Title

6 Transdifferentiation between Fibroblasts, Myofibroblasts, and Smooth Muscle Cells in Infarcted Myocardium and the Clinical Implication

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Chromatin Remodeling during Differentiation of ES Cells into Cardiac Myocytes

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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 program. 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 chromatin 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 embryo- body, 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-3/4 near GATA 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.

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(to be announced)

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

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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 potency 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 ischaemic cardiomyopathy without significant adverse effects. In conclusion, MSC transplantation improved cardiac function in heart failure, possibly through induction of angiogenesis and myogenesis. The beneficial effects of MSCs might be mediated not only through 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.

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Role of Embryonic Epicardial Cells in Cardiomyocyte Proliferation and Coronary Vessel Formation during Cardiac Development

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Elucidation of the molecular mechanisms to regulate embryonic cardiac myocyte proliferation and coronary vessel formation is critical for the development of regenerative therapy for heart failure patients. Interactions between different types of cells often play an important role during organogenesis. We hypothesized that signals from the epicardium may be required for cardiomyocyte proliferation, since cardiomyocytes close to epicardial cells have a maximum proliferative capacity and mutant mice lacking the epicardium had a defect in myocardial proliferation. Moreover, signals from the myocardium may also be required for the differentiation of epicardial cells into coronary endothelial and smooth muscle cells. In this study, we analyzed embryonic epicardial cells as an inducer of myocardial proliferation and as an acceptor of signals that mediate coronary vessel formation. We established primary culture of embryonic epicardial cells and constructed an embryonic epicardium cDNA library. From this library, we cloned more than 500 clones of secreted or transmembrane proteins using a signal sequence trap method. We focused on 4 secreted and 2 transmembrane proteins shown to be specifically expressed in the embryonic epicardium by in situ hybridization. The 4 secreted proteins have been preliminarily analyzed and may be involved in cell proliferation or angiogenesis. One of the transmembrane proteins may inhibit proliferative signals and the other may be involved in epithelial-mesenchymal transformation. We will present a comprehensive list of secreted or transmembrane proteins expressed in the embryonic epicardium and demonstrate in vitro and in vivo analysis of the 6 proteins that may play an important role in embryonic cardiac myocyte proliferation and coronary vessel formation.

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Transdifferentiation between Fibroblasts, Myofibroblasts, and Smooth Muscle Cells in Infarcted Myocardium and the Clinical Implication

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Myocardial infarction (MI) progress from acute ischemic death of cardiac myocytes accompanying acute inflammatory cell infiltration (acute stage) into granulation tissue containing abundant cell components such as myofibroblasts, neovascularization, and macrophages (subacute stage), and finally into scar tissue with scarce cell component (chronic stage). Acute inflammatory cells and granulation tissue cells disappear via apoptosis as we previously reported. We noted a dramatic rise and fall of population of α-smooth muscle actin-positive myofibroblasts during the healing process of MI; myofibroblasts were negligible at the acute stage, but surprisingly increased so as to occupy up to 40% of the infarcted area during subacute stage, and again became scarce at the chronic stage. Blockade of granulation tissue cell apoptosis by treatment with a panapoptase inhibitor or by soluble Fas gene therapy prolonged survival of myofibroblasts and vessels until chronic stage, resulting in a cell-rich scar tissue. These treatments improved cardiac function and remodeling at the chronic stage. Ultrastructural examination of the scar tissue subjected to the anti-apoptosis treatment revealed existence of extravascular smooth muscle cells with the contractile phenotype, which accumulated to make bundles. These findings suggest that myofibroblasts that escaped from apoptotic death during granulation tissue phase might have transdifferentiated into smooth muscle cells at scar phase. Previous in vitro studies showed that fibroblasts transformed to myofibroblasts by some inflammatory cytokines. Therefore, we propose a possible transdifferentiation between fibroblasts and smooth muscle cells with a relay by myofibroblasts in infarcted myocardium. In addition, acceleration of such plasticity by anti-apoptotic treatments may be a novel therapeutic strategy against post-MI heart failure.

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