Stem cells and heart tissue engineering

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Over the past decade methods have been developed to engineer spontaneously contracting, force-generating 3-dimensional cardiac muscle tissues, both as a target validation model in drug development and as material for cardiac replacement therapy. The present techniques depend on primary cardiac cells from newborn rat or mouse or embryonic chick that have no significant capacity for cell division. Consequently, cardiac tissue engineering at present is essentially a mean to reassemble a heart tissue in vitro that had been dissociated before. Primary cardiac cells are not suitable for potential human applications and their usefulness as a medium- to high throughput target validation assay is limited for practical and ethical reasons. Our research therefore focuses on 3 goals ? (i) to optimize engineered heart tissue from newborn rat (EHT) for cardiac repair, (ii) to miniaturize and automatize the EHT procedure for target validation and drug screening purposes and (iii) to generate EHT from embryonic stem cells (ES cells). To this end, size and contractile force of EHTs could be increased by weaving several circular EHTs to one multi-loop EHTs and culture them under insulin-supplementation, 40% oxygen and auxotonic load. Implantation of multi-loop EHTs onto infarcted hearts of immunosuppressed rats demonstrated survival, formation of a layer of heart muscle tissue and vascularization of the implanted tissue. This was accompanied by undelayed anterograde impulse propagation over the scar and diastolic and systolic improvement of cardiac function. In the second approach, we aim at medium-throughput screening for drug effects on cardiac rhythm, force of contraction and cardiac toxicity and have developed prototypes to do the experiments in a multi-well format. ES cells have an unlimited capacity of self-renewal and generate spontaneously contracting embryoid bodies that display functional properties of immature cardiac myocytes. Over the past years we have developed methods to generate EHTs both from mouse and human embryonic stem cells (ES cells). These constructs beat coherently and develop contractile force. Histologically, ES cell-EHTs are cell rich with strands of cross striated, actinin-positive muscle tissue and show functional characteristics of immature myocardium with typical drug responses. Human ES cell-EHTs will offer the unique opportunity to perform target validation and drug screening on human heart muscles in a relatively simple, cheap and instructive assay.