DOWNLOAD PDF CARDIAC REMODELING AND CELL DEATH IN HEART FAILURE

Chapter 1 : The fibrosis-cell death axis in heart failure

Remodeling may be defined as changes in the morphology, structure, and function of the heart related to alterations in loading conditions and/or cardiac injury. This process is critical to the progression of HF, and understanding its mechanism may allow us to better understand the pathophysiology of.

Mending a Broken Heart: The Disease and its Causes Cardiovascular disease CVD , which includes hypertension, coronary heart disease CHD , stroke, and congestive heart failure CHF , has ranked as the number one cause of death in the United States every year since except , when the nation struggled with an influenza epidemic. Nearly Americans die of CVD each day, roughly one death every 34 seconds. Moreover, within a year of diagnosis, one in five patients with CHF will die. Given the aging of the U. However, improvements in the acute treatment of heart attacks and an increasing arsenal of drugs have facilitated survival. Ischemic heart failure occurs when cardiac tissue is deprived of oxygen. When the ischemic insult is severe enough to cause the loss of critical amounts of cardiac muscle cells cardiomyocytes , this loss initiates a cascade of detrimental events, including formation of a non-contractile scar, ventricular wall thinning see Figure 6. However, endogenous repair mechanisms, including the proliferation of cardiomyocytes under conditions of severe blood vessel stress or vessel formation and tissue generation via the migration of bone-marrow-derived stem cells to the site of damage, are in themselves insufficient to restore lost heart muscle tissue myocardium or cardiac function. Moreover, while implantation of mechanical ventricular assist devices can provide long-term improvement in heart function, complications such as infection and blood clots remain problematic. The left ventricle has a thick muscular wall, shown in cross-section in A. After a myocardial infarction heart attack , heart muscle cells in the left ventricle are deprived of oxygen and die B , eventually causing the ventricular wall to become thinner C. A number of stem cell types, including embryonic stem ES cells, cardiac stem cells that naturally reside within the heart, myoblasts muscle stem cells , adult bone marrow-derived cells, mesenchymal cells bone marrow-derived cells that give rise to tissues such as muscle, bone, tendons, ligaments, and adipose tissue , endothelial progenitor cells cells that give rise to the endothelium, the interior lining of blood vessels , and umbilical cord blood cells, have been investigated to varying extents as possible sources for regenerating damaged myocardium. All have been tested in mouse or rat models, and some have been tested in large animal models such as pigs. Preliminary clinical data for many of these cell types have also been gathered in selected patient populations. However, clinical trials to date using stem cells to repair damaged cardiac tissue vary in terms of the condition being treated, the method of cell delivery, and the primary outcome measured by the study, thus hampering direct comparisons between trials. Even among patients undergoing comparable procedures, the clinical study design can affect the reporting of results. Some studies have focused on safety issues and adverse effects of the transplantation procedures; others have assessed improvements in ventricular function or the delivery of arterial blood. Furthermore, no published trial has directly compared two or more stem cell types, and the transplanted cells may be autologous i. Despite the relative infancy of this field, initial results from the application of stem cells to restore cardiac function have been promising. This article will review the research supporting each of the aforementioned cell types as potential source materials for myocardial regeneration and will conclude with a discussion of general issues that relate to their clinical application. Mechanisms of Action In , Menasche, et. When they examined patients 5 months after treatment, they concluded that treated hearts pumped blood more efficiently and seemed to demonstrate improved tissue health. This case study suggested that stem cells may represent a viable resource for treating ischemic heart failure, spawning several dozen clinical studies of stem cell therapy for cardiac repair see Boyle, et. These trials have revealed the complexity of using stem cells for cardiac repair, and considerations for using stem cells in the clinical setting are discussed in a subsequent section of this report. The mechanism by which stem cells promote cardiac repair remains controversial, and it is likely that the cells regenerate myocardium through several pathways. Initially, scientists believed that

