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Stem Cells in Cardiac Diseases: Using Always-new Material to Fix the Crucial Organ

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ABSTRACT

Heart diseases is one of the most common diseases that people are facing currently, including coronary artery disease, arrhythmia, cardiomyopathy, and heart failure. Heart disease is responsible for most of the death globally, causing about 1 in 4 deaths, since heart is one of most important organs in organisms. There already have been several ways dealing with the heart diseases, such as medical treatment, operations, regulation in daily diet, coronary artery bypass graft, heart transplantation and so on. A entirely new approach, which is called stem cell therapy tßechnique was also developed and gradually introduced to the public. Stem cells are able to differentiate into the different type of cells needed for the treatment. Whenever the therapies take place or what ever the organs needed, stem cells can always fulfill the requirement. As an always-new material, stem cells have broad prospects since it can help figure out some diseases that have no treatment now as it provides a entirely new approach of thinking.

Introduction

Heart disease, or cardiovascular disease (CVD), is the class of diseases that involve the heart or blood vessels. It mainly includes coronary artery disease (CAD), including stroke, heart failure, and so on. The underlying mechanisms vary depending on the disease. CVD, stroke, hypertensice heart disease is always caused by smoking, obesity, lack of exercise, and so on. These behaviors will lead to atherosclerosis, which is the developing of abnormalties, called lesions, in blood vessels and caused vessels to be narrower. The therapy mainly includes operations that either remove the lesions or broaden the radius of vessels, daily diet and exercise regulating, and medicines taking. However, there are demerits of all these three approaches on treating CVD. Operations may damage on the inner membrane of blood vessels, or even the damage on some crucial blood vessels and cause the leakage of blood. Controlling daily diet and exercise is effective, but it is not suitable for those patients who are in emergency since it requires a period of time. Besides, its effect is also different to patients. Taking medicines is a good approach. However, it also requires a relatively long period of time for showing its effect. Some side effects of taking medicines are also not negligible. By contract, stem cell therapy, which is a new development approach, has nearly none of these disadvantages mentioned above. It can both show its effect immediately after it is carried out and have few side effects.

Stem cells are the cells from which all other cells with specialized functions are generated. The process of the development from a stem cell to different types of cells required is call differentiation. The ability of stem cells of self-replicating also allows cells multiplication. Nowadays, stem cell therapy has already utilized in several diseases,

including Crohn's Disease, Multiple Sclerosis, Lupus, and of course, cardiovascular diseases (Yamanaka, 2020).

There are several merits that stem cells therapy have but those traditional ones don't. For instance, stem cell therapy is nearly suitable for every patient since doctors can artificially match the most suitable stem cells to offer a tailored therapy. According to their body conditions, such as their blood types, their doctors can determine their human leucocyte antigens (HLA) value and help find them suitable stem cells so that they doesn't need to suffer from rejection reaction (Clausen & Hakomori, 1989; Ito & Hirota, 1992; Taylor et al., 2011). One such example is cord-tissue derived mesenchymal stem cells, which are cells that have not differentrated yet. There are some similarities between the stem cell therapy and organ transplantation since both of them are the introducing a new part into human body. Nevertheless, there is a high possibility that organ transplantation may cause body rejection, which means that extra medicines have to be taken in order to suppress such reaction. In addition, compared with simple medication, stem cell therapy takes effect more quickly. And its side effects are far fewer than those brought by taking medicine. At the same time, patients do not need to spend a lot of money for follow-up continuous treatment after receiving stem cell therapy. However, if medication is long-term, the total amount of money consumed will be much greater than stem cell therapy.

