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Review

Stem Cell Technology in Cardiac Regeneration: A Pluripotent Stem Cell Promise

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ABSTRACT

Despite advances in cardiovascular biology and medical therapy, heart disorders are the leading cause of death worldwide. Cell-based regenerative therapies become a promising treatment for patients affected by heart failure, but also underline the need for reproducible results in preclinical and clinical studies for safety and efficacy. Enthusiasm has been tempered by poor engraftment, survival and differentiation of the injected adult stem cells. The crucial challenge is identification and selection of the most suitable stem cell type for cardiac regenerative medicine. Human pluripotent stem cells (PSCs) have emerged as attractive cell source to obtain cardiomyocytes (CMs), with potential applications, including drug discovery and toxicity screening, disease modelling and innovative cell therapies. Lessons from embryology offered important insights into the development of stem cell-derived CMs. However, the generation of a CM population, uniform in cardiac subtype, adult maturation and functional properties, is highly recommended. Moreover, hurdles regarding tumorigenesis, graft cell death, immune rejection and arrhythmogenesis need to be overcome in clinical practice. Here we highlight the recent progression in PSC technologies for the regeneration of injured heart. We review novel strategies that might overcome current obstacles in heart regenerative medicine, aiming at improving cell survival and functional integration after cell transplantation.

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1. Introduction

Cardiovascular disorders remain the major cause of morbidity and mortality throughout the world. Over the last decades, death rates have even increased significantly (Nichols et al., 2014; Go et al., 2014). The heart, previously considered as a terminally differentiated organ with no regenerative capacity in post-natal life, has been documented to exhibit a limited degree of regeneration. As a consequence, the human heart regeneration capacity is unable to counteract the severe loss of heart muscle tissue during myocardial infarction (MI) or other myocardial disorders. Heart transplantation is the standard therapy to replace the injured heart. Several experimental studies and recent clinical trials assumed that stem cell-based transplantation might be indicated as an alternative and promising therapeutic strategy for heart failure. Multiple candidate stem cell types, including pluripotent stem cells (PSCs), have been evaluated in animal models and in clinical human studies for their ability to regenerate cardiac damage and reconstitute the cardiomyocyte (CM) loss.

This review describes the current research status on cell transplantation in animal models and humans. We discuss various stem cell types with cardiac regenerative potential in a clinically relevant setting, such as human embryonic (ESCs) and induced pluripotent stem cells (iPSCs), as well as adult stem cells derived from the bone marrow, mesenchymal tissues and the heart. In addition, we summarise some challenges that need to be overcome, and the future directions of stem cell-based therapies for *in vivo* cardiac regeneration.

2. Lessons From Embryonic Cardiac Development: Translating Embryology to PSCs

The formation of the three developmental germ layers, known as ectoderm, mesoderm and endoderm, is one of the most important hallmarks in embryogenesis. In the mouse, the early phase of gastrulation is characterised by the generation of the primitive streak (PS) in the epiblast that ultimately will form the posterior end of the embryo (Tam and Behringer, 1997). Uncommitted epiblast cells undergo epithelial-mesenchymal transition (EMT) and migrate through the PS to contribute to the embryonic structures and, finally, egress either as mesoderm or definitive endoderm derivatives (Fig. 1). Patterning in the PS is defined as anterior, mid and posterior regions with differential gene expression profiles and developmental potential. The heart originates from the cardiac mesoderm, which arises from the anterior PS. *Brachyury* (*T*) (Herrmann and Kispert, 1994) and *Mixl1* (Hart et al., 2002) are expressed throughout the PS, while *Foxa2* and *Goosecoid* are expressed mainly in the anterior regions (Kinder et al., 2001) and *HoxB1* and *Evx1* posterior (Forlani et al., 2003; Dush and Martin, 1992). The patterning of distinct subpopulations of mesoderm and endoderm is not random but seems to be a regulated temporal and spatial process. Mobilised epiblast cells diffuse through the anterior parts of the PS and generate cranial and cardiac mesoderm, and subsequently paraxial and axial mesoderm. Epiblast cells, which cross the most anterior region of the PS, derive definitive endoderm. Ectoderm develops also from the epiblast anterior region, although without entering the PS.