transplanted cells differentiated into cardiac cells, blood vessels, or other cells damaged by CVD. Methods of Cell Delivery Regardless of which mechanism s will ultimately prove to be the most significant in stem-cell mediated cardiac repair, cells must be successfully delivered to the site of injury to maximize the restored function. In preliminary clinical studies, researchers have used several approaches to deliver stem cells. Common approaches include intravenous injection and direct infusion into the coronary arteries. These methods can be used in patients whose blood flow has been restored to their hearts after a heart attack, provided that they do not have additional cardiac dysfunction that results in total occlusion or poor arterial flow. However, these strategies may be of limited benefit to those who have poor circulation, and stem cells are often injected directly into the ventricular wall of these patients. This endomyocardial injection may be carried out either via a catheter or during open-heart surgery. Types of Stem Cells Investigated to Regenerate Damaged Myocardial Tissue Embryonic and adult stem cells have been investigated to regenerate damaged myocardial tissue in animal models and in a limited number of clinical studies. A brief review of work to date and specific considerations for the application of various cell types will be discussed in the following sections. Embryonic Stem ES Cells Because ES cells are pluripotent, they can potentially give rise to the variety of cell types that are instrumental in regenerating damaged myocardium, including cardiomyocytes, endothelial cells, and smooth muscle cells. To this end, mouse and human ES cells have been shown to differentiate spontaneously to form endothelial and smooth muscle cells in vitro 19 and in vivo, 20 , 21 and human ES cells differentiate into myocytes with the structural and functional properties of cardiomyocytes. However, several key hurdles must be overcome before human ES cells can be used for clinical applications. Foremost, ethical issues related to embryo access currently limit the avenues of investigation. In addition, human ES cells must go through rigorous testing and purification procedures before the cells can be used as sources to regenerate tissue. First, researchers must verify that their putative ES cells are pluripotent. To prove that they have established a human ES cell line, researchers inject the cells into immunocompromised mice; i. Under these conditions, pluripotent cells will form a teratoma, a multi-layered, benign tumor that contains cells derived from all three embryonic germ layers. Teratoma formation indicates that the stem cells have the capacity to give rise to all cell types in the body. The pluripotency of ES cells can complicate their clinical application. While undifferentiated ES cells may possibly serve as sources of specific cell populations used in myocardial repair, it is essential that tight quality control be maintained with respect to the differentiated cells. Any differentiated cells that would be used to regenerate heart tissue must be purified before transplantation can be considered. If injected regenerative cells are accidentally contaminated with undifferentiated ES cells, a tumor could possibly form as a result of the cell transplant. Predictable control of cell proliferation and differentiation requires additional basic research on the molecular and genetic signals that regulate cell division and specialization. Furthermore, long-term cell stability must be well understood before human ES-derived cells can be used in regenerative medicine. The propensity for genetic mutation in the human ES cells must be determined, and the survival of differentiated, ES-derived cells following transplantation must be assessed. Furthermore, once cells have been transplanted, undesirable interactions between the host tissue and the injected cells must be minimized. Cells or tissues derived from ES cells that are currently available for use in humans are not tissue-matched to patients and thus would require immunosuppression to limit immune rejection. Studies in rats and humans have demonstrated that these cells can repopulate scar tissue and improve left ventricular function following transplantation. The expression of two key proteins involved in electromechanical cell integration, N-cadherin and connexin 43, are downregulated in vivo, 28 and the engrafted cells develop a contractile activity phenotype that appears to be unaffected by neighboring cardiomyocytes. Most of these procedures were carried out during open-heart surgery, although a couple of studies have investigated direct myocardial injection and transcoronary administration. Sustained ventricular tachycardia, a life-threatening arrhythmia and unexpected side-effect, occurred in early implantation studies, possibly resulting from the lack of electrical coupling between SM-derived cardiomyocytes and native tissue. While several subsequent studies have questioned whether these cells actually differentiate into

