenous cardiac β-myosin heavy chain during the differentiation. These findings demonstrate that acetylation of GATA-4 as well as of histones is involved in the differentiation of ES cells into cardiac myocytes.

Transplantation of Mesenchymal Stem Cells Improves Cardiac Function in Heart Failure Through Angiogenesis and Myogenesis

Noritsuki Nagaya
Hajime Ohgushi, Kunio Miyatake, Soichiro Kitamura
Department of Regenerative Medicine and Tissue Engineering, National Cardiovascular Center Research Institute, Osaka, Tissue Engineering Research Group, Research Institute for Cell Engineering, National Institute of Advanced Industrial Science and Technology, Amagasaki city, Hyogo, Department of Internal Medicine, National Cardiovascular Center, Osaka, Department of Cardiovascular Surgery, National Cardiovascular Center, Osaka

Mesenchymal stem cells (MSCs) are pluripotent cells that differentiate into a variety of cells including cardiomyocytes and vascular endothelial cells. However, little information is available regarding the therapeutic potential of MSC transplantation for the treatment of heart failure. Accordingly, we investigated whether transplantation of MSCs improved left ventricular (LV) dysfunction in animals and humans. MSCs or vehicle was directly injected into the myocardium in a rat model of heart failure. Some engrafted MSCs were positive for cardiac markers: desmin, cardiac troponin T, and connexin-43, whereas others formed vascular structures and were positive for von Willebrand factor or smooth muscle actin. MSC transplantation significantly increased capillary density and decreased the collagen volume fraction in the myocardium, resulting in decreased LV end-diastolic pressure and increased LV maximum dp/dt. MSCs secreted large amounts of angiogenic, antiapoptotic, and mitogenic factors: vascular endothelial growth factor, hepatocyte growth factor, adrenomedullin, and insulin-like growth factor-1. Based on these experimental results, we started clinical trials to examine the therapeutic effects of MSCs in patients with heart failure refractory to conventional treatment. Catheter-based MSC transplantation improved cardiac function in patients with dilated or ischemic cardiomyopathy without significant adverse effects. In conclusion, MSC transplantation improved cardiac function in heart failure, possibly through induction of angiogenesis and angiogenesis. The beneficial effects of MSCs might be mediated not only by their differentiation into cardiomyocytes and vascular cells, but also by their ability to supply large amounts of angiogenic, antiapoptotic, and mitogenic factors. Thus, MSC transplantation may be a new therapeutic strategy for the treatment of severe heart failure.