THE APPLICATION OF STEM CELL THERAPY IN CARDIOVASCULAR DISEASES

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INTRODUCTION

Heart injuris can lead to immediate death as a result of ischemia injury and tissue necrosis or to a progressive deterioration of the organ which may end up with heart failure. With the lost of contractile function, the remaining cardiomyocytes suffer a hypertrofic process, which is aimed to compensate for the loss. However, due to the overstraining, it could lead to a more debilitated muscle and, therefore, an increase of future infarctions. Indeed, **cardiovascular diseases (CVD)** are one of the main causes of mortality in the developed countries. In United States, CVD is reckoned to be the cause of 1 of every 3 deaths while in Catalonia, CVD are the second death cause in 45-84-year-old men and 45-74-year-old women. Current treatments are based on drugs and heart transplant but the limitations that these techniques present have lead to the research of new strategies. In this field, stem cell (SC) therapy is becoming more appealing due to its enormous potential. However, before clinical application is possible there are some questions to be answered.

THE APPLICATION OF STEM CELLS IN CARDIOVASCULAR DISEASES

EMBRYONIC STEM CELLS (ESCs)

• **What are embryonic stem cells (ESCs)?** ESCs are stem cells obtained from the inner mass cell of an embryo. They are considered pluripotent cells, which mean that they can become any kind of cell.

• **Advantages and disadvantages:** If it were not for ethical issues, their differentiation potential would make them the most promising stem cells for regenerative therapies. Ethical issues are not the only problem the ESCs have to face; evidences demonstrated tumorigenic properties and the fact that the use of ESCs for cellular therapies involves allogenic transplantation could lead to immunologic reactions.

• **How can we obtain cardiomyocytes (CM) from ESCs? :** Aggregates of ESCs form **embryoid bodies**, which mimic the body plan in embryo and spontaneously turn into CM. CM could also be achieved by inducing the expression **of cardiac identifying markers Isl1 and Flk-1.**

• **Important trials:**
  - ○ CMs derived from mouse ESCs were directly injected into mouse's heart. Only a few of them actually engrafted.
  - ○ Human-ES cells derived CM could normalise electrical heart block .
  - ○hES cells derived CM were directly injected into infracted myocardiom in rats and confirmed survival.

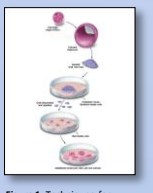

Figure 1: Techniques for Generating Embryonic Stem Cell Cultures [1].

Induced pluripotent stem cells (iPSCs)

• **What are induced pluripotent stem cells (iPSCs)?** iPSCs are pluripotent cells obtained from somatic cells that have followed a reprogramming process where transcription factors such as **Oct3/4, Sox2, c-Myc** and **Klf4 (Yamanaka cocktail)** are re-activated.

• **Advantages and disadvantages:** iPSCs become a solution for ESCs' ethical issues; and the ability to create autologus iPSCs from patients themselves prevents transplant rejection. Nevertheless, epigenetic characteristics of cells from which iPSCs are created could influence the differentiation patterns. Moreover, tumour formation remains a risk with iPSCs.

• **How can we obtain CM from iPSCs?** Human iPSCs can spontaneously differentiate into CMs. However, by the administration of compounds such as growth factors and/or cytokines, this ability is being potentiated.

• **Important trials:**
  - ○ Different populations of iPSCs have shown different cardiac differentiation efficiency → Nanog-iPSCs exhibit a greater beating efficiency than Fbx-15-iPSCs.
  - ○ To bypass the risk of producing tumors, cardiac cells were delivered from iPSCs *in vitro* and then injected into the infracted heart.

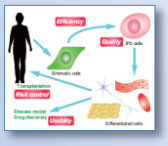

Figure 2: A shematic ilustration of iPS cell research and the applications [2].

ADULT STEM CELLS

MESENCHYMAL STEM CELLS

• **What are mesenchymal stem cells (MSCs)?** They are a group of undifferentiated cells of the bone marrow. Like any adult stem cell, they maintain their multipotent feature.

• **Advantages and disadvantages:** The main advantage of these cells is that they are easy to obtain, apart form the fact that they can be obtained from the patients themselves so there are not problems of transplant rejection. The fact low rate to differentiate into another cell type could be considered as a disadvantage.

