Induced Pluripotent Stem Cells for Post Myocardial Infarction Repair

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Introduction

The aim of this review is to study translational aspects of induced pluripotent stem cell technology in cardiac repair after myocardial infarction. This will be achieved by illustrating the current state of the art of this technology and, furthermore, by evaluating the limitations for clinical translation.

Induced pluripotent stem cells (IPSCs), are pluripotent stem cells obtained from somatic cells by the transient expression of four transcription factors: Oct4, Sox2, Klf4, C-Myc (OSKM). IPSCs are able to differentiate to any cell type. Therefore iPSC technology might be used to generate cells and used in regenerative medicine.

Figure 1. IPSC generation from a somatic cell. Later it can be differentiated into any cell type [*].

Myocardial infarction (MI) and derived complications are a source of high morbidity and mortality in the world. After MI, cardiomyocytes are replaced by fibrotic non-functional tissue and many complications can occur. IPSCs technology could be used to reverse the pathologic effects of MI.

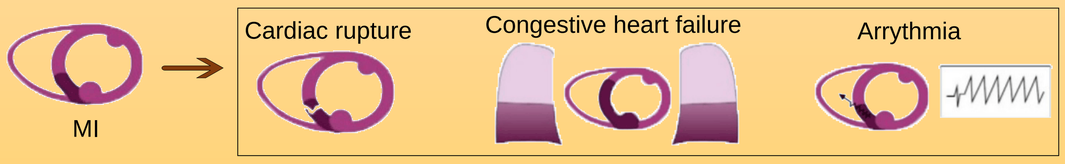


Figure 2. MI, and some complications derived of it. Adapted from [1].

Methods

The material used in this scientific review has been mainly obtained from books and scientific databases such as Pubmed, Google scholar and Researchgate. The literature was selected by journal relevance and sometimes limited to the past 5 years in order to obtain actual information. Some of the key words used were: myocardial infarction, iPSCs, scafolds, cardiomyocyte differentiation, reprogramming factors, among others.

Objectives

Search relevant information of the reviewed topic in scientific databases
Summarize the information obtained, make a scientific poster and a bibliographic review
Learn about the future perspectives of iPSCs technology and its clinical translation

Results

1 Reprogramming

Vectors are needed to introduce the OSKM reprogramming factors into somatic cells to induce pluripotency.

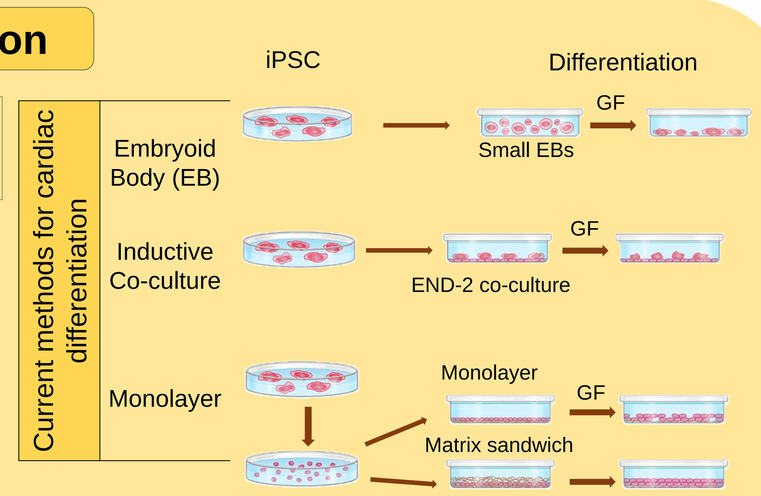
Integrative vectors	Non integrative vectors
Sendai Virus	Retrovirus
Episomal Plasmid	Lentivirus
mRNAs	

Plasmid and mRNAs are the preferred vectors for clinical translation. However, their efficiencies must be improved before

NOT FOR CLINICAL USE
Possible tumor formation due to insertional mutagenesis risk

2 iPSCs Differentiation

Figure 3. Current methods for iPSC cardiac differentiation. Adapted from [2]. GF: growth factor



