THE APPLICATION OF STEM CELL THERAPY IN CARDIOVASCULAR DISEASES

INTRODUCTION

Heart injury can lead to immediate death as a result of schema 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 hypertrophic process, which is aimed to compensate for the loss. However, due to the overstretching, it could lead to a more destabilized muscle and, therefore, an increase of future failures. 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.

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• What are embryonic stem cells (ESC)? 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: It is 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 ESC have to face; evidences demonstrated tumorigenic properties and the fact that the use of ESCs for cellular therapies involves allagic transplantation could lead to immunologic reactions.

• How can we obtain cardiomycytes (CM) from ESC?: 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 Nkx2.5 and Fil-1.

• Important trials:
  • CMs derived from mouse ESCs were directly injected into mouse’s heart. Only a few of them actually engrafted.
  • Human ESCs derived CM could normalise electrical heart block.
  • CMs derived ESCs were directly injected into myocardial ischaemia in rats and confirmed survival.

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

• Advantages and disadvantages: The main advantage of these cells is that they are easy to obtain, apart from 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 tools to act by means of paracrine-signalling.

• Important trials:
  • Studies showed that MSCs die within few days after heart transplantation. Only 2% of MSCs engraftment 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.

• 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 (PG) cells (Progenitor Cells): Progenitor Cells (PG) are unipotent 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 cardiovascular-derived cells (CDGs): CDCs are multicellular clusters from cardiac cells cultured in nonadhesive substrates.

• Advantages and disadvantages: Apart from developing new CM, CS/PGs could help by paracrine factors and angiogenesis. They could be obtained directly from the patient’s heart itself (although allogenic transplantation 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/PGs?: Firstly, CS cells are obtained by biopsy specimens. Once they are obtained, they are harvested and cardiac progenitor markers, such as CD45, CD133 and CD105 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/PGs. Two of them, CADUCUS and SPIDCO have encouraging results.

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

• iPSCs are 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/PGs: 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 function of heart cells, 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.

REFERENCES