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Functional performance of human cardiosphere-derived cells delivered in an *in situ* polymerizable hyaluronan-gelatin hydrogel

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ABSTRACT

The vast majority of cells delivered into the heart by conventional means are lost within the first 24 h. Methods are needed to enhance cell retention, so as to minimize loss of precious material and maximize effectiveness of the therapy. We tested a cell-hydrogel delivery strategy. Cardiosphere-derived cells (CDCs) were grown from adult human cardiac biopsy specimens. *In situ* polymerizable hydrogels made of hyaluronan and porcine gelatin (*Hystem®-C™*) were formulated as a liquid at room temperature so as to gel within 20 min at 37 °C. CDC viability and migration were not compromised in *Hystem-C™*. Myocardial infarction was created in SCID mice and CDCs were injected intramyocardially in the infarct border zone. Real-time PCR revealed engraftment of CDCs delivered in *Hystem-C™* was increased by nearly an order of magnitude. LVEF (left ventricular ejection fraction) deteriorated in the control (PBS only) group over the 3-week time course. *Hystem-C™* alone or CDCs alone preserved LVEF relative to baseline, while CDCs delivered in *Hystem-C™* resulted in a sizable boost in LVEF. Heart morphometry revealed the greatest attenuation of LV remodeling in the CDC + *Hystem-C™* group. Histological analysis suggested cardiovascular differentiation of the CDCs in *Hystem-C™*. However, the majority of functional benefit is likely from paracrine mechanisms such as tissue preservation and neovascularization. A CDC/hydrogel formulation suitable for catheter-based intramyocardial injection exhibits superior engraftment and functional benefits relative to naked CDCs.

1. Introduction

Cardiovascular disease remains the leading cause of death and disability in Americans, claiming more lives each year than cancer, diabetes mellitus, HIV and accidents combined [1]. Ischemic heart disease is the predominant contributor to cardiovascular morbidity and mortality; ~1 million myocardial infarctions (MIs) occur per year in the United States while ~5 million patients suffer from chronic heart failure [2]. Death rates following MI have improved dramatically over the last four decades [3], but new approaches are nevertheless urgently needed for those patients who deteriorate and develop ventricular dysfunction [4]. Over the past ten years, stem cell transplantation has emerged as a promising therapeutic strategy for acute or chronic ischemic cardiomyopathy. Over the last six years, we have taken a unique cell therapy product, cardiosphere-derived cells (CDCs) from proof-of-concept animal studies [5–13] to a recently completed phase I clinical trial. Data from our clinical trial (CADUCEUS, NCT00893360 at clinicaltrials.gov) indicates that CDCs augment cardiac function and reduce scar size in mild to moderate ischemic cardiomyopathies [14]. However, CDCs face the same fate as most other cell types, that is extremely low retention rates in the heart shortly after delivery, which certainly cripples the efficiency and efficacy of cell therapies in general [15]. In fact, the vast majority of cells delivered into the heart by conventional means are lost within the first 24 h [16]. Methods are needed to enhance retention.

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