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Heart regeneration☆

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ABSTRACT

Regenerating an injured heart holds great promise for millions of patients suffering from heart diseases. Since the human heart has very limited regenerative capacity, this is a challenging task. Numerous strategies aiming to improve heart function have been developed. In this review we focus on approaches intending to replace damaged heart muscle by new cardiomyocytes. Different strategies for the production of cardiomyocytes from human embryonic stem cells or human induced pluripotent stem cells, by direct reprogramming and induction of cardiomyocyte proliferation are discussed regarding their therapeutic potential and respective advantages and disadvantages. Furthermore, different methods for the transplantation of pluripotent stem cell-derived cardiomyocytes are described and their clinical perspectives are discussed.
This article is part of a Special Issue entitled: Cardiomyocyte Biology: Integration of Develomental and Environmental Cues in the Heart edited by Marcus Schaub and Hughes Abriel.

1. Introduction

Cardiomyocytes in the adult human heart appear to turn over at a very low rate, estimated at 0.5–1% per year [1,2]. The low rate of cardiomyogenesis is not sufficient to compensate for the enormous loss of cells after injury such as myocardial infarction. Animal data suggest that the low turnover rate results from proliferating cardiomyocytes rather than differentiation of resident or invading cardiac progenitor cells into cardiomyocytes [3–6]. While scientifically interesting in a general sense, the question of whether and, if yes, how the heart regenerates has important therapeutic implications, because even little regenerative capacity offers means for therapeutic augmentation. Such regenerative approach would constitute a paradigm shift as current therapies can slow down the progression of heart failure in early stages, but fail to reverse it. End-stages of the disease are essentially therapy-refractory, leaving heart transplantation (Tx) and implantation of left ventricular assist devices (LVAD) the only therapy options. Tx faces donor organ shortage and immunological long-term complications, LVAD time-dependent complications. Though the effectiveness and safety of the latter has seen dramatic improvement with a 1-year mortality of patients with LVADs of only 20% [7], the overall prognosis of patients with acute decompensated heart failure remains grim with a 1-year mortality of >30% plus 16% Tx or LVAD [8].

Numerous strategies to regenerate a broken heart are currently pursued worldwide, ranging from small molecules such as microRNAs over cell infusion/injection to surgical approaches such as the implantation of engineered cardiac tissue grafts. They all share the common goal of improving heart function after injury, but differ widely in concept. In this article we use the term “cardiac regeneration” solely for attempts to replace damaged or necrotic heart muscle cells by new cardiomyocytes or to add new myocytes/muscle tissue to the injured heart. We use the term “cardiomyocyte” only for cells that express cardiac marker proteins, exhibit cross-striated sarcomeric organization and contract either spontaneously or under electrical stimulation. The review will focus on cardiac tissue engineering approaches and unanswered questions in this field. For other concepts the reader is referred to recent reviews with a wider scope [9–11].

2. Approaches to cardiac regeneration

Cardiac regeneration requires new cardiomyocytes. Three scenarios can be envisioned today to increase the number of cardiomyocytes in an injured heart (Fig. 1). (i) Fibroblasts, amply abundant in infarct scars,

Abbreviations: AAV, adeno-associated virus; CM, cardiomyocyte; EHT, engineered heart tissue; ESC, embryonic stem cell; hEHT, human engineered heart tissue; hESC, human embryonic stem cell; hiPSC, human induced pluripotent stem cell; HLA, human leucocyte antigen; hNT-ESC, human nuclear transfer-mediated ESC; hPGSC, human parthenogenetic stem cell; hPSC, human pluripotent stem cell; iPSC, induced pluripotent stem cell; LVAD, ventricular assist devices; PSC-CM, pluripotent stem cell-derived cardiomyocyte; SCNT, somatic cell nuclear transfer; Tx, heart transplantation.

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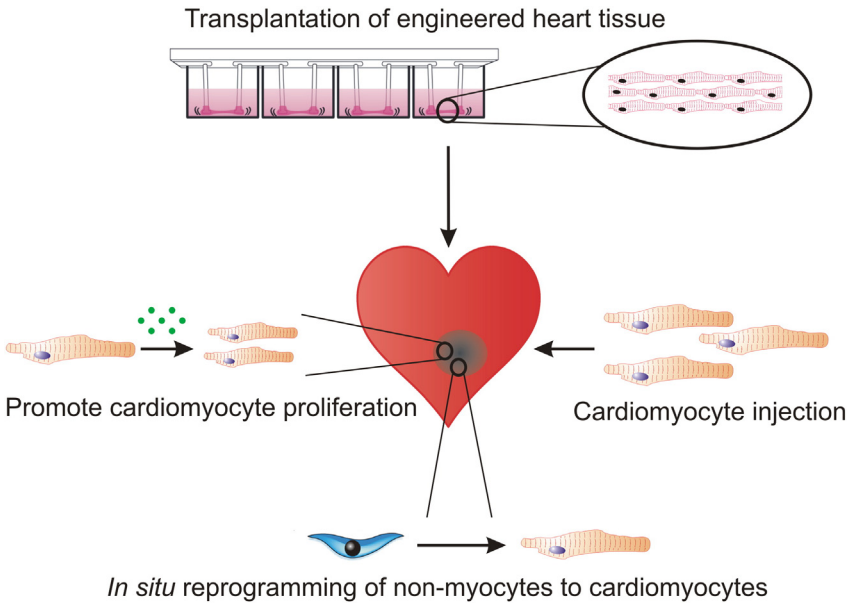