During gastrulation, the temporal and spatial determination of cell fates in different PS regions towards specific developmental lineages depends on the signalling cues in the surrounding environment. Members of the Transforming Growth Factor Beta (TGFβ) family (including BMP4 and Nodal) (Hogan, 1996; Conlon et al., 1994) and Wnt family members (Yamaguchi, 2001) play an essential role. Moreover, germ layer formation is a dynamic process that is tightly regulated by the coordinated activation and inhibition of BMP4, Activin/Nodal and Wnt signalling pathways (Gadue et al., 2005).

The BMP4, Activin/Nodal and Wnt signalling pathways are required in establishing the cardiovascular system. Mouse and human PSCs represent distinct development stages, although the signalling pathways regulating human PSC differentiation are comparable to pathways controlling differentiation in mice. Knowledge, obtained from mouse embryonic development studies, has been translated to *in vitro* differentiation of human PSCs to improve their differentiation efficiency towards CMs (Sumi et al., 2008). The Wnt/β-catenin pathway has a stage-specific biphasic role in cardiomyogenesis. It is required for mesoderm induction, whereas inhibition occurs during the specification of the cardiac progenitor phase (Naito et al., 2006). Stimulating mouse and human PSCs with BMP4 alone or in combination with Activin/Nodal induces *BRACHYURY* and *MIXL1* expression and the subsequent formation of KDR^+ and $PDGFR^+$ cardiac mesoderm (Laflamme et al., 2007; Kattman et al., 2011). The heart originates from the lateral plate mesoderm and develops in two distinct cardiomyogenesis waves from the primary (PHF) and secondary heart field (SHF). Both heart fields express *KDR* and the transcription factor *NKX2.5*, whereas the SHF is marked selectively by the transcription factor *ISL1*. These markers are useful to identify cardiac progenitor cells (CPCs) from PSCs. Finally, the PHF gives rise to the left ventricle and both atria, while the SHF develops into the right ventricle and outflow tract (Wu et al., 2006).

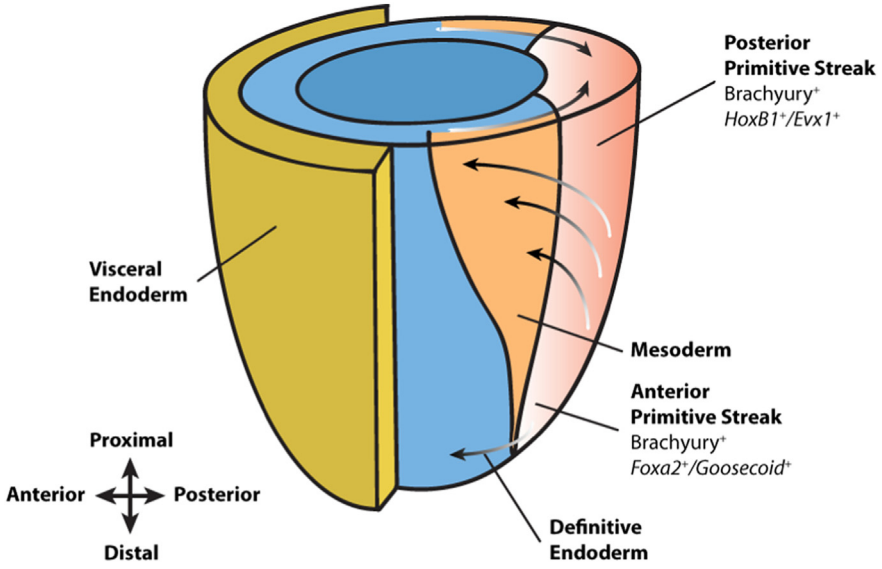

Fig. 1. Mouse gastrulation. Early primitive streak (PS) formation at 6.5 days after fertilisation. The posterior region of the PS coexpresses *Brachyury* and *HoxB1*/*Evx1*. The anterior region coexpresses *Brachyury* and *Foxa2*/*Goosecoid*. Epiblast cells enter the anterior PS (black arrows on top of the embryo) and generate cardiac mesoderm.

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