Genes and stem cells: New therapeutical concepts

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Gene und Stammzellen: Neue Therapiekonzepte


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Summary Modern treatment of acute myocardial infarction and other ischemia-related heart diseases has enhanced acute survival, but the long-term problem of deterioration of myocardial function due to loss of damaged myocytes remains a therapeutic challenge. In this context, new approaches including stem cell implantation and gene therapy have gained much scientific interest. These strategies aim at replacement of lost cardiomyocytes and at revascularization of tissue areas at risk in order to regenerate destroyed myocardium. Though still in an experimental stage, some of these concepts are currently being tested in patients with encouraging results. Here we will describe stem cell properties, suitable sources that could provide sufficient cell numbers
and experimental as well as clinical results of their application for regeneration of the myocardium. Among the therapeutic strategies, bone marrow-derived stem cells and gene therapy with vascular growth factors are presented as the most promising and advanced methods presently available. Nevertheless, we require still better insights into biology of regeneration processes in order to improve these novel therapeutic procedures.

Key words Myocardial infarction – ischemic heart disease – bone marrow stem cells – therapy concepts

Introduction

Cardiovascular diseases remain the prevailing cause of death among Western societies and their incidence is expected to rise further as the mean life expectancy continues to grow. Acute myocardial infarction and chronic ischemic heart disease lead to necrotic and apoptotic cell death. The surviving cardiomyocytes have only a very limited capacity to divide and replace damaged cells. Instead, their place will be taken over by fibroblasts resulting in the formation of a scar. Within certain limits the remaining vital myocardium adapts to compensate for the functional loss of the scarred areas. Besides other mechanisms, the adaptational processes include activation of AT1-receptors and their downstream signal transduction pathways that will eventually promote remodeling of the ventricles leading to wall thinning, chamber dilation (27), and functional deterioration (39).

Despite successful acute management of myocardial infarction with anticoagulant and thrombolytic drugs, β-blockers, angiotensin converting enzyme (ACE) inhibitors, and prompt revascularization techniques (16), long-term development of heart failure can at best be delayed but not altogether be prevented. Therefore, apart from effectively protecting the existing myocardium, there is an urgent need for techniques to restore lost contractile function. At present, terminal heart failure is best treated by transplantation; however, limited availability of suitable donor hearts, the need for lifetime immunosuppression and high treatment cost make this solution far from ideal.

The three major novel therapeutic concepts that will be addressed here are i) gene therapy to improve formation of new blood vessels, ii) implantation of stem cells and iii) engineered heart tissue to replace damaged myocardium. Securing blood supply to the myocardium will undoubtedly prevent ischemic cell damage. This concept has been proven by the impressive clinical benefit of early revascularization of occluded coronary vessels by percutaneous transluminal coronary angioplasty (21). For preventive therapy, existing coronary vessels could be stimulated to form collaterals or neovascularize ischemic tissue by local administration of growth factors and cytokines, or by transfected cells that will produce these factors. Alternatively, endothelial progenitor cells may be implanted that integrate into blood vessels and form de novo vessels (4), for review see (51).

Replacement of scarred tissue with functional myocardium is attempted by grafting stem cells that are assumed to divide, differentiate into myocytes, replace damaged cells and thus improve contractile function. In this context, stimulation of neovascularization would not be an alternative, but rather a complementary strategy. Approaches involving implantation of engineered cardiac tissue are still at a very early experimental stage. One major challenge is to provide the engineered tissue with a sufficient number of blood vessels.

Gene therapy

In the wake of the full description of the human genome, the therapeutic goal of replacing defective genes or modifying gene expression currently attracts a lot of attention. Also in cardiology, transient or stable introduction of a gene might be therapeutically useful. Treatment options could be direct transfection of heart cells as well as implantation of cells that were genetically modified in vitro in order to regulate the specific protein expression. It is likely that in some cases the optimal therapy should embrace these two approaches in the form of cell replacement therapy with genetically modified cells.

Many cardiac diseases are associated with altered gene expression (47) that could be therapeutically modified. The genes of interest can be introduced with intramuscular injection of naked plasmid DNA, by adenoviral delivery or liposomal transfection. Genetic approaches to cure ischemic heart disease have focused on transient overexpression of angiogenic growth factors. In animal experiments, expression of vascular endothelial growth factor (VEGF) induced by gene transfer provoked growth of new capillaries and improved blood flow and muscle function (26). Similar results were found for transfection with fibroblast growth factors.