Fig. 1. Approaches to cardiac regeneration.

can be reprogrammed *in situ* into cardiomyocytes ("direct reprogramming"). (ii) The low rate of endogenous cardiac regeneration can be stimulated. (iii) Cardiomyocytes can be generated *in vitro* and transplanted into or onto the injured heart. The only cell source that undisputedly gives rise to relevant numbers of human cardiomyocytes *in vitro* are human pluripotent stem cells (hPSC, Fig. 2), i.e. human embryonic stem cells (hESC), human induced pluripotent stem cells (hiPSC), human parthenogenetic stem cells (hPGSC) and human nuclear transfer-mediated ESC (hNT-ESC).

2.1. Direct cardiac reprogramming

In 2008 Zhou et al. showed that pancreatic exocrine cells can be directly reprogrammed to beta-cells by overexpressing a set of

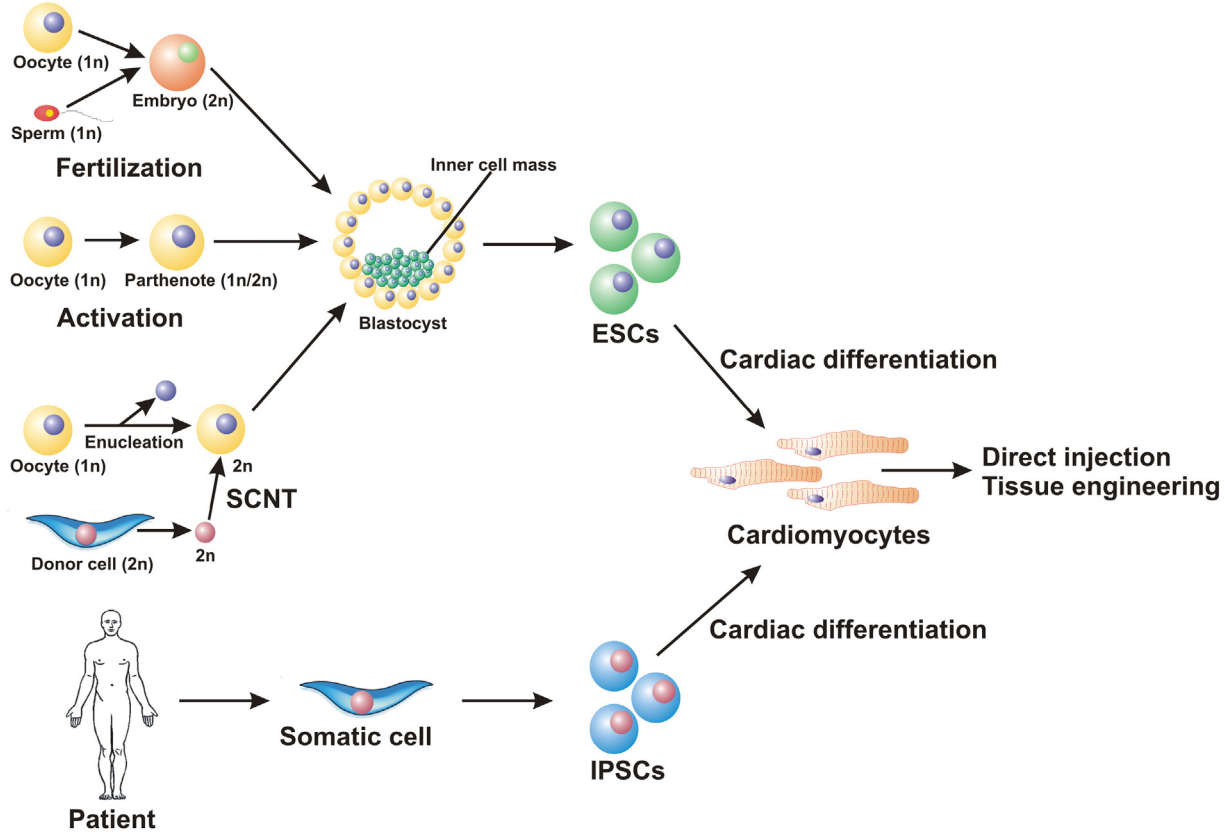

Fig. 2. Strategies for the production of cardiomyocytes from hESCs or hiPSCs.