According to different differentiation potential, stem cells can be divided into three categories, listed from high including totipotent stem cells, pluripotent stem cells and unipotent stem cells. Totipotent is the type of stem cell that have differentiational potential to become a complete organism, such as zygote. In other words, totipotent stem cells are the stem cells that can differentiate into the largest number of different types of cells. Pluripotent is the descendent of totipotent. It fails to develop into an individual but is able to develop into multiple tissues. Unipotent cells can only produce themselves,but have the property of self-renewal. Because of the limitation of unipotent stem cells, it is seldom used in stem cells treatment. Totipotent stem cells can also serve as a tool of therapy assistance, but its application is also relatively limited. The most widely used one is pluripotent stem cells. This is also the field this review going to focus on.

Totipotent stem cells

The totipotent stem cells are the type of stem cells that contribute the most to the development of heart diseases treatment since it is able to differentiate into every cell required in different experiments or treatment.

What makes totipotent stem cells different from pluripotent stem cells is their ability and potential to differentiate and proliferate into a whole organism, which enables and makes them suitable for long-term organ regeneration. Totipotent cells can replicate nearly unlimited and differentiate into almost every type of stem cells, such as heart(Avasthi et al., 2008). Moreover, these cells can also keep their totiponcy while replicating into 16 genetically identical cells within 4 days. By contrast, when zygote replicates into 16 cells, it loose its totiponcy, which shows the special characteristics of totipotent stem cells(Makhani et al., 2015).

The high ability of keeping totiponcy in totipotent stem cells were also tested. Researches and results had shown that after stem cells that were pretreated with special chemicals were injected into the mouse were observed, they differentiate into myeloid and lymphoid progeny with a long term in vivo reconstituting ability even after 7 months of transplantation(Fraser et al., 1992). Also, the research conducted using totipotent cells which were pre-induced to

differentiate into a variety of cells has also resulted in the generation of myocytes, which are muscle cells(Clarke et al., 2000; Keller, 1995).

Because of the nearly infinity capability to differentiate, totipotent stem cells can be used in those crucial organs, such as heart. Even if the heart of patients receiving treatment were continue damaged, cardiomyocytes differentiated through totipotent stem cells can continue to make up for and replace those cells with incomplete function.

Totipotent stem cells usage in the area of medicine production

In addition to the normal usage of totipotent stem cell in therapy, it can be also used in medicing producing industry. Due to the ethical relationship, there are still many heart-disease-related drug trials can't be carried out. However, cardiomyocytes and organoids produced by the totipotent stem cells can perfectly solve this problem(Huang et al., 2021). The "cells" produced in this way not only have almost the same characteristics as normal human beings, but also can respond to drugs(Sobhani et al., 2017). Moreover, totipotent stem cells from mice can also offer some help on the process of drug testing. By transcript the totipotent stem cells, scientists are able to observe and then find out some possible reasons of the diseases and thus offer some ideas on drug production on the diseases that existed on both mouse and human(Li et al., 2019; Saitou & Yamaji, 2012; Xu et al., 2021). At the same time, because it does not completely have all the characteristics of biology, the ethical and moral problems it produces and faces are not as many as those produced by doing experiments directly on patients(Lo & Parham, 2009). If pharmaceutical companies can master this technology, the time of drug research and development will be greatly reduced, because there is no need to conduct RCTs on patients in hospitals(Rikhtegar et al., 2019; Sobhani et al., 2017). This series of tests and observation can be carried out in the laboratory, and it will become more convenient in the measurement of various indexes(Xia et al., 2019). However, it is also because it does not have all the characteristics of the human body, there are some side effects not related to the heart will be difficult to predict(Rikhtegar et al., 2019).

Pluripotent stem cells

Except for totipotent stem cells, pluripotent stem cells are the type of stem cells that creates most of the value. It is used in several areas related to heart diseases to help develop possible treatment for the patients.