cardiomyocytes, 32 , 33 the evidence to support their ability to prevent remodeling has been demonstrated in many laboratories. In the past three years, the transplantation of bone marrow mononuclear cells BMMNCs , a mixed population of blood and cells that includes stem and progenitor cells, has been explored in more patients and clinical studies of cardiac repair than any other type of stem cell. However, it should be noted that these studies have been conducted under a variety of conditions, thereby hampering direct comparison. The cells have been delivered via open-heart surgery and endomyocardial and intracoronary catheterization. As larger trials are developed, these issues can be explored more systematically. They remain multipotent following expansion in vitro, exhibit relatively low immunogenicity, and can be frozen easily. While these properties make the cells amenable to preparation and delivery protocols, scientists can also culture them under special conditions to differentiate them into cells that resemble cardiac myocytes. This property enables their application to cardiac regeneration. MSCs differentiate into endothelial cells when cultured with vascular endothelial growth factor 40 and cardiomyogenic CMG cells when treated with the dna-demethylating agent, 5-azacytidine. Resident Cardiac Stem Cells Recent evidence suggests that the heart contains a small population of endogenous stem cells that most likely facilitate minor repair and turnover-mediated cell replacement. However, their potential as a convenient resource for autologous stem cell therapy has led the National Heart, Lung, and Blood Institute to fund forthcoming clinical trials that will explore the use of cardiac stem cells for myocardial regeneration. Endothelial Progenitor Cells The endothelium is a layer of specialized cells that lines the interior surface of all blood vessels including the heart. This layer provides an interface between circulating blood and the vessel wall. Endothelial progenitor cells EPCs are bone marrow-derived stem cells that are recruited into the peripheral blood in response to tissue ischemia. Clinical trials are currently underway to assess EPC therapy for growing new blood vessels and regenerating myocardium. Although these cell types have not been investigated in clinical trials of heart disease, preliminary studies in animal models indicate several potential applications in humans. Umbilical cord blood contains enriched populations of hematopoietic stem cells and mesencyhmal precursor cells relative to the quantities present in adult blood or bone marrow. When injected directly into the infarcted area in a rat model of MI, human mononuclear UCB cells improved ventricular function. Results similar to these have been observed following the injection of human unrestricted somatic stem cells from UCB into a pig MI model. Recent studies that involve the direct injection of blood-borne or bone marrow-derived hematopoietic stem cells into the infarcted region of a mouse model of MI found no evidence of myocardial regeneration following injection of either cell type. Whether these cells will ultimately find application in myocardial regeneration remains to be determined. Autologous fibroblasts offer a different strategy to combat myocardial damage by replacing scar tissue with a more elastic, muscle-like tissue and inhibiting host matrix degradation. Considerations for Using These Stem Cells in the Clinical Setting As these examples indicate, many types of stem cells have been applied to regenerate damaged myocardium. In select applications, stem cells have demonstrated sufficient promise to warrant further exploration in large-scale, controlled clinical trials. However, the current breadth of application of these cells has made it difficult to compare and contextualize the results generated by the various trials. Most studies published to date have enrolled fewer than 25 patients, and the studies vary in terms of cell types and preparations used, methods of delivery, patient populations, and trial outcomes. However, the mixed results that have been observed in these studies do not necessarily argue against using stem cells for cardiac repair. Rather, preliminary results illuminate the many gaps in understanding of the mechanisms by which these cells regenerate myocardial tissue and argue for improved characterization of cell preparations and delivery methods to support clinical applications. Future clinical trials that use stem cells for myocardial repair must address two concerns that accompany the delivery of these cells: Although stem cells appear to be relatively safe in the majority of recipients to date, an increased frequency of non-sustained ventricular tachycardia, an arrhythmia, has been reported in conjunction with the use of skeletal myoblasts. Additionally, animal models have demonstrated that stem cells rapidly diffuse from the heart to other organs e. This migration may or may not cause side-effects in patients; however, it remains a concern

