The Role of Stem Cells in Degenerative Heart Diseases

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ABSTRACT
Degenerative heart diseases remains a burden both in modern and developing countries despite the advances in medical treatment. One key factor is that heart muscle (cardiomyocyte) has few capability to regenerate. Various source and type of stem cells might be potential to overcome the problem, but the results of several studies are mixed, some showed benefits, but also showed adverse effects. Further investigations are still needed.

Keywords: Stem Cells, Heart, Cardiomyocyte, Heart Failure

BACKGROUND
Despite the advantages in the management of degenerative heart diseases, including the availability of several new lines of medicine and invasive cardiology, the rate of hospitalization and mortality still remains high.

In 2002, McMurray reported that people suffering from CHF is around 5 million in the US and 6.5 million in Europe with a very high mortality rate. It was once believed that cardiac myocyte has poor or very limited capability to regenerate and create new cells, thus unable to overcome the damage caused by degenerative diseases with high mortality and morbidity rate.

Heart transplant might be the last option, but among several problems, the biggest is the availability of suitable donor. Other problems are the cost of the procedure, the prolonged use of immunosuppressive drugs and risk of organ rejection.

In the past few years, scientists have found that heart muscles (cardiomyocyte) are actually capable of regeneration, and there are several hypotheses on the mechanism. First, it was suggested that the adult cardiac myocyte itself, triggered by injury, might reenter the cell cycle and divide. Second, stem cells originated from bone marrows, guided by certain cellular signal, might enter the heart via vascular route, and then differentiate into cardiomyocyte in the injured area. Third, the repair is performed by stem cells within the heart itself.

Based on the hypothesis, scientists began to experiment on a different approach to treat degenerative heart diseases such as myocardial infarction and heart failure, using stem cells which in nature has the capability to regenerate and differentiate; early studies showed some very promising results. The still unanswered questions, among others, are: is this procedure really useful?, what is the risk?, which is the most suitable stem cell?, and what is the best route of administration?

INTRODUCTION
Stem cells has been recognized for decades, the most widely used source of stem cell is bone marrow, used as treatment for various blood diseases, mainly leukemia. Other source of stem cell were searched; scientists isolated stem cells from animal embryo, and in 1988, stem cells were isolated from human embryo. The other breakthrough is perhaps the discovery of the cord blood as the potential source of stem cells. In 1988 the first cord blood transplant for Fanconi anemia patient was performed. This success has expanded the source of stem cells that can be used to treat diseases.

STEM CELLS TYPE
Stem cells can be classified according to sources: embryonic stem cells from human embryo, and adult stem cells from bone marrow or peripheral blood. Recently stem cells is also collected from the umbilical cord blood and placenta, expanding stem cells source, as well as their potential use in treatment. Embryonic stem cells (ES or ESC) this is the most primitive form of stem cells found in early form of embryo, called blastocyst. These cells can differentiate into any cells from the human three embryonic layer (exoderm, mesoderm, endoderm). Blastocty contains two layers of cells; after attachment to the uteruus wall, the outer layer will form the placenta, the body of fetus. The embryonic stem cells is collected from the inner layer of the blastocyst and then cultured.

Since it is an undifferentiated stem cells there is a probability to develop teratoma. But the main issue is perhaps the legal and ethical aspects. Collections of the inner layer will prevent further development of blastocyst, and is considered to be unethical. Other ethical issue is regarding the source of blastocyst, which is usually obtained from the excess of IVF (in vitro fertilization) process. Many countries prohibit the use of embryonic stem cells as experiment material.

Adult stem cells
Because of issues surrounding the use of embryonic stem cells, scientists look for other sources of stem cells in various tissue such as, bone marrow, peripheral blood, muscle, adipose, umbilical cord and even local heart tissue.

a. Haemopoietic stem cells
Sometimes abbreviated as HSC, these cells can be found in adult bone marrow, peripheral blood circulation and cord blood. These cells are known for their capability to reproduce and differentiate into all kind of blood cells. One cell is capable of producing up to 1015 cells. But although HSC has been used widely for treating blood disorders, their benefit in the treatment of heart diseases remains unclear. Markers related to this cell are CD34, CD45low, Thy-1 (CDw90), c-kit receptor (CD117), CD13, and negativity towards CD38 and lineage markers (Lin−).

