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Bio-technologies for a glandular stem cell cardiomyopexy

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Summary

The glandular stem cell cardiomyopexy should become a treatment option for end-stage heart failure. It combines an expected regenerative potential of transformed adult glandular stem cells into cardiomyocytes within the myocardium or onto the myocardium of the recipient and the potential of a hypercapillarized latissimus dorsi muscle (LDM) wrapped around the heart for stem cell nutrition and girdling.

Introduction

In contrast to dynamic cardiomyoplasty, which is a muscle wrap with latissimus dorsi muscle (LDM) around a failing heart for systolic augmentation, a cardiomyopexy using LDM is directly attached to the myocardium after scrubbing off the epicardium for the purpose of indirect revascularization or for the nutrition of the stem cells. The additional elastic girdling of the heart reduces wall tension and therefore reduces oxygen consumption of the myocardium (Hagège et al., 1995) (Figure 1).

Goat and human adult glandular stem cells (pancreatic and parotic) are able to form tissue with the distinct ability to generate cell types of all three germ layers (Kruse et al., 2004). We have shown that mesenchymal cells from these tissues differentiate into cardiomyocytes, promoted in co-culture with human myocardial biopsies (Guldner et al., 2006).

Electrical continuous and intermittent stimulation of LDM has been shown to enhance capillary

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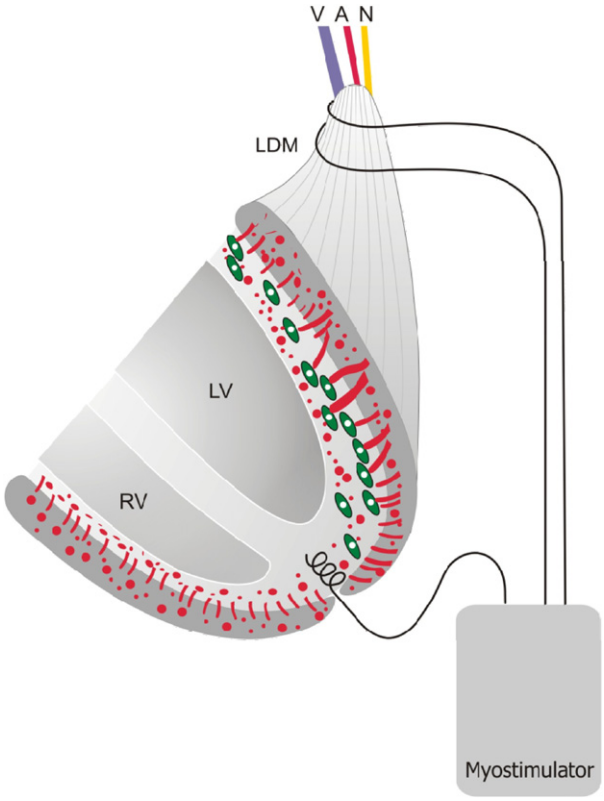

Figure 1. The concept of the glandular stem cell cardiomyopexy combines an expected regenerative potential of transformed adult glandular stem cells into cardiomyocytes within or on the myocardium and the potential of a muscular wrap around the heart by a hypercapillarized latissimus dorsi muscle (LDM) for stem cell nutrition and a muscular girdling. LDM is stimulated on demand, depending on an increased heart rate under physical work.

density of skeletal muscle tissue in small animals (Skorjanc et al., 1998; Mathieu-Costello et al., 1996; Dawson and Hudlicka, 1989; Hudlicka and Tyler, 1984). To date unknown are data on capillary density in intermittently stimulated human-sized animals, correlated with functional data such as blood flow at rest and under exercise which is evaluated here.

Adult stem cells for myocardial regeneration

We have been able to demonstrate that human adult stem cells differentiate into autonomously contracting cardiomyocytes. Co-cultures with biopsies of human myocardium could increase number and activation of cardiomyocytes as shown in Figures 2 and 3.

Glandular stem cells were characterized (Kruse et al., 2004, 2006; Guldner et al., 2006; Kajahn et al., 2008) and generated as described (Kruse et al., 2004, 2006; Guldner et al., 2006). In brief, pancreatic tissue of patients undergoing pancreatic surgery was obtained with informed consent (ethical accreditation of the Ethics Committees, University Hospital of Lübeck, AZ 03-065). Stem cells were selected, cultured in fetal calf serum (FCS) and passaged more than 21 times as previously described (Kruse et al., 2006). The pancreatic tissue was treated with digestion medium containing HEPES-Eagle medium (pH 7.4), 0.1 mM HEPES buffer (pH 7.6), 70% (v/v) modified Eagle medium, 0.5% (v/v) Trasylol (Bayer AG, Leverkusen, Germany), 1% (w/v) bovine serum albumin, 2.4 mM $CaCl_2$ and collagenase (0.63 PZ/mg, Serva, Heidelberg, Germany). After digestion, the acini were dissociated, centrifuged and further purified by washing in Dulbecco's modified Eagle's medium (DMEM, Gibco, Germany) supplemented with 20% FCS. The washing procedure was repeated 5 times. The acini were resuspended in DMEM and cultured at 37 °C in a 5% CO_2 humidified atmosphere. After 1–2 days of culture, spindle-shaped stem cells were observed on the bottom of the cell culture flask. After reaching confluence, pancreatic stem cells were subcultured by trypsinization, counted and reseeded at a density of $2–4 \times 10^5$ cells/cm^2. This procedure was repeated until sufficient cells were available.

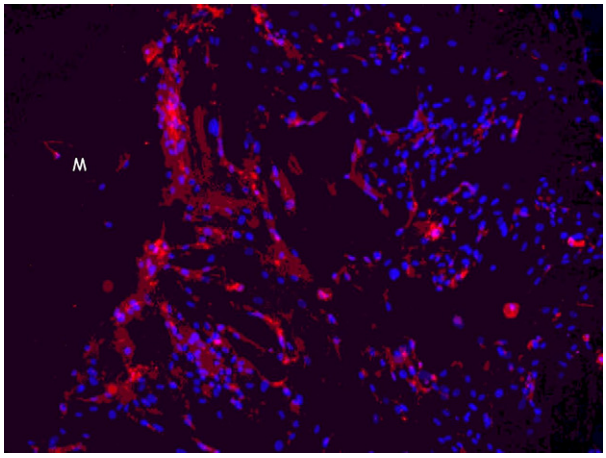

Figure 2. Immunocytochemical visualization of sarcomeres (red) in transformed adult pancreatic stem cells (blue nuclei, due to DAPI-staining) which had been co-cultured with human myocardium (M) for 2 days. A decreasing gradient of myosin-containing cells from M to the periphery is to be seen.

Immunocytochemical visualization of sarcomeres (red) in transformed adult pancreatic stem cells (blue nuclei) which had been co-cultured with human myocardium (M) for 2 days is shown in Figure 2. Cells were seeded on chamber slides and cultured for at least 2 days before they were fixed