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Gene therapy for heart failure

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ABSTRACT

Novel strategies are needed to treat the growing population of heart failure patients. While new drug and device based therapies have improved outcomes over the past several decades, heart failure patients continue to experience amongst the lowest quality of life of any chronic disease, high likelihood of being hospitalized and marked reduction in survival. Better understanding of many of the basic mechanisms involved in the development of heart failure has helped identify abnormalities that could potentially be targeted by gene transfer. Despite success in experimental animal models, translating gene transfer strategies from the laboratory to the clinic remains at an early stage. This review provides an introduction to gene transfer as a therapy for treating heart failure, describes some of the many factors that need to be addressed in order for it to be successful and discusses some of the recent studies that have been carried out in heart failure patients. Insights from these studies highlight both the enormous promise of gene transfer and the obstacles that still need to be overcome for this treatment approach to be successful.

Keywords: Gene therapy, Heart failure, Adeno-associated virus, SERCA2a.

Heart failure (HF) is a major and growing public health problem throughout the world. In the United States (U.S.) alone, an estimated 6 million adults suffer from HF and worldwide prevalence is believed to be in the range of 23 million [1–4]. Costs to the U.S. healthcare system currently exceed 30 billion dollars annually, a figure that is anticipated to rise substantially over the next several decades as both the prevalence of HF and cost of care rise. Patients with HF experience amongst the poorest quality of life of any chronic disease and their likelihood of being hospitalized over the course of any given year is substantial. Most importantly, HF patients have marked reductions in survival with only about 50% surviving for greater than 5 years after the diagnosis is made [5,6]. Although recently approved treatments have improved outcomes [7,8], the clinical course remains poor and there is a major need for new approaches to prevent and treat HF.

Insights into the cellular and molecular mechanisms involved in the development of HF have helped identify a variety of abnormalities in cell function and signaling that could serve as potential therapeutic targets [9–11]. Gene transfer (GT) is a very promising approach for treating these abnormalities and studies assessing this therapeutic approach have been carried in experimental animal models as well as in HF patients. This review will provide a general overview of GT, discuss the conditions that must be satisfied for it to be successful in treating HF, describe the various approaches that have been used or are being developed and summarize the results of recent clinical trials assessing the effects of GT in HF patients.

Gene transfer therapy

Gene transfer therapy involves the introduction of recombinant human genetic material to a patient in order to alter levels of a protein that will directly or indirectly (e.g. through paracrine or systemic effects) improve the function of a targeted organ. For GT of HF, the goal in most cases is to deliver genetic material directly to the myocardium. Cardiac dysfunction could also be treated by GT that is designed to enhance the production and release of therapeutic molecules from blood vessels into the circulation. Since HF is characterized by global myocardial dysfunction in the vast majority of cases, GT should be aimed at all (or at least a substantial portion) of the affected cardiomyocytes. Expression of the targeted gene needs to be sustained over an extended period of time unless therapy is meant to repair a specific structural

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defect. Most importantly, the gene that has been identified must encode a molecule that plays a critical role in the pathogenesis of HF such that by altering expression of that gene alone, cardiac function will be improved sufficiently to favorably alter the clinical course.

The success of GT therapy depends on a variety of factors that will ultimately determine the level of transgene expression within the targeted cells. These factors include the vector used for delivery, the method and conditions of delivery of the vector to the myocardium, the dose that is given and interactions between the host and the vector that alter the efficiency of transfection of myocardial cells.

Vectors used for GT (Fig. 1)

For GT to work, genetic material must be delivered in sufficient quantity to affect the function of the targeted organ. Selection of the vector is a critical element for achieving adequate uptake into the myocardium. A variety of vectors have been used in experimental and human studies [12]. Attributes of an ideal vector for GT of HF include the ability to carry large genes, ease of amplification so that sufficient quantities can be manufactured for large-scale use, low likelihood of producing an inflammatory or immune response, and ability to maintain long-term gene expression. For vectors that are delivered through the circulation, tropism for the myocardium, resistance to inactivation by neutralizing anti-bodies (NAbs) and other serum factors and ability to successfully traverse the endothelium to reach the myocardium are other important considerations.