• **How can we obtain CM from MSCs?** Indeed, their capacity to become CM is being dubious. Instead, they are thought to act by means of **paracrine signalling.**

• **Important trials:**
  - ○ Studies showed that MSCs die within few days after heart transplantation. Only 2% of MSCs engraftments differentiated into CM. Nonetheless, long term effects have been proved. → The low percentages could not explain heart regeneration. Thus, effects may only be explained by paracrine functions.

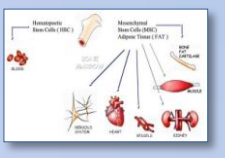

Figure 3: Bone marrow as a source of adult stem cells [3].

CARDIAC STEM CELLS and PROGENITOR CELLS

• **What are cardiac stem (CS) cells?** CS cells are adult stem cells located in heart tissue. Before their discovery, human heart was considered a non-regenerative organ. **And progenitor cells?** Progenitor cells (PCs) are unspecialized or partially specialized cells that are capable of undergoing cell division and yielding two specialized cells. They are considered unipotent cells (or oligopotent). Sometimes they are equiparable to adult stem cells. **And what are cardiosphere-derived cells (CDCs)?** CDCs are multicellular clusters from cardiac cells cultured in nonadhesive substrates.

•**Advantages and disadvantages:** Apart from developing new CM, CS/PCs could help by paracrine factors and angiogenesis. They could be obtained directly from the patient's heart itself (although allogenic transplant is also possible). Moreover, due to their origin, they are already committed to become cardiac cells, so it is easier to differentiate them into CM.

• **How can we obtain CM from CS/PCs?** Firstly, CS cells are obtained by biopsy specimens. Once they are obtained, they are harvested and cardiac progenitor markers, such as **c-kit, sca-1 and islet-1** are selected by antibodies. Within 1-2 months, millions of CS cells can be obtained, ready to administered to the patient.

• **Important trials:** Thus far, all the clinical trials focusing on the potentiality of SC for treating heart diseases are based on CS/PCs. Two of them, CADUCEUS and SPICIO have encouraging results.

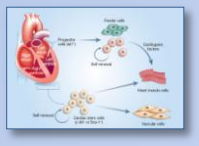

Figure 4: Cardiac cells for cardiac transplantation therapy [4].

CLINICAL TRIAL

• **CADUCEUS (CArdiosphere-Derived aUtologous Stem Cells to Reverse ventricular dySfunction)**

  - ○ **Purpose:** determine whether giving CDCs to patients with decreased heart function was safe + examined whether it could decrease the amount of heart muscle damage and/or improve heart function after a heart attack.

  - ○ **Results:** Decrease in scar mass and an increase of viable heart mass and regional contractility 6 months after treatment.

• **SCIPIO (Cardiac Stem Cell Infusion in Patients With Ischemic CariOmyopathy)**

  - ○ **Purpose:** study the safety of intracoronary CS therapy in humans.

  - ○ **Results:** increase of 9% in LVEF (Left ventricular ejection fraction) 4 months after the treatment. Moreover, infarct size was significantly reduced.

TISSUE ENGINEERING

One of the main problems the stem cell therapy has to face is **the washing out of injected cells** through coronary circulation. **Tissue engineering** become a possible solution to this issue. It is focus on creating a functional myocardial tissue graft that could be implanted on the surface of the infracted heart and act as a cellular delivery vehicle. The injected cells are mainly immature cardiomyocytes or stem cells. However, there is still controversy about whether their maturation should take place before or after the transplantment.

• Scaffolds:
  - Biodegradable scaffolds
  - Hydrogels
  - Scaffold-free tissues

CONCLUSIONS

• **ESCs** are the ones with the highest differentiation potential but they cannot be used in clinical application due to their ethical and tumorigenic issues.

• **iPSCs** a really promising group due to their pluripotential features, yet improvements in techniques are required to avoid tumorigenic reactions, as well as to control cell reprogramming.

• **CS/PCs**. The fact that they are already committed to become CM makes them good candidates for cardiac regeneration. They are the ones leading clinical trials thus far.

• The use of **engineering techniques** does not only seem to improve the survival and cardiac function but also the retention of transplanted cardiogenic cells.

To sum up, although the use of SC in cardiac regeneration represents an innovative and appealing treatment for CVD, there are still many challenges that need to be solved before they could be used in clinical applications.

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