The progress of cardiac stem cell study

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Abstract

It summarized the recent results and clarified the kinds of cardiac stem cells. Then the paper overviews the method inducing stem cells into cardiomyocytes. It also shows the clinic works having been made about cardiac stem cells. Almost all clinic studies have a significative conclusion increasing ejection fraction of heart. Through that it discusses the modifying technology regulating stem cells. At last the article reveals the biological organ future of clinic transplantation.

Key Words

Heart failure; Cardiac stem cell; Modification; Transplantation

At present the treatment of heart disease have much difficulty. The main causes are due to that drug therapy and percutanenus coronary intervention (PCI) or coronary artery bypass grafting (CABG) could not increase the number of cardiomyocytes, so the cardiac function does not enhanced much better. According to this, the numbers of cardiomyocytes is the key. In a single day the heart failure happens, both drug therapy and PCI can also not increase the number of cardiomyocytes and the heart function. With the development about stem cell researches, many studies have testified that transplanting of cardiac stem cells can enhanced the ejection fraction (HF) and cardiac function [1]. The stem cell treatment outstandingly prolongs life-span and improves the prognosis of the patient suffering from heart failure [1, 2].

1 The kinds of cardiac stem cells

1.1 **The cardiac stem cell (CSC)** At past the heart has been thought no stem cell and is final-stage cell. But until recent years, people find that the heart just like other tissue as having stem cell. The speed of heart self-healing is very slow about 1% per year [3, 4]. This cannot satisfy the need of clinic treatment. So we must study a new treating method with cardiac stem cell to enhance the number of myocardium. It's the future for treating heart failure.

1.2 **Bone mesenchymal stem cells (BMMSCs)** Because of the source enough, processing easy and possible adopting repeatedly it has been used wide field. BMMSCs can be induced and differentiated cardiac cells with many methods [5, 6]. However the number of cardiac differentiated cell is too little to renovate the myocardium. So at present many studies mainly researches the inducing method to increase the number of myocardium. Only the heart has enough number of myocardium to ensure the contractility and ejection fraction. The heart failure could not be happened.

1.3 **Adipose-derived stem cell (ADSC)** Due to drawing ADSC simple and the number enough it has much usage broadly. At present ADSC mainly used as the regeneration of skin and skeletal muscle [7, 8]. This has made obvious progress and clinic effect.

1.4 **Hematopoietic stem cell (HSC)** It is early discovered as stem cell and used to clinic treatment. Now HSC can go through simple cultivating to treat the disease of hemopoietic system [9]. HSC can be extracted from blood and bone marrow. Until now few million patients have treated hemopoietic disease with HSC.

1.5 **Neural stem cell (NSC)** NSC is originated from neural tissue. Many studies have showed treating neural disease with NSC is very effective, especially in the patient of spinal cord injury and Alzheimer disease.

1.6 **Hepatic stem cell (HPSC)** HPSC is originated from hepatic tissue. It can differentiate cardiac cells with appropriate inducing method [9, 10]. But because of achieving hepatic tissue difficulty few studies do it. At present HPSC mainly used as the repair of liver.

1.7 **Embryonic stem cell (ESC)** Now ESC is one of hotspot problem in stem cell field. ESC can differentiate and cultivate myocardium tissue easy. In the future ESC may be the main material of biology organ [11, 12]. But ESC has ethical issue. So at present ESC method has law problem.

1.8 **Induced Pluripotent stem cells (IPSC)** With biotechnology we can draw IPSC from somatic cell. DNA PCR can help to improving IPSC gene sequence [13, 14, and 15]. This makes the IPSC more effectively. Now the world researchers pay close attention to IPSC studies. It may be the future of stem cell filed.

2 Induced methods of cardiac stem cell

2.1 5-azacytidine technology (5-azaT) It is a typical method inducing stem cell transforming to myocardium cell. Although many inducing methods are discovered, but 5-azacytidine technology is still frequently adapted to experiment. Many new inducing methods of stem cell also compares with it for best result. The ratio inducing stem cell to myocardium cell of 5-azacytidine technology is about 17% ~ 19% [16-17].

2.2 **Angiotensin-II technology (Ang-IIT)** This method can markedly enhance the differentiating ratio of stem cell about 10 percent. It also has low cell toxicity and can promote the growing of myocardium cell. The ratio inducing stem cell to myocardium cell of Angiotensin-II technology is about 22% ～ 24% [18-20].

2.3 **P53-inhibitor technology (P53-IT**) This inducing method is recently researched. Until now it is best technology to induce stem cell differentiating to myocardium cells. It also has low tumorigenicity and high safety. The ratio inducing stem cell to myocardium cell of P53-inhibitor technology is about 27% ~ 29% [21, 23].

2.4 **Matrix metalloproteinase technology (MMPT)** Matrix metalloproteinase is nature in the body. Its toxicity is only due to the concentration super to the tolerance degree of human. Under the degree it is very safety. The ratio inducing stem cell to myocardium cell of Matrix metalloproteinase technology is about 19% ~ 23% [24].