TINJAUAN PUSTAKA
b. Endothelial progenitor cells

Sometimes abbreviated as EPC, EPCs have the capability to enter circulation, proliferate, and differentiate into mature endothelial cells. Thus it might be a reasonable treatment for endothelial disorder. This cell is also proven to be involved in the neovascularization process when injected into animal models with ischemia.1-6. EPCs can be found in bone marrow, scarcely in the peripheral blood, and is abundant in cord blood. EPCs from umbilical cord blood also seems to have greater proliferation capability and lower apoptosis, and therefore might be a better option in vasculogenesis and heart tissue therapies.6,7

A strong correlation is found between the number of circulating endothelial progenitor cells and the subject’s combined Framingham risk factor score − lower EPCs are related to higher risk of cardiovascular event, or higher score. Another report also showed similar result.9 These findings suggested that endothelial damage is actually a balance between injury and repair capacity, and EPCs are thought to be an important part of the process. It might be difficult to distinguish the EPCs from the MSCs, since they share some similarity due to their same origin, which is the hematopoietic — common markers associated with these cells are CD34+ CD133+ and CD45.1,2

c. Mesenchymal stem cells

These cells have the capability to proliferate and differentiate into various mesenchymal tissue, depending on the location, such as osteogenic, adipogenic, chondrogenic, myogenic, cardiac-myogenic and others.2

Bone marrow is still the most common source of these cells, but their capability to proliferate and differentiate increase at increasing age. There is also concern on the invasive procedure needed to collect the cells from the bone marrow. Recently, it has been shown that umbilical cord blood (UCB) also contain this type of stem cells, it is also suggested that umbilical cord placental stroma contain the MSCs as well.2,12 Markers for MSCs are still controversial, some research showed expression of certain markers, while others showed the absence of the same marker. The widely accepted phenotyping is perhaps the absence of the hematopoietic marker, CD34 and CD45.1,13.4

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The activity of hMSCs is increased in acute pathologic state, but in prolonged ventricular decompensation and end-stage cardiac failure their ability is decreased.1,13 Markers related to these stem cells are c-kit, CD105, or Sca-1 reac-
tive protein and negativity towards the anti-
gens of hematopoietic markers.5,12,13

hMSCs are naturally involved in the regenera-
tion of the heart, and will mostly differentiate into cardiac myocyte. This fact made hMSC the ideal stem cells for repairing damaged heart.1,13 hMSCs studies and trial on human have been performed, but the main obstacles are that adult cardiac stem cells are scarce in nature, and hard to be identified.3

e. Muscle-derived stem cells

Also known as myoblast or satellite cells, these cells are more suitable to be classified as pre-
cursor cell rather than stem cell, and can be found in the basal membrane of skeletal muscle fibre.3,13

After injection into the damaged myocardium, these cells can proliferate and differentiate into striated muscle within the heart, which will improve cardiac function, but problems of anyhymia occurs may be affected when tissue is affected by ischemia.13 The repair mechanism is still undergoing debate on the mechanism of repair, but there is evidence that stem cells injection has resulted in formation of new cardiac myocyte, vasculogenesis and improving blood flow.13

Unlike cardiomyocyte, skeletal myocytes are more resistant to apoptosis, more easily cultured and require shorter period, enabling to collect suffi-
cient number of cells for transplantation.1,2 But some experiments showed that myoblasts might induce ventricular anhymia in model rat.1,3

f. Other stem cells

Other-stem cells include adipose-derived stem cells, neural stem cells, hepatic stem cells, pan-
createic stem cells, stem cells of the skin, lung epithelial stem cells, intrastem cells.4,6,7 Other stem cells are also being searched within bone marrow or cord blood, but their presence and usage still require further studies.11

DELIVERY METHOD

Currently, there are three known methods of deliv-
ering stem cells into the heart: the peripheral intravenous stem cell mobilization and direct injection into cardiac muscle no study shows the superiority of certain technique over the other.11,13

The peripheral intravenous administration and mobilization are the easiest and minimal invasive way, it is based on the thought that in-
jured area in the heart can attract and activate stem cells by certain homing signal via the cytokines and other cellular mediator, and after reaching the injured muscle, the stem cells will then proliferate and differentiate into cardiac muscle. However, scientist must find the correct “signal” so the regeneration process is actually performed in the heart and not in other organ.9