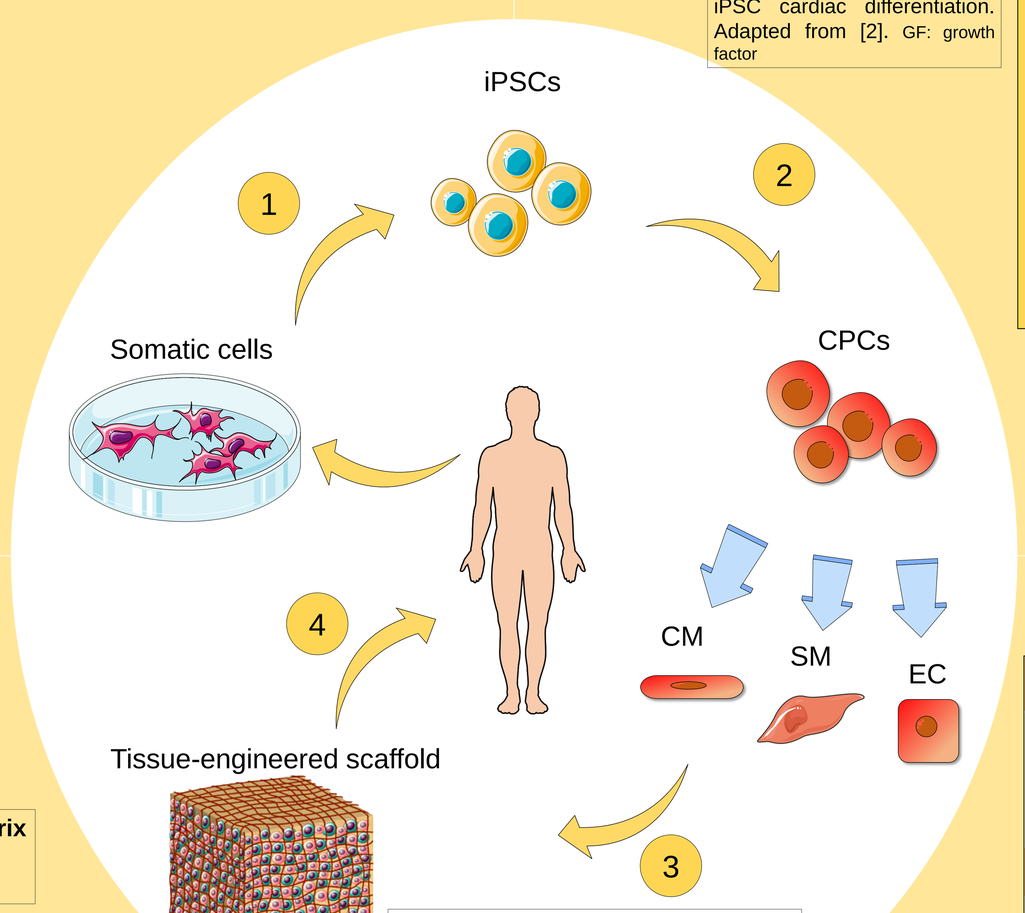


Figure 4. Cardiac cell therapy using iPSCs derivatives. CPC: Cardiac progenitor cell; CM: Cardiomyocyte; EC: Endothelial cell [*]

EBs Inductive	Co-culture	Monolayer
High cell heterogeneity Low reproducibility	Low differentiation rate	High efficiency Highly reproducible Allows full defining media conditions

3 Cell source

Undifferentiated iPSCs	Cardiac Progenitor Cells
Differentiate *in vivo* to cardiac cells Lead to tumor formation	Differentiate *in vivo* to cardiac cells Cardiac function improvement Prevent adverse remodeling Reduce scar size
Mature cardiomyocytes	**Endothelial Cells**
Increase cell proliferation Improve cardiac function Reduce scar size	Together with cardiomyocytes avoid electromechanic impairment Enhance reparation mechanisms

A combination of cardiac pluripotent cells and their derivatives seem to act synergistically increasing their therapeutic effect.

Undifferentiated iPSCs must be avoided

4 Delivery

Intramyocardial injection
Intravenous injection
Intracoronary injection

Low survival
Low cell retention (<10%)
Failed electrical coupling

Natural scaffolds
- Biocompatible
- Biodegradable
- Mimic myocardial function

Decellularized extracellular matrix
- Matches myocardium features
- Possible immune response

Fibrin
- Approved by the FDA
- Easy generation *in vitro*
- Positive outcomes with and without cells.

Epicardial scaffold implantation

Figure 5. Combined approach for amelioration injured heart. dECM: decellularized extracellular matrix. Based on [3]

Therapeutic effects

Cardiomyocyte proliferation		Paracrine signaling	
Infarcted size reduction	Increment of the graft size	Mobilization of endogenous progenitors	Cardiac remodeling prevention
		Neovascularization	Improved cardiac function

IPSCs use limitations

Limitation	Solution
Tumor formation	Use non-integrative vectors
	Not undifferentiated iPSC administration
Arrhythmia	Co-administration with EC
Immunogenic response	Autologous transplant
Low reproducibility	Standardize techniques
Low efficiency	Optimize current approaches

Conclusions

- iPSCs can differentiate to cardiac cells *in vitro* and *in vivo*
- iPSCs derived cardiac cells produce therapeutic effects in hearts after suffering from MI.
- Therapeutic effects mainly occur through paracrine signaling.
- Combination of multiple cell types, tissue engineering and prosurvival factors enhance graft therapeutic effect
- Some problems still need to be solved before clinical translation is occur

References

[1] Rozman, C. "Farreras-Rozman: Medicina Interna" 17ª edition. Volume I. Elsevier, Barcelona. (2012).
[2] Mummery C, Zhang J, Ng E, Elliott D, Elefanty A, Kamp T. Differentiation of human embryonic stem cells and induced pluripotent stem cells to cardiomyocytes: a methods overview. Circulation Research. 2012;111(3):344–358.
[3] Chen C, Sereti K, Wu B, Ardehali R. Translational aspects of cardiac cell therapy. J Cell Mol Med. 2015 Aug;19(8):1757-72
[*] Images created by the author