At present, there is no single vector that fulfills all of these goals. Plasmids, which are relatively easy to produce in large quantities, have been used as an alternative to viral vectors [12]. However, this approach results in only short-term gene expression, a situation that does not lend itself well to the treatment of a chronic disease like HF. As a result, viral vectors have been most commonly used for treating HF. Adenoviruses (AVs) have been used to deliver genes of interest to cells in culture, experimental models and, more recently to HF patients. While AVs are capable of incorporating large genes into the viral backbone and transducing a wide variety of cells, they exhibit no specific tropism for cardiomyocytes. Although AVs are capable of producing high levels of gene expression, the effect (similar to that of modified RNA and plasmid vectors) tends to be short-lived. The fact that AVs induce a strong immune response to the viral capsid [13] raises questions both about safety and feasibility of repeat administration. Lentiviral vectors have also been used for GT [12]. They integrate into the patient's genome and are capable of producing long-term gene expression. In most cases, they provoke only a moderate immune response. However, lentiviruses do not demonstrate specific tropism for the myocardium and, as a result, require direct injection into the heart, a condition that limits their usefulness in most settings for treating HF patients. Gene therapy to treat cardiac disease using a lentivirus vector has not yet been tested in patients. Adeno-associated viruses (AAVs) have many properties of the ideal vector and there has been considerable enthusiasm for using them to deliver genes for treating HF [11,14–16]. Several AAV serotypes have been shown to exhibit high degrees of tropism for the heart [17,18]. In addition, AAVs are minimally immunogenic, are not cell cycle dependent and have the capability for long-term transgene expression. Recombinant AAVs don't integrate into the patient's own genome. Important limitations of AAVs include relatively small insert capacity and, as will be discussed, the presence of neutralizing antibodies (NAbs) in a substantial segment of the population.

Delivery methods

Delivery methods considered for GT of HF include injection of the vector into either the epicardial (during surgery) or endocardial (using catheter based techniques) surface of the heart, seeding in the pericardium and delivery through the systemic venous or coronary (either arterial or venous) circulations [19–22]. Intramyocardial injection of the vector into the heart has the advantage of direct introduction into the myocardium and avoids problems related to dilution in the blood and distribution of the vector to regions where there is little viable myocardium present (i.e. intense scar tissue) or to other organs around the body. However, the number of injection sites is limited (particularly with catheter based techniques) and whether or not a sufficient number of cardiomyocytes can be transfected to improve global cardiac function is uncertain. Pericardial seeding allows broad distribution and could be used for GT designed to produce

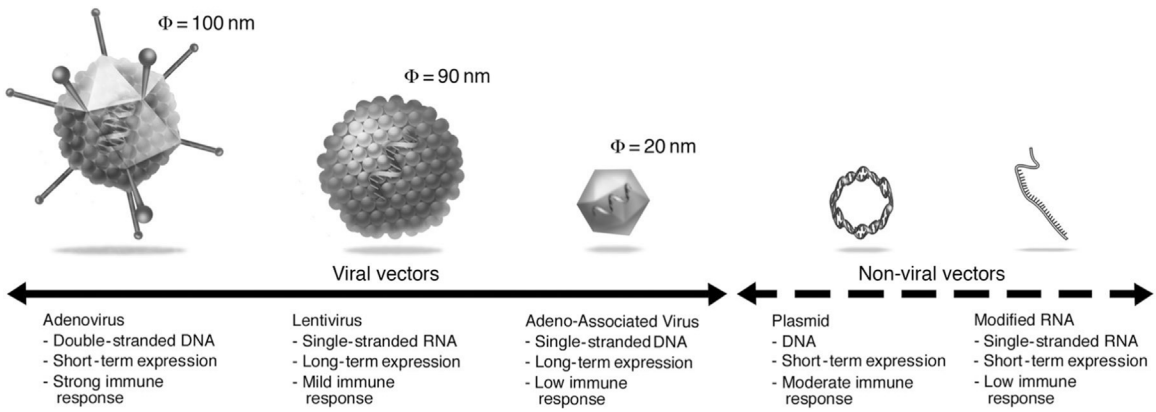

Fig. 1 – Vectors used for gene therapy of cardiac disease. A variety of different vectors have been used. Several of the more commonly used ones and some of their characteristics are depicted above. From Reference [12] with permission.