2.5 **Combined inducing technology (CIT)** Such as 5-azaT and Ang-IIT, 5-azaT and P53-IT, 5-azaT and MMPT, Ang-IIT and P53-IT, Ang-IIT and MMPT, P53-IT and MMPT etc, many studies have shown that combining two kinds of inducer can promote the differentiation rate of stem cell. The inducing ratio could be enhanced about 6%～10% [25].

3 Clinic work about stem cell

3.1 **Ischemic cardiomyopathy (ICP)** When coronary heart disease progressing to ischemic cardiomyopathy, the patient will capture heart failure. This means that the number of myocardial cell is absolutely or relatively cut down. That can't keep up the contractility of myocardium, so the ejection fraction and circulating blood volume are descending [26]. The key treating this condition is increasing the numbers of myocardial cells. Many studies about stem cell have shown good conclusions improving heart function [1, 6, and 27]. These studies include

intra-myocardium injection during surgery and percutaneous coronary artery injection of stem cells. The ejection fraction of the heart could increase about 5% ~ 10% [28].

3.2 **Hypertensive heart disease (HHD)** Hypertension not treating for long time can result in myocardial hypertrophy and less contractility. Then it will happen to ejection fraction lower and heart failure. In a short time the effect on heart failure treating with the cardio tonic drug is unsatisfactory. Some studies about HHD treating with stem cell have shown good results [29]. EF almost can get well normally.

3.3 **Postpartum cardiomyopathy (PCM)** It is due to delivery and amniotic fluid absorbing. The patient often has serious heart failure and edema. Common drug treatment for PCM heart failure does not have good effect [3, 7]. Most patients have long-time heart failure. Since 2005 year we try to treat PCM with stem cell. About 15 patients being systematically treated for 3～6 M every one almost gets very good effect and ejection fraction recovery normally. This conclusion shows that treating PCM with stem cell is better perspective [14].

3.4 **Dilated cardiomyopathy (DCM)** The cardiac gene abnormal can result in DCM. Most DCM patients have serious heart failure. Routine therapy of medicine is difficulty to maintain the heart function. Many patients only live for about 5 years [2, 8, and 11]. Most effective therapy is heart transplantation. Though some studies have treat DCM with stem cell, but the curative effect is poor. Then a few studies adopting stem cell to treat DCM more one times can enhance the ejection fraction about 10 percent. Maybe the number of stem cell is the key to treat it well [10].

3.5 **Other kinds of heart failure** These kinds of heart failure commonly treat with medicine and the therapeutic effect is very good [16, 19, 24]. These patients include of arrhythmia, valvular heart disease, other special myocardiopathy etc. Until now no paper reports the effect of stem cell on them.

4 Cell regulating and controlling

4.1 **The gene coding regulating and controlling** Many studies have shown that changing some cardiac gene coding can control the stem cell growing and dividing course [1, 8, 26]. According to this result people can cultivate perfect stem cell and organ tissue or biological organ. Such as regulating microRNA should extend the stem cell life-span [17, 19]. Regulating some coding or chemical material can make the somatic cell into induced pluripotent stem cell. These cells could renovate and supersede the damaged and dead cardiomyocytes and tissue.

4.2 **Cell signal pathway regulating** Some researches have confirmed that regulating cell signal pathway can not only intervene metabolic level but also regulate the cell dividing and growing. Such as P51 to P53 pathway etc suppressing P53 expressing can enhance the dividing speed of BMSCs to 37% [16, 25]. Some researchers have combined this method with chemical material to induce stem cell, gotten satisfied result.

4.3 **Protein regulating** Many protein such as MAC and PIM can regulate the growth and cell dividing [23, 28]. One study about MAC has shown that it can induce stem cell or IPS cell into myocardial cell and has the function of myocardium. Another study about PIM also has the similar result. By this token the protein regulating stem cell into myocardial cell is another very important way.

4.4 **Physical chemistry factors** It is clear that these two kinds of factors can affect stem cell dividing and growing. Most researches have confirmed this conclusion [5, 12]. Such as magnetic field, electric field, PH value, etc. all could impact the stem cell dividing and growing. Some researches cultivate stem cell by vibrating moving, they have developed some special myocardial tissue.

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5 Future developments

5.1 **Regenerative medicine of stem cell repair** The mechanism treating heart disease with stem cell is mainly repairing the impaired myocardial cell. This action almost relies on cell fusion and signal transduction [7, 15, and 22]. These make the damaged myocardial cell renewing and recovering the function. Some studies have shown this effect.

5.2 **Biological organ** Gene modifying of stem cell or iPS by PCR can cultivate out biological heart in the near future [7, 11, and 19]. Doctors would transplant it into the patient with heart failure. The patient would recover from the disease. It will be main curing method in this filed. This can enhance the level treating myocardiopathy [23].

5.3 **Prolong life-span** Some studies have shown that injecting stem cell into the heart and brain can make the organ tissue cell becoming more archaeus and younger [13, 19, 24]. This would enhance the immunity and life-span. Doctors have pay attention to the results. In the near future peoples would like to make use of this kind of method to prolong life-span [22～26].

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