Using hPSCs to regernerate cardiacvascular cells

Using hPSCs on heart regeneration is the most popular usage of hPSCs, and also the most basic usage of pluripotent stem cells. Virtually, there are also several ways that stem cells can help regenerate the cardiac cells. The very first way is the let the stem cells regenerate into the type of cells required by the patient, such as blood vessels cells, or muscle cells. The process of differentiation required the type of pluripotent stem cells correspondingly. This always requires embryonic stem cells, which can develop into the type of cells that the patient required(Clevers et al., 2014; Kadota et al., 2020; Kanji & Das, 2017; Rink, 2013; Vujic et al., 2020). The second way that can help regenerate the cardiac cells are through proliferation. Researches have shown that lower vertebrates have ability to re-differentiate the damaged myocardium, which is lost in mammals(Borchardt & Braun, 2007). However, some new researches showed that human infants have such an ability, but is will lose soon(Sattler & Rosenthal, 2016). Thus, if human's stem cells are extracted

while they are infants, which makes the cells have the ability to regenerate, when they get damaged myocardium, the stem cells extracted can somehow save their lives. Another way to help heart regenerate is to extract the patient's own stem cells from their bone marrow and transplant it. Researches have shown that while the stem cells extracted from the bone marrow of the patient, the cells damaged can be regenerated up to a rate of 68%, which is relatively high(Zhang et al., 2015). However, a new statement states that the engrafted stem cells cannot directly differentiate into cardiacvascular cells. Instead, they just facilitate the regeneration of cells by the patient's body its own(Tang et al., 2010). This statement still requires the testing of individual labs. The approach is to inject the stem cells directed to the region arount the heart tissues damaged. In this way, damaged cells can be replaced by new cells formed from stem cells. Current studies have shown that this treatment has a significant effect in non-primates(Povsic & Gersh, 2021). Even to a certain extent, it can form new blood vessels in the infarcted area. However, due to the ethical relationship, this kind of experiment has not been carried out on human beings. At the same time, another question worth thinking about is the unknown rate of stem cells to produce new cells(Jung et al., 2017). If this speed cannot be greater than or equal to the speed of cell damage caused by myocardial infarction, then this method can't be used to completely treat heart disease, but can only slow down its symptoms; In other words, more in-depth research is needed to accelerate the process of stem cell generation and differentiation.

Nevertheless, there are still some problems while transplanting bone marrow stem cells into the heart. The stem cells in bone marrow are highly structured, which is completely different from heart cells(Orlic et al., 2001). Besides, since heart requires continuously contracting and relaxing, the cells are always in the situation of high pressure. In this case, the cells produced are facing both permissive and repressive challenges. Furthermore, the scars between the old cells and new cells may also affect the normal flowing of bloods, causing some potential problems.

Combining hPSCs with other methods to treat cardiovascular diseases.

In addition to traditional stem cell therapy, stem cells can also be combined with other methods to help treat heart related diseases. For instance, bone marrow mesenchymal stem cells (BMSCs) modified by adiponectin (APN) can be used to treat diabetic cardiomyopathy(Meng et al., 2021). The previous researches have pointed out that using BMSCs can improve cardiac functions to some extent(Li et al., 2008), but whether it can reduce cardiac fibrosis still requires optimized. Since APN can attenuated liver and renal fibrosis, scientists are trying to combine the two different types of therapy together so that they may work together to give a surprising result. And the conclusion of the experiments shows that the combination of the two therapies is effective(Meng et al., 2021). However, to date, all experiments have only been performed on animals, and their effects in humans have not been truly validated. No one knows whethter patients will, when used, produce better results resulting in an excess of effects, or will have side effects that are not experienced in the animals. If more experiments as well as refinements can be implemented, the future harm due to cardiac fibrosis caused by diabetes will be greatly reduced, as will access to an alternative on treatment for those with type 1 diabetes.