To accurately deliver the stem cells into the injured area, several techniques have been used, including direct epicardial myocard cell injection, usually performed during a surgical intervention (e.g. coronary artery bypass graf-
ing, anhymia surgery, cellular assist device implantation, and valve repair).10 Other delivery method using catheter to deliver the stem cells had also been used.10

THE REPAIR MECHANISM

There is still ongoing debate on the mecha-
nism of repair, but there is evidence that stem cells injection has resulted in formation of new cardiac myocyte, vasculogenesis and improving blood flow.11,13

Improvement in perfusion, differentiation of myocytes, increase in vessel numbers, improving in vivo viability and viability in infarct area, restoration of wall viability, increase in life quality and NYHA class, improvement in haemodynamic parameter, survival and enlargement of myocytes and reduced angular symptoms.11,13,14 Remodelling of the extracellular matrix (ECM) play an important role in the development of ventricular dilatation and ultimately lead to heart failure. Stable matrix is essential to pre-
vent cell lost and improving heart function. Stem cells have the capability to increase the matrix stability by preventing ECM degrada-
tion or restoring damaged ECM.10,16,17

Clinical Trial

Different trials, using various source of stem cells, delivery method, patients diagnosis, follow up period and result have been done in the past few years. The reported trials show promising results, such as improvement in cardiac function, angiogenesis and vasculogenesis plays a crucial role, not only by improving perfusion to the

REFERENCES

b. Endothelial progenitor cells

Some time ago it was believed that EPCs had the capability to enter circulation, proliferate, and differentiate into mature endothelial cells. Thus this might be a reasonable treatment for endothelial disorder. This cell is also proven to be involved in the neovascularization process when injected into animal models with ischemia. EPCs can be found in bone marrow, scarcely in the peripheral blood, and is abundant in cord blood. EPCs from umbilical cord blood also seems to have greater proliferation capability and lower apoptosis, and therefore might be a better option in vasculogenesis and heart tissue therapies.

A strong correlation is found between the number of circulating endothelial progenitor cells and the subject's combined Framingham risk factor score - lower EPCs are related to higher risk of cardiovascular event, or higher score. Another report also showed similar result. These findings suggest that endothelial damage is actually a balance between injury and repair capacity, and EPCs are thought to be an important part of the process.

It might be difficult to distinguish the EPCs from the MSCs, since they share some similarity due to their same origin, which is the hematopoietic, common markers associated with these cells are CD45, CD34, CD133, and KDR. EPCs are naturally involved in the regeneration of the heart, and will mostly differentiate into cardiac myocytes. This fact made it hard to distinguish the ideal stem cells for repairing damaged heart, since all these cells are CD34+ CD133+, and KDR. Recent studies have shown that umbilical cord blood also contain this type of stem cells, and bone marrow is still the most common source of these cells, depending on the location, such as osteogenic, myogenic and others. As a result, the bone marrow is the best delivery method, dose and other issues. Some experiments showed that myoblasts might induce vascular anastomosis in model rat.

Recently, it has been shown that umbilical cord blood (UCB) also contain this type of stem cells, as well as that umbilical cord placental stroma contain the MSCs as well. Markers for MSCs are still controversial, some research showed expression of certain markers, while others showed the absence of the same marker. The widely accepted phenotype is perhaps the absence of the hematopoietic marker, CD34 and CD45. The widely accepted phenotype is perhaps the absence of the hematopoietic marker, CD34 and CD45. The activity of hKSCs is increased in acute pathologic state, but in prolonged ventricular decompensation and end-stage cardiac failure their ability is decreased. Markers related to these stem cells are CD34, CD133, or SC-1, react to re- active protein and negativity towards the anti- genic hematopoietic markers.

In most cases, the cell of origin is unknown. It was a long-held belief that heart muscles as well as neurons, are a static object in term of regeneration, which mean they cannot proliferate. But recent data shows that there are some stem cells in human heart, cardiac myocytes can undergo both hyperthrophy and hypoplasia. These cells also known as hKSCs, have the capability to reproduce itself and differentiate into various type of cells, mainly cardiac myocyte, also capable of forming smooth muscle and endothelial cells.

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