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Abstract

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Grant Number: 5P01HL003174-450027
PI Name: MURRY, CHARLES E.
PI Email:
PI Title:
Project Title: MYOCARDIAL INFARCT REPAIR

Abstract: Myocardial infarcts heal by scarring because cardiocytes cannot replicate after injury, and because there are no muscle stem cells in the heart. Previous studies showed that MyoD gene transfer or skeletal myoblast grafting can form new contractile tissue in injured hearts, but that skeletal muscle does not form electromechanical junctions with surrounding myocardium. The goals of this project are 1) to develop strategies to repair infarcts with muscle that integrates electrically and mechanically with the remaining myocardium; and 2) to understand how cardiac wound healing is normally regulated to permit rational design of therapies to enhance infarct repair. Specific Aim 1 will determine whether cardiac myocytes from developing or adult hearts can be grafted into injured adult hearts. Physiological studies will determine if cardiocyte grafting improves regional contractile function in vivo. In Specific Aim 2, skeletal myoblasts will be genetically modified to express N-cadherin and connexin 43, the principal proteins of cardiac adherens and gap junctions, respectively. Co-cultures of cardiocytes and transfected skeletal muscle will be studied structurally and functionally for adherens and gap junction. In vivo studies will determine if the genetically modified cells integrate into host myocardium and restore regional contractile function after injury. Specific Aim 3 focuses on the role of osteopontin, a matrix adhesive protein highly expressed by macrophages, in cardiac wound repair. We will administer anti-osteopontin antibodies to rats with cardiac injury and also study cardiac repair in osteopontin- deficient mice. Cell culture studies will determine if osteopontin promotes phagocytosis by macrophages or adhesion and migration of cardiac fibroblasts. In Specific Aim 4 we will study the time course of growth factor (bFGF, VEGF, PDGF, TGF-beta) production following cardiac injury to identify candidate mitogens. Individual growth factors will be studied by administering recombinant molecules systematically and through the use of blocking antibodies in rats with healing infarcts.

Thesaurus Terms:
cardiac myocyte, cell transplantation, myoblast, myocardial infarction, wound healing cadherin, cell growth regulation, cell migration, gap junction, growth factor, heart contraction, histopathology, macrophage, mitogen, muscle transplantation, myocardium, myogenesis, osteopontin, phagocytosis, tissue engineering

laboratory mouse, laboratory rat, mixed tissue /cell culture, transfection

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Fiscal Year: 2000
Department:
Project Start:
Project End:
ICD: NATIONAL HEART, LUNG, AND BLOOD INSTITUTE
IRG:

Version 2.0

Abstract

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Grant Number: 5R01HL061553-02
PI Name: MURRY, CHARLES E.
PI Email:
PI Title:
Project Title: CARDIAC GRAFTS--SKELETAL MYOBLASTS

Abstract: DESCRIPTION: (Adapted from the applicant's abstract) Cardiomyocyte death is a common feature of many forms of heart disease. Since the myocardium lacks a substantive endogenous regenerative potential, cardiomyocyte death is essentially irreversible. It has recently become apparent that exogenous myocytes can be successfully engrafted into the adult myocardium, thereby increasing the number of cells present in the heart. This procedure may be of considerable therapeutic value if engrafted cells can augment function in a diseased heart. Indeed, strategies aimed at increasing myocyte number was viewed with the highest priority by the NHLBI Special Emphasis Panel on Heart Failure Research and by this RFA. However, several rather formidable issues and obstacles must be addressed before any therapy based on myocyte engraftment can be realized. The five highly integrated Collaborative RO1s proposed herein are designed to directly address these issues. A major goal of the proposed studies is to establish the fate of donor cells following engraftment. Particular emphasis is being placed on identifying factor(s) which enhance donor cell viability (Dr. Kedes), and on determining the degree to which donor and host myocytes can interact (Field and Murry). Other studies (Field, Murry and Hauschka) will establish the relative merits of a variety of different donor cells (fetal cardiomyocytes, skeletal myoblasts, ES- and EC- derived cardiomyocytes, and smooth muscle cells). Particular emphasis will be placed on weighing the issue of donor cell availability versus the functional characteristics of their respective grafts. Functional analyses of the engrafted hearts will rely largely on highly sensitive 2D echocardiography (Kloner). These latter studies will also establish to what degree cellular engraftment has a direct versus indirect effect on cardiac function (that is, participation in contractile force generation versus a positive effect on remodeling). The assembled investigators have established track records in relatively new field of cardiac engraftment, and additionally bring a diverse spectrum of experimental expertise which collectively provides a comprehensive battery of molecular, cellular and functional experimental methods.

Thesaurus Terms:
cardiac myocyte, cell growth regulation, cell transplantation, muscle cell, myoblast, myocardial infarction, myocardial ischemia /hypoxia, regeneration

cooperative study
laboratory rat, mixed tissue /cell culture

Institution:	UNIVERSITY OF WASHINGTON 3935 UNIVERSITY WAY NE SEATTLE, WA 98195
Fiscal Year:	2000
Department:	PATHOLOGY
Project Start:	01-JAN-1999
Project End:	31-OCT-2005
ICD:	NATIONAL HEART, LUNG, AND BLOOD INSTITUTE
IRG:	ZHL1