Using hPSCs to model cardiac disease

Instead of offering direct help to the treating of CVD, some other indirect help can also be offered by using hPSCs in some fields that are not directly related to the treatment. One example is modeling. Cardiac disease modeling is the

main core of understanding how the diseases is affecting human's heart and only by doing so, scientists can get a high accuracy on the prediction of how the disease can be cured(Huang et al., 2021). Although doing experiments on other animals may also works since some of them have similar structures with that of human, there are still differences between human and other animals, and these small differences may cause great influences to the final results. No one can make sure what will happen. Thus, there are still a high risk on using the treatment modeling on animal's hearts(Tompkins et al., 2018). The introduction of hPSCs modeling is a breakthrough on this situation. If this refinement can be popularized one day, the time required for a patient's treatment can be shorten and the accuracy can increase a lot.

Using the hPSC-derived cardiomyocytes and organoids to test drugs

Another indirect way of utilizing hPSCs is drug testing. Due to the ethical relationship, there are still many heart-disease-related drug trials can't be carried out. However, cardiomyocytes and organoids produced by stem cells perfectly solve this problem(Huang et al., 2021). The "cells" produced in this way not only have almost the same characteristics as that of normal human beings, but also can respond to drugs. At the same time, because it does not completely have all the characteristics of biology, the ethical and moral problems it produces and faces are not as many as those produced by doing experiments directly on patients. If pharmaceutical companies can master this technology, the time consumption of drug research and development will be greatly reduced, because there is no need to conduct randomize controlled trials on patients in hospitals(Rikhtegar et al., 2019). This series of tests and observation process can be carried out in the laboratory, and it will become more convenient in the measurement of various indexes. However, it is also because it does not have all the characteristics of the human body, there are some side effects not related to the heart will be difficult to predict(Rikhtegar et al., 2019).

Conclusion

Stem cells therapy are gradually becoming the most potential technology that will be used on heart diseases treatment because of its always-new characteristics. And it also has relatively little risk compare with doing operations. The resources required on doing stem cell therapy is also much lower than regular treatment. Its convenience is also much higher than doing operations. Meanwhile, the question required solved as soon as possible is the sources of stem cells. If stem cells are extracted from embryo, ethical problems may be caused. On the other hand, if stem cells are extracted from bone marrows, its functions are limited. In this case, the problem that how to get stem cells that have no rejections from immune system, no ethical problems caused, but full functions need to be solved so that stem cell therapy can go on well.

Besides, there are also disadvantages on stem cell therapy. The most obvious one is the difficulties in finding stem cells. There are limited sources of cord-base stem cells which can differentiate vary types of cells. Moreover, the process of inducing stem cells are also low efficient. It always takes a long time for only a few goal cells produced. Furthermore, even though stem cell therapy can alleviate the symptoms of heart disease to a certain extent, different stem cells can produce different effects when used. For example, when using stem cells to treat non ischemic dilated cardiomyopathy, CD34 + stem cells extracted from bone marrow have more significant therapeutic effect for other stem cells(Campos de Carvalho et al., 2021). If we use other stem cells for treatment, although the quality of life can

be improved, the need for heart transplantation and mortality rate have not decreased. However, after the use of CD34 +, the situation has improved significantly. At the same time, different injection methods of stem cells will also affect the therapeutic effect. Studies have shown that the retention rate and utilization rate of stem cells in endocardial injection and intracoronary injection are higher, which can produce better effect(Martino et al., 2015).

There are still other ways that stem cells can provide benefits to heart diseases, such as using stem cells as an always-new raw material on bioprinting. Since cells are the basic components of every organism, it is sure that organs are also made up of cells. Thus, using stem cells as raw materials combining with 3D printing technology can somehow achieve the goal of produce an artificial heart for those patients who have waited for a suitable heart for a long time but haven't found yet (Ong et al., 2018). What are required to do is to guide the way stem cells differentiate and use the machine to guide it combine into the heart shape. Nevertheless, the problems that happen on the basic stem cell therapy still exist in the organ printed, such as the structure differences and the ethical problems pre-existed. In addition, the technologies nowadays are not mature enough to produce such an artificial organ since the nerve cells inside the heart are difficult to control and produce. Therefore, there are still plenty of refinements and developments waiting for utilizing stem cells in large scales.

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