related to the delivery of stem cells in humans. Techniques to label stem cells for tracking purposes and to assess their safety are discussed in more detail in other articles in this publication. In addition to safety and tracking, several logistical issues must also be addressed before stem cells can be used routinely in the clinic. While cell tracking methodologies allow researchers to determine migration patterns, the stem cells must target their desired destination s and be retained there for a sufficient amount of time to achieve benefit. To facilitate targeting and enable clinical use, stem cells must be delivered easily and efficiently to their sites of application. Finally, the ease by which the cells can be obtained and the cost of cell preparation will also influence their transition to the clinic. Conclusions The evidence to date suggests that stem cells hold promise as a therapy to regenerate damaged myocardium. Given the worldwide prevalence of cardiac dysfunction and the limited availability of tissue for cardiac transplantation, stem cells could ultimately fulfill a large-scale unmet clinical need and improve the quality of life for millions of people with CVD. However, the use of these cells in this setting is currently in its infancyâ€”much remains to be learned about the mechanisms by which stem cells repair and regenerate myocardium, the optimal cell types and modes of their delivery, and the safety issues that will accompany their use. As the results of large-scale clinical trials become available, researchers will begin to identify ways to standardize and optimize the use of these cells, thereby providing clinicians with powerful tools to mend a broken heart. References American Heart Association.

Chapter 2 : Mending a Broken Heart: Stem Cells and Cardiac Repair | blog.quintoapp.com

Remodeling may be defined as changes in the morphology, structure, and function of the heart related to alterations in loading conditions and/or cardiac injury.

This article has been cited by other articles in PMC. Abstract Cardiac stress can induce morphological, structural and functional changes of the heart, referred to as cardiac remodeling. Myocardial infarction or sustained overload as a result of pathological causes such as hypertension or valve insufficiency may result in progressive remodeling and finally lead to heart failure HF. HF is strongly associated with age, and cardiomyocyte loss and fibrosis are typical signs of the aging heart. Fibrosis results in stiffening of the heart, conductivity problems and reduced oxygen diffusion, and is associated with diminished ventricular function and arrhythmias. As a consequence, the workload of cardiomyocytes in the fibrotic heart is further augmented, whereas the physiological environment is becoming less favorable. This causes additional cardiomyocyte death and replacement of lost cardiomyocytes by fibrotic material, generating a vicious cycle of further decline of cardiac function. Breaking this fibrosis-cell death axis could halt further pathological and age-related cardiac regression and potentially reverse remodeling. In this review, we will describe the interaction between cardiac fibrosis, cardiomyocyte hypertrophy and cell death, and discuss potential strategies for tackling progressive cardiac remodeling and HF. Fibrosis is an essential process in the repair of damaged tissues and wounds, but its accumulation in organs and tissues can lead to scarring, organ dysfunction and, ultimately, failure. In many chronic diseases, sustained progressive fibrosis can be very detrimental, like in fibrotic kidney and liver disease, and this is also true for chronic heart failure [3]. Heart failure HF is a complex clinical syndrome in which reduced cardiac function results in insufficient perfusion of peripheral tissues [4 , 5]. Cardiac remodeling, which can be described as any structural and functional change of the heart, underlies HF development. Cardiac remodeling is a reaction of the heart to reduce ventricular wall stress in response to changes in after load pressure load , preload volume overload or myocardial injury [7]. Amongst others, main risk factors for HF include coronary artery disease and hypertension [6]. Regardless of the initiating events, cardiac hypertrophy, cardiomyocyte cell death and fibrosis constitute key features of pathological cardiac remodeling. Fibrosis is a hallmark of pathological cardiac remodeling and is absent under physiological stress conditions, such as exercise and pregnancy [9 â€” 11]. Cardiac fibrosis appears to be an irreversible process [12] and is increasingly recognized as a major cause of morbidity and mortality in many chronic diseases. In the myocardium, fibrosis can be divided into interstitial fibrosis, replacement fibrosis and perivascular fibrosis, which all have their characteristics Fig. The distinction between different types of fibrosis is made based on cause and anatomical localization [13]. As a response to increased wall stress generated by a cardiac stressor, like hypertension, interstitial reactive fibrosis is developed in the myocardium [14 , 15]. Reactive interstitial fibrosis is located in the ECM surrounding cells and is defined as the expansion of ECM without cardiomyocyte loss and is characterized by a widespread deposition of collagens throughout the myocardium [13 , 14]. In perivascular fibrosis, which is also associated with hypertension, fibrillar collagens accumulate in the adventitia of intramural coronary arteries [14 , 16 , 17]. With ongoing hypertension, the accumulation of collagens progresses [17].

