

Immunohistochemical analyses of rat hearts (A-F) and cardiac fibroblasts 12 weeks after myocardial infarction.

ANIMAL MODEL SYSTEMS FOR CARDIAC ISCHEMIA – RAT / MOUSE

Background

Heart disease, particularly coronary heart disease and myocardial infarction is leading cause of death worldwide. Despite a high mortality after acute coronary artery occlusion, the irreversible loss of cardiomyocytes and the resulting process of cardiac remodeling leads to progressively reduced cardiac pump function and heart failure, ultimately. The acute mortality after myocardial infarction decreased in the past years due to improved early recognition and timely start of therapy. However, there are only limited therapies available to effectively treat impaired heart function and developing heart failure.

Aims

The group aims to develop cell-based therapeutic strategies for ischemic heart disease in small animal models of myocardial infarction and ischemia / reperfusion injury. Furthermore, the underlying mechanisms are studied in order to enhance and optimize the treating process as to improve cardiac pump function.

In further studies, cardioprotective mechanisms and ischemic preconditioning are investigated as well as strategies for an effective application of cardioprotective agents tested. These studies aspire to provide protection to the cardiomyocytes from ischemic or stress-induced injury.

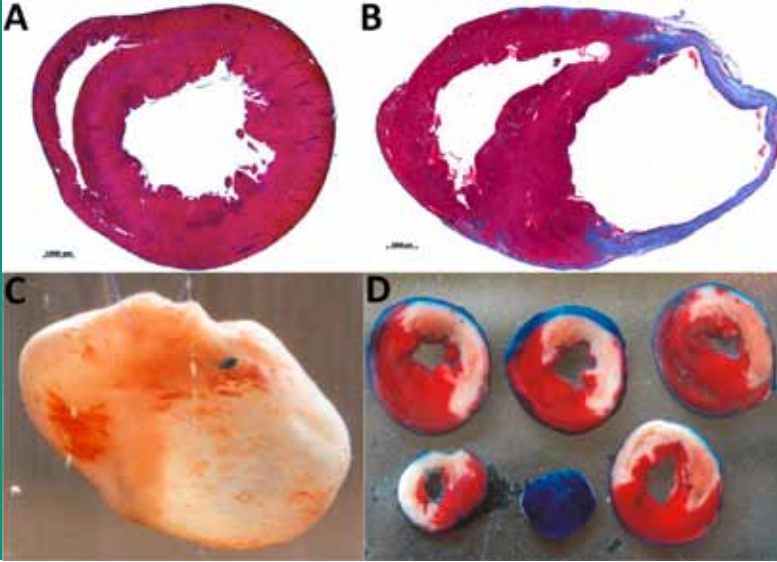
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Animal model systems for cardiac ischemia

The effectiveness of therapeutic strategies to treat myocardial infarction is investigated in animal model systems of cardiac ischemia. Additionally, methods to protect cardiomyocytes against ischemic injury can be developed and optimized.

The small animal systems facilitate quick and straightforward studies to verify the effectiveness of a therapy but also detailed and extensive studies to optimize the therapy including dose-effect relationship and various routes and times of application. Of primary interest is the functional characterization employing echocardiographic investigations over the course of time and cardiac catheterization. Histological and molecular biological investigations serve to objectify success of therapy on cellular and molecular level as well as to comprehend paracrine mechanisms and to identify new therapeutic targets. These studies are established in small laboratory animals (rats, and also mice in order to investigate genetically modified organisms). Studies in large animals (sheep / pig) are in preparation.

Methods

Myocardial ischemia is induced by ligation of the left coronary artery. The ligature can be removed to establish reperfusion after various periods of time as needed. The therapeutics (cells or agents) can be applied

p.o., s.c., i.v., or by direct intramyocardial injections. Also pretreatment to induce pathophysiologically relevant conditions (age, diabetes, ischemic or hypoxic preconditioning) is possible.

Investigation methods

- Echocardiography: investigations over the course of time for morphological and functional characterization
- Right and left heart catheterization: measurements of heart function
- Histology und Immunohistochemistry: measurements of infarct size and detailed histological investigation including labeled cells
- Molecular biology: analysis of gene / protein expression profiles and signal transduction cascades
- Characterization and screening of stem / progenitor cells and isolated cardiomyocytes
- In vitro evaluation of active agents and culture condition (preconditioning) for further in vivo application

Selected Applications

- Development of novel therapeutic strategies to treat myocardial infarction
- Evaluation of cardioprotective agents and cell therapies
- Allogenic and xenogenic cell therapy
- Dose-effect studies and evaluation of application-specific procedures (times and routes)

- Long term studies of safety and efficacy
- Functional and histological characterization of success of a therapy
- Characterization of mechanisms and identification of new therapeutic targets
- Analysis of novel drug delivery technologies evaluation of diagnostic-therapeutic markers

The applied in vivo models of ischemic heart disease build the basis for further investigations of mechanisms and effectiveness of a variety of cell-based and cardioprotective therapeutic strategies. Moreover, they can be utilized to analyze new drug delivery technologies and to test different diagnostic and therapeutic markers.

Summary

The group aims to develop cardioprotective and therapeutic strategies for ischemic heart disease. The effectiveness regarding relevant functional parameters and the underlying mechanisms are studied in in vivo models of myocardial infarction, ischemia / reperfusion and ischemic preconditioning.

Overview of rat (A and B, Masson Trichrome) and mouse hearts (C, native) 8 weeks after sham operation (A) myocardial infarction (B and C).