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Chapter 3 : Ventricular remodeling - Wikipedia

Heart failure and cardiac remodeling. Fibrosis is the excessive deposition of extracellular matrix (ECM), such as collagens and fibronectin, resulting in the excessive accumulation of fibrous connective tissue [1, 2].

Pathophysiology[edit] Myocardiocyte The cardiac myocyte is the major cell involved in remodeling. Fibroblasts , collagen , the interstitium, and the coronary vessels to a lesser extent, also play a role. A common scenario for remodeling is after myocardial infarction. There is myocardial necrosis cell death and disproportionate thinning of the heart. This thin, weakened area is unable to withstand the pressure and volume load on the heart in the same manner as the other healthy tissue. As a result, there is dilatation of the chamber arising from the infarct region. The initial remodeling phase after a myocardial infarction results in repair of the necrotic area and myocardial scarring that may, to some extent, be considered beneficial since there is an improvement in or maintenance of LV function and cardiac output. Over time, however, as the heart undergoes ongoing remodeling, it becomes less elliptical and more spherical. Ventricular mass and volume increase, which together adversely affect cardiac function. Post MI, as fatty acid oxidation decreases, it leads to reduced energy supply for the cardiac myocytes, accumulation of fatty acids to toxic levels, and dysfunction of mitochondria. These consequences also led to the increase in oxidative stress on the heart, causing the proliferation of fibroblasts , activation of metalloproteinases , and induction of apoptosis, which would be explained below. Besides, inflammatory immune response after MI also contributes to the above changes. Cardiac collagen is synthesized by fibroblasts and degraded by metalloproteinases. However, atrial natriuretic peptide is thought to be cardio-protective. The size and function of the atria and ventricles can be characterized using this test. Treatment[edit] Many factors influence the time course and extent of remodeling, including the severity of the injury, secondary events recurrent ischemia or infarction , neurohormonal activation, genetic factors and gene expression , and treatment. Medications may attenuate remodeling. Angiotensin-converting enzyme ACE inhibitors have been consistently shown to decrease remodeling in animal models or transmural infarction and chronic pressure overload. Clinical trials have shown that ACE inhibitor therapy after myocardial infarction leads to improved myocardial performance, improved ejection fraction , and decreased mortality compared to patients treated with placebo. Likewise, inhibition of aldosterone , either directly or indirectly, leads to improvement in remodeling. Often, reverse remodeling, or improvement in left ventricular function, will also be seen.

Chapter 4 : Congestive Heart Failure - Google Books

11 Cardiac Remodeling and Cell Death in Heart Failure Progression of Cardiac Remodeling and Transition to Overt HF The mechanisms of cardiac remodeling, particularly those.

Chapter 5 : Myocyte apoptosis in heart failure | Cardiovascular Research | Oxford Academic

Cardiac remodeling is generally accepted as a determinant of the clinical course of heart failure (HF). Defined as genome expression resulting in molecular, cellular and interstitial changes and manifested clinically as changes in size, shape and function of the heart resulting